AIJR Preprints
Section: Coronavirus
Article Id: 282, Version: 1, 2021
URL: https://preprints.aijr.org/index.php/ap/preprint/view/282
{Click on above link to see the latest available version of this article}

NOT PEER-REVIEWED

Version 1: Received: 06 February 2021 / Approved: 07 February 2021 / Online: 08 February 2021

Role of N-Acetylcisteine as Antioxidant in COVID-19

Fadel Fikri Suharto

Internal Medicine, Medical Faculty Sriwijaya University/RSUP Dr. Mohammad Hoesin Palembang

Article Type: Literature Review.

First Author's Full Name: Fadel Fikri Suharto
Highest Qualification: Medical Doctor
Department: Internal Medicine
Post/Rank: Internal Medicine Residency, 2021
Affiliation with postal address: Medical Faculty Sriwijaya University, Jl. Srijaya Negara, Bukit Lama, Kec. Ilir Bar. I, Kota Palembang, Sumatera Selatan 30139
email id: **********
ORCID: 0000-0003-4665-8580

ABSTRACT

At the end of December 2019, there was an outbreak of pneumonia of unknown etiology with symptoms of fever, dry cough, fatigue and gastrointestinal symptoms at seafood market, Huanan Market, Wuhan, Hubei, China. Initial outbreak was reported on the market in December 2019 and involved about 66% population of the workers there. Coronavirus Disease 2019 (COVID-19) is a contagious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is a new type of coronavirus that has never been previously identified in humans. N-acetylcysteine (NAC) is a metabolite of sulfur-containing amino acid cysteine. This drug has molecular formula $HSCH_2CH(NHCOCH_3)CO_2H$ and a molecular weight of 163.19. In human, it can be given orally or by intravenous infusion and can also be inhaled using a nebulizer. Significant increases in blood serum glutathione reductase (GR) levels, due to an imbalance of oxidative stress, have occurred in COVID-19 patients, especially when admitted to intensive care unit (ICU). From data set of several literature, endogenous deficiency in GSH can underlie severe manifestations and deaths due to COVID-19. N-acetylcisteine (NAC) is used in a variety of conditions for recovery or protection from decreased GSH levels and has a wide margin of safety. This is useful in treating ARDS from other causes and can reduce or prevent lung damage in COVID-19 patients. NAC has been shown to have protective mechanisms against various conditions associated with COVID-19 and its comorbidities, including cardiovascular disease. NAC given intravenously has been shown to potentiate vasodilator, anti-inflammatory and anti-aggregating effects of nitroglycerin, and these beneficial interactions have translated into improved outcomes, such as in acute myocardial infarction, unstable angina, and acute pulmonary edema. NAC administration has been incorporated into a strategy aimed at maintaining endothelial function and limiting microthrombosis in severe cases of COVID-19.

Keywords: N-acetylcisteine, acetylcisteine, COVID-19, SARS-CoV-2, antioxidant.

How to Cite:

Fadel Fikri Suharto, "Role of N-Acetylcisteine as Antioxidant in COVID-19". *AIJR Preprints*, 282, Version 1, 2021.

1 Introduction

At the end of December 2019, there was an outbreak of pneumonia of unknown etiology with symptoms of fever, dry cough, fatigue and gastrointestinal symptoms at seafood market, Huanan Market, Wuhan, Hubei, China. Initial outbreak was reported on the market in December 2019 and involved about 66% population of the workers there. Then, market was closed on January 1, 2020, after an epidemiological warning was announced by local health authorities on December 31, 2019. However, following month thousands of people in China, including many provinces (such as Hubei, Zhejiang, Guangdong, Henan, Hunan) and cities (Beijing and Shanghai) were hit by sporadic spread of the disease. Furthermore, this disease spreads to other countries, such as Thailand, Japan, Republic of Korea, Viet Nam, Germany, United States, and Singapore [1].

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is a new type of coronavirus that has never been previously identified in humans. There are two types of coronavirus that are known to cause diseases that can cause severe symptoms, such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). Common signs and symptoms of COVID-19 infection include acute respiratory symptoms such as fever, cough and shortness of breath. Average incubation period is 5-6 days with the longest incubation period of 14 days. Severe cases of COVID-19 can cause pneumonia, acute respiratory distress syndrome, kidney failure, and even death [2].

2 COVID-19

2.1 Classification

Suspected Case

Person who has one of the following criteria [1]:

- People with Acute Respiratory Infection (ARI) and in the last 14 days before symptoms develop have a history of travel or live in countries/regions of Indonesia that report local transmission.
- People with one of the symptoms/signs of ARI and in the last 14 days before symptoms develop had a history of contact with a confirmed / probable COVID-19 case.
- People with severe ARI/severe pneumonia requiring hospitalization and no other cause based on a convincing clinical picture.

Probable Case

- Suspected cases with severe ARD / ARDS / died with a convincing clinical picture of COVID-19 and no RT-PCR laboratory test results [1].

Confirmed Case

A person who tested positive for the COVID-19 virus as evidenced by an RT-PCR laboratory examination. Confirmation cases are divided into 2 [1]:

- Confirmed case with symptoms (symptomatic)
- Confirmed case without symptoms (asymptomatic)

2.2 Virology

*Coronavirus*is an RNA virus wrapped in a single positive chain. Virus belongs to the subfamily Orthocoronavirinae, true to its name, with characteristic "crown-like" spikes on its surface. Along with SARS-CoV, SARS-like bat CoVs and others are also included in beta-coronavirus genus. Beta-coronavirus genus can be divided into subgroups. CoV COVID-19, SARS-CoV, and SARS-Sarbecovirus which are bat-like, while MERS-CoV belongs to Merbecovirus. SARS-CoV, MERS-CoV, and COVID-19 all cause disease in humans but each subgroup has different biological properties and virulence [2].

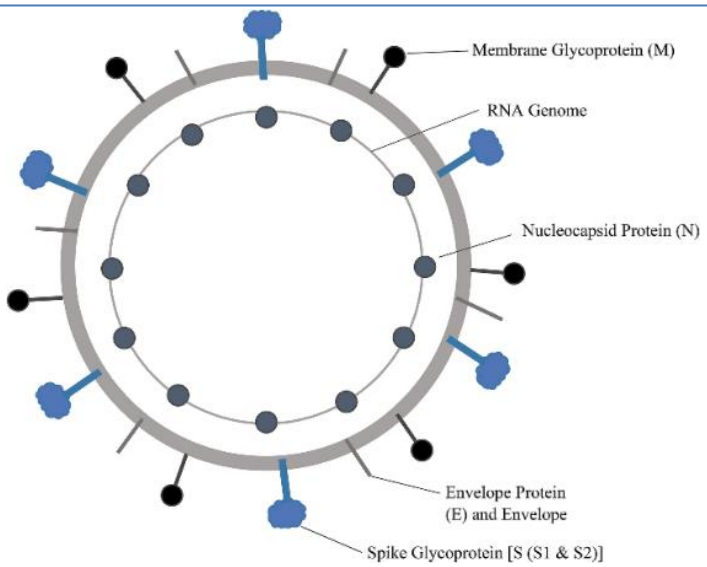

Figure 1. Structure of coronavirus [2].

Origin, location, and exact natural reservoir of COVID-19 are still unknown, although it is believed that the virus is zoonotic and bats are suspected to be origin cause of infection. According to previous research on SARS- and MERS-CoV, epidemiological research, their natural reservoir is bats, bats are considered as natural hosts of SARS-like coronavirus. However, until now the origin or natural host of COVID-19 is not clear, although it may have originated from wild animals in the market [2].

Theoretically, if someone has contact with or eats infected meat or animals, they can be infected. However, to produce large-scale person-to-person transmission as in the previous SARS outbreak, virus had to spread efficiently. Initially, 2019 CoV outbreak was reported as limited person-to-person transmission and a contaminated source from infected or sick wild animals on the market [2].

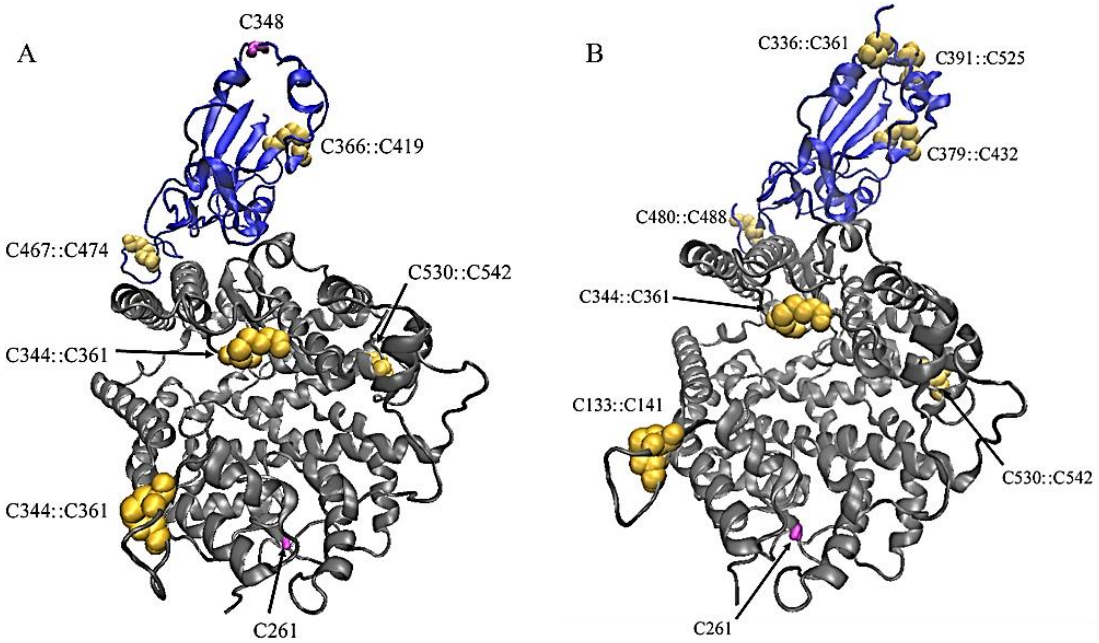

Figure 2. Protein structure of COVID-19 [2].

2.3 Clinical Manifestations

COVID-19 has an average incubation period of 5.2 days. Symptoms usually begin with atypical symptoms, such as fever, dry cough, and fatigue. Multiple organ systems can be involved, including

breathing (coughing, shortness of breath, sore throat, rhinorrhea, hemoptysis, and chest pain), gastrointestinal symptoms (diarrhea, nausea, and vomiting), musculoskeletal (muscle pain), and neurological (headache or confusion). Another common signs and symptoms are fever (83% -98%), cough (76% -82%), and shortness of breath (31% -55%). About 15% suffer from fever, cough and shortness of breath. Disease may progress to shortness of breath (± 8 days), acute respiratory distress syndrome (ARDS) (± 9 days), and use of mechanical ventilation (± 10.5 days) in approximately 39% of patients.

COVID-19 virus can enter the host via respiratory tract or mucosal surfaces (such as conjunctiva). Transmission through feces has not been found. Viruses have preferential tropism in human airway epithelial cells and cellular ACE-2 receptors. However, pathological changes of the disease and their pathogenesis in humans have not been clearly described. Theoretically lung is the main target organ to be attacked by this disease [3].

2.4 Diagnosis

Laboratory diagnosis for COVID-19 must be carried out in a laboratory equipped with a level 3 biosafety facility for viral cultures. Reported definitions of COVID-19 include (as of 7 February 2020): (1) Clinical condition, meeting any of the following symptoms (1.1) fever (≥38 ° C) or acute respiratory infection (1.2) clinical, radiological, or evidence pathological pneumonia. (2) Laboratory conditions, with one of the following: (2.1) clinical specimen (nasopharyngeal swab, sputum, or lower respiratory tract aspiration) isolated and identified as COVID-19 (2.2) Clinical specimen showing positive RT-PCR results. (3) Epidemiological conditions, with one of the following 14 days before the onset of symptoms (3.1) travel history of or evidence of contact of patients with fever or respiratory symptoms in COVID-19 red zone (3.2) travel history from or living in other parts of mainland China (including Hong Kong and Macau) (3.3) history of contact with criteria for probable or confirmed cases of COVID-19, including visits to health care facilities, living under one roof, direct contact of mucus or bodily fluids.

Confirmatory laboratory diagnoses use real-time RT-PCR assays to detect viral RNA targeting E pan beta-CoV consensus areas or other more specific areas (such as RdRp or N regions). Chest X-ray and computer-tomography (CT) reveal bilateral pneumonia (75–98%) with multiple spots and ground-glass opacity. Routine laboratory data in early stages of COVID-19 epidemic are similar to those of common viral infections: lymphopenia, prolonged prothrombin time, elevated D-dimers, liver enzymes (alanine aminotransferase), total bilirubin, and lactic dehydrogenase, with a worsening trend in ICU cases. Leukocytosis can occur when complications occur with secondary bacterial infection [3].

3 N-Acetylsisteine (NAC)

N-acetylcysteine (NAC) is a metabolite of the sulfur-containing amino acid cysteine. This drug has molecular formula $HSCH_2CH(NHCOCH_3)CO_2H$ and a molecular weight of 163.19. In humans it can be given orally or by intravenous infusion and can also be inhaled using a nebulizer. These drugs are used as antioxidants and mucolytic agents [4,5].

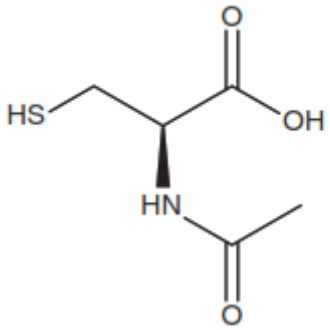

Figure 3. Chemical structure of NAC [4].

Therapeutic potential of NAC is known and is currently being further investigated in a variety of diseases as an antidote to paracetamol intoxication, as a bioprotective agent against oxidative stress and ischemic injury, and as a treatment for psychiatric illness. In addition, NAC is also used as a dietary supplement, by athletes in particular. It is used in intravenous preparations for management of paracetamol (acetaminophen) overdose, and as a second-line drug for the treatment of acrylonitrile and methacrylonitrile poisoning [4,6].

3.1 Pharmacology of NAC

Mechanism action of NAC and its dosage varies according to indications. For treatment of paracetamol overdose, NAC must be given within 10 hours of taking paracetamol. When used as a mucolytic agent for treatment of bronchopulmonary disease, NAC can be administered in water or saline solution and inscribed for administration by inhalation or orally. For oral use NAC is usually given as a tablet or capsule [6].

3.2 Pharmacokinetics of NAC

Pharmacokinetic parameters for NAC have not been defined because most of older studies and early studies used low doses. Most of the studies demonstrated wide inter-subject variation in plasma NAC concentrations after oral administration. In addition, NAC is synthesized endogenously, and as a result reported circulating rates ranging from 23.3 to 137.7 nm, further complicating pharmacokinetic calculations. Bioavability of oral NAC is estimated to be 6–10%, due to extensive first-pass metabolism, with T-max 1–2 h after first dose [8].

3.3 Metabolism of NAC

NAC forms dimer N-acetylcystine and N, N-diacetylcystine, covalently binds to plasma proteins and can be deactylated to form cysteine. Latter is a rate-limiting precursor for endogenous antioxidant glutathione. Supplementation with NAC has been shown to increase glutathione availability by 5-10% in a malnourished population. However, rate of increase and subsequent return to baseline endogenous levels for glutathione after NAC administration has not been studied, although significant glutathione turnover is known to occur in kidneys, liver and pancreas [9].

3.4 Mechanism Action of NAC

NAC has a number of major mechanisms of action that have potentially therapeutic benefits such as [4,6,9]:

- Precursors of antioxidants and glutathione
  NAC is a collector of reactive oxygen species, but its primary role as a therapeutic antioxidant stems from its role as a precursor to cysteine, a rate-limiting step in glutathione synthesis. Under conditions of oxidative stress, glutathione levels are depleted and this can be overcome by administering NAC. Cellular defenses against oxidative stress can include reduction of hydroperoxides by glutathione peroxidase and glutathione-S-transferase catalyzed conjugate reactions. Therefore, glutathione is essential for body's antioxidant defenses. By administering glutathione, NAC can prevent paracetamol toxicity. Hepatotoxic metabolite paracetamol is rapidly cleared by glutathione through the formation of cysteine and mercapturic acid conjugates, and prevents cell death.
- Mucolytic
  NAC cuts disulfide bonds that bind to glycoproteins in sputum. Breaking of glycoprotein crosslinks reduces viscosity by producing greater mucosal fluidity which in turn facilitates clearance of bronchial tubes.
- Anti inflammatory

NAC has been claimed to have anti-inflammatory properties. Induction of the pro-inflammatory activator protein-1 (AP-1) and NF-κB transcription factor was inhibited by NAC. This transcription factor has been found to be induced in response to oxidative stress, the anti-inflammatory properties of NAC due to its antioxidant mechanism.

- Chelating agent
  Methylmercury is formed from food or environmental contamination. Administration of NAC may increase urinary methylmercury excretion in a dose-dependent manner. This detoxification is thought to be due to formation of the MeHg-NAC complex, which is actively transported through renal tubular cells and excreted in urine.
- Glutamate precursors
  Glutamate is thought to have a key role in neurobiology of mood, psychosis, and addiction. In nucleus accumbens, basal extracellular glutamate levels are maintained primarily by exchange of extracellular cysteine for intracellular glutamate, via cysteine-glutamate exchange system. NAC increases extracellular glutamate levels and thereby stimulates group II metabotropic glutamate receptors.
- NAC and homocysteine
  Increased homocysteine levels have been studied as a risk factor for cardiovascular disorders, dementia, and psychiatric disorders. NAC acts as a methyl donor in conversion of homocysteine to methionine which subsequently becomes a protective factor against these diseases.

4 N-Acetylcisteine (NAC) and COVID-19

Significant increases in blood serum glutathione reductase (GR) levels, due to an imbalance of oxidative stress, have occurred in COVID-19 patients, especially when admitted to intensive care unit (ICU). From data set of several literature, endogenous deficiency in GSH can underlie severe manifestations and deaths due to COVID-19. N-acetylcisteine (NAC) is used in a variety of conditions for recovery or protection from decreased GSH levels and has a wide margin of safety. This is useful in treating ARDS from other causes and may reduce or prevent lung damage in COVID-19 patients [10,11].

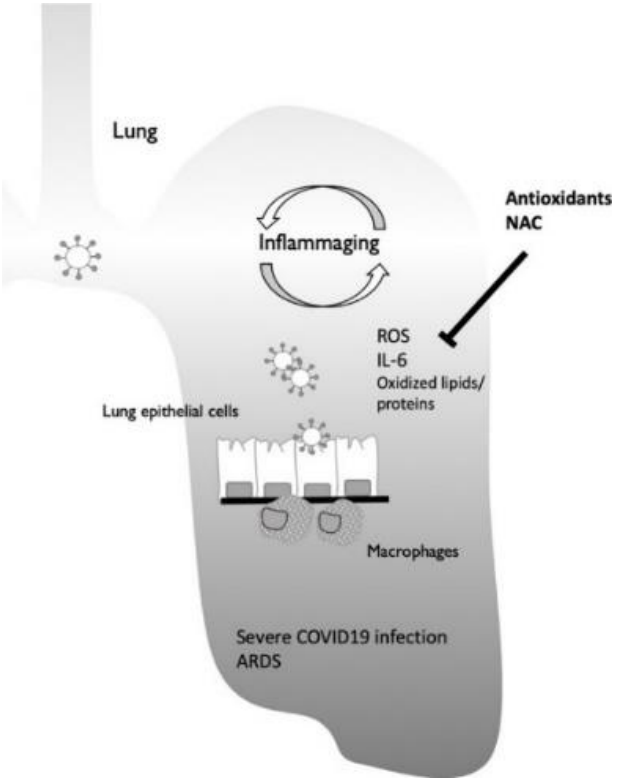

Figure 4. Role of NAC in COVID-19 [12].

4.1 Inhibition by thiol from SARS-COV-2 binding to cells

Enzyme angiotensin-convertase 2 (ACE2) is a functional receptor for severe acute respiratory syndrome coronavirus (SARS), which is responsible for entry into cells of both SARS-CoV and SARS-CoV-2, causative agent for COVID-19. Therefore, viral spike-protein interaction with ACE2 is an important step in viral replication cycle. Viral and ACE2 spike-protein receptor binding domains have some cysteine residues. Molecular dynamics simulations show that binding affinity is significantly impaired when all of disulfide bonds of ACE2 and SARS-CoV / CoV-2 spike-proteins are reduced to thiol groups[10]. Reduction of disulfides to sulfhydryl groups can impair binding of SARS-CoV / CoV-2 spike-protein to ACE2 and provide a molecular basis for severity of COVID-19 infection due to oxidative stress. Furthermore, animal studies and clinical studies suggest that administration of NAC, which can weaken tolerance to nitrates, modifies function of renin / angiotensin system in vivo. This effect is mediated by inhibition of ACE activity. By blocking ACE, NAC can provide protection against detrimental effects of angiotensin II, a potentially useful activity in SARS-CoV-2 infection [11,12].

4.2 Oxidative Stress, Inflammation, And Immune Response

Oxidative stress and inflammation are closely related. Cell exposure to either hydroxyl radical (OH) or superoxide radical anion (O2) induces dose-dependent release of pro-inflammatory cytokines. Lipopolysaccharide (LPS) induces accumulation of intracellular reactive oxygen species (ROS) and increases release of interleukin (IL) -1beta, IL-6, and tumor necrosis factor - alpha (TNF-α). Kappa B (ϰB - α) / nuclear kappa B (NF - ϰB) independent pathway mediates redox-dependent regulation of inflammatory cytokines, and this process is amplified by decreased GSH levels [14].

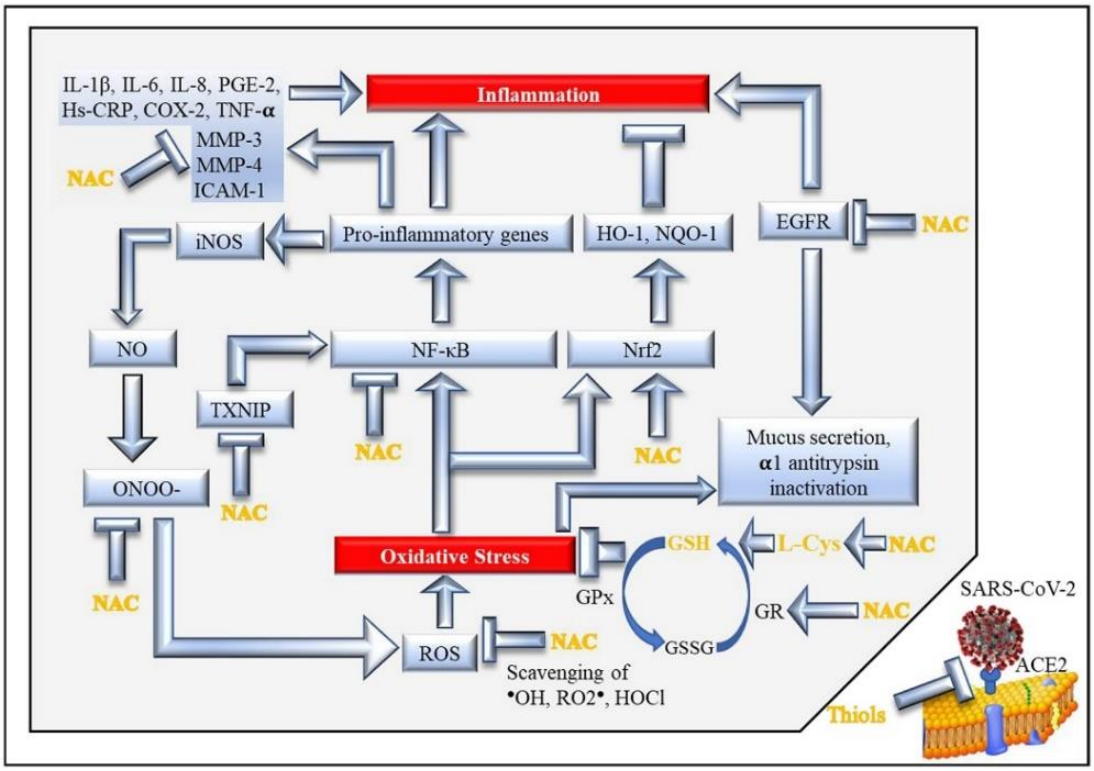

Figure 5. Main mechanisms involved in the antioxidant and anti-inflammatory action of NAC are via GSH (modified and updated from Sadowska, 2012). Blue arrows indicate activity stimulation or downstream pathways, while T-shaped symbols indicate activity inhibition or downstream pathways [15].

Antioxidants ROS and thiol, including GSH, regulate innate immunity at multiple levels, as studied by extensive literature. GSH is not only important as an antioxidant, but also as a signaling molecule in

redox-sensitive steps of cellular mechanisms involved in inflammation and body's defense against infection. GSH not only affects certain factors involved in immunological processes, but also modifies complex immune reactions such as fever, and there are data suggesting that fever induction is associated with oxidative stress [15].

Although complement system is a key mediator of innate immune response that protects against infectious agents, complement system also plays an important role in inducing inflammatory processes that lead to tissue injury. In particular, complement is involved in pathogenesis of coronavirus, as inferred from finding that SARS-CoV-infected C3 knockout mice had less lung disease than wild-type mice. Baseline data provide evidence of complement activation (sC5b - 9 and C5a) in patients with COVID-19, with significantly higher plasma levels in patients with severe disease than in patients with moderate disease. Therefore, complement activation is proposed as a new therapeutic target in COVID-19 [12-14].

Chronic oxidative stress, causes biomolecular damage, contributes to age-related decline in physiological functions, including immune function. Daily administration of NAC (600 mg) to postmenopausal women strengthens immune defenses thereby reducing likelihood of immune system-related diseases in aging, such as infection, as demonstrated by monitoring multiple lymphocyte function (adherence, chemotaxis, proliferation, NKC, and activity) and neutrophil function (adherence, chemotaxis, phagocytosis, and superoxide) and levels of cytokines (IL-2, IL-8, and TNF-α) [12-14].

4.3 Antioxidant and Anti-Inflammatory Mechanisms of NAC

NAC works through various mechanisms, which in cell are mediated by replenishment of GSH. One of main ones is its nucleophilicity, which consists in ability of sulfhydryl (-SH) groups to react with electrophilic metabolites, either directly or via transferase GSH. This capability results in binding of reactive metabolites to DNA and blocking of reactive intermediates. An example of a reactive intermediate is paracetamol metabolite N-acetyl-p-benzoquinone-imine (NAPQI) which is formed by enzyme cytochrome P450. Additionally, NAC can utilize antioxidant activity via p53-mediated apoptosis. L-Cys, which is lowered by catabolism of NAC, is easily converted into a vasodilator, anti-inflammatory and diffuse hydrogen sulfide. Therefore, NAC is considered a hydrogen sulfide donor [13-15].

NAC is most effective collector of ROS and especially hypochlorous acid (HOCl) and OH. Inhibition by NAC of ROS NAD (P) H-producing vascular oxidase is associated with prevention of hypertension and pathologic conditions associated with uncontrolled growth and inflammation, such as atherosclerosis. SH-group in NAC molecule can also bind to several reactive nitrogen (RNS) species that play a role in oxidation of lipids, proteins and DNA. NAC potentiates vasodilator and antiaggregation effects of nitric oxide, which are very important interactions clinically, and which have been shown to be useful in conditions of acute heart failure, acute myocardial ischemia and infarction [16].

Inhibition by NAC of epidermal growth factor receptor (EGFR), a tyrosine kinase involved in inflammation, also results in decreased α1-antitrypsin inactivation. In particular, NAC has ability to enhance efficacy and integrity of α1-antitrypsin structural conformation via GSH-mediated mechanisms, and enhance α1-antitrypsin transcytosis thereby enhancing its absorption and cellular function [15,16].

In experimental studies, oral administration of NAC to pregnant mice increased expression of gene coding for α1-antitrypsin precursor in fetal liver. Together with redox imbalance, α1-antitrypsin deficiency is involved in pathogenesis of COPD. NAC was found to reduce IL-8 levels, normalized C-reactive protein (CRP) levels, and improve clinical outcomes in patients with COPD exacerbations. A prospective, randomized, controlled trial in Shandong Province, China that enrolled adult bronchiectasis patients with at least two exacerbations in previous year showed that oral NAC (600 mg twice daily for 12 months) was able to reduce risk of exacerbations [16].

Additionally, NAC has been shown to have a protective effect on ARDS. It is well known that ROS plays a key role in pathogenesis of acute lung injury and alveolar epithelial lining fluid in ARDS patients with GSH deficiency, which may affect patient's severity. A prospective randomized, double-blind, placebo-controlled clinical trial in 5 ICUs in US and Canada has shown that intravenous administration of NAC (70

mg / kg body weight), every 8 hours for 10 days, effectively replenishes GSH on red blood cells, decreasing prolonged count. care for acute lung injury, and significantly increase cardiac index [15,16].

A further mechanism is that NAC further enhances stimulation of erythroid-related core factor 2 (Nrf2) by oxidative stress, which supports transcription of phase II enzyme genes and downregulates inflammation. Nrf-2 is essential for induction mediated by antioxidant responsive elements (ARE) of endogenous antioxidant enzymes such as heme oxygenase 1 (HO-1), NAD (P) H dehydrogenase [quinone] 1 (NQO-1), and GCL. NAC is also being researched to target heme-heme oxygenase system which can prevent severe complications following COVID-19 infection. In parallel, NAC inhibits oxidative stress activation mediated by kappa-light-chain-enhancer core factor of activated B cells (NFkB) and biochemical pathways regulating pro-inflammatory genes [16].

NAC also reduces intracellular hydrogen peroxide concentrations and restores total intracellular thiol concentrations by inhibiting translocation of NFkB to cell nuclei and phosphorylation of p38 mitogen-activated protein kinase (MAPK p38). In influenza infection, NAC inhibits induction of a pro-inflammatory cytokine response via ROS-induced 3 / hemagglutinin receptor (TLR3 / HA), activation of NFkB associated with ROS [17].

In addition, NAC has anti-inflammatory activity independent of its antioxidant activity, as demonstrated by finding that it inhibits LPS-mediated neurogenic inflammation by counteracting release of Na, K-ATPase (NKA), a marker of cell necrosis, which may explain IL-6 reduction with NAC. A multicenter, randomized, placebo-controlled, sequential trial testing initial use of intravenous NAC, followed by 12 weeks of oral ramipril, was based on premise that this agent has ability to limit nitrosative stress and expression of proteins that interact with thioredoxin activator inflammasome (TXNIP) [15-17].

5 Conclusions

NAC has been shown to have protective mechanisms against various conditions associated with COVID-19 and its comorbidities, including cardiovascular disease. NAC given intravenously has been shown to potentiate vasodilator, anti-inflammatory and anti-aggregating effects of nitroglycerin, and these beneficial interactions have translated into improved outcomes, such as in acute myocardial infarction, unstable angina, and acute pulmonary edema. NAC administration has been incorporated into a strategy aimed at maintaining endothelial function and limiting microthrombosis in severe cases of COVID-19. In cases of symptomatic COVID-19 with pulmonary and / or systemic organ involvement, NAC given intravenously at high doses commonly used in cases of paracetamol poisoning, which is given at the onset of pulmonary symptoms, is expected to act as adjuvant therapy in combination with antivirals or other drugs.

6 Competing Interests

Author indicate no potential conflict of interest from this literature.

References

[1] Kementerian Kesehatan. Pedoman Pencegahan dan Pengedalian Coronavirus Disease (COVID-19) Revisi V. Pedoman Pencegah dan Pengedalian Coronavirus Dis. 2020;5:1-214. doi:10.33654/math.v4i0.299

[2] Wu YC, Chen CS, Chan YJ. The outbreak of COVID-19: An overview.J Chinese Med Assoc. 2020; 83 (3): 217-220. doi: 10.1097 / JCMA.0000000000000270

[3] Rahman S, Bahar T. COVID-19: The New Threat. Int J Infect. 2020; 7 (1): 1-6. doi: 10.5812 / iji.102184

[4] Liu Y, Wang M, Luo G, et al. Experience of N-acetylcysteine airway management in the successful treatment of one case of critical condition with COVID-19: A case report.Medicine (Baltimore). Published online 2020. doi: 10.1097 / MD.0000000000022577

[5] Jaiswal N, Bhatnagar M, Shah H. N-acetycysteine: A potential therapeutic agent in COVID-19 infection. Med Hypotheses. 2020; 144. doi: 10.1016 / j.mehy.2020.110133

[6] Dekhuijzen PNR. Antioxidant properties of N-acetylcysteine: Their relevance in relation to chronic obstructive pulmonary disease.Eur Respir J. Published online 2004. doi: 10.1183 / 09031936.04.00016804

[7] Ezeriņa D, Takano Y, Hanaoka K, Urano Y, Dick TP. N-Acetyl Cysteine Functions as a Fast-Acting Antioxidant by Triggering Intracellular H 2 S and Sulfane Sulfur Production.Cell Chem Biol. Published online 2018. doi: 10.1016 / j.chembiol.2018.01.011

[8] Nasi A, McArdle S, Gaudernack G, 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. Published online 2020. doi: 10.1016 / j.toxrep.2020.06.003

[9] Dodd S, Dean O, Copolov DL, Malhi GS, Berk M. N-acetylcysteine for antioxidant therapy: Pharmacology and clinical utility. Expert Opin Biol Ther. Published online 2008. doi: 10.1517 / 14728220802517901

[10] Rangel-Méndez JA, Moo-Puc RE. N-acetylcysteine as a potential treatment for COVID-19.Future Microbiol. Published online 2020. doi: 10.2217 / fmb-2020-0074

[11] Shi Z, Puyo CA. N-acetylcysteine to combat COVID-19: An evidence review.Ther Clin Risk Manag. Published online 2020. doi: 10.2147 / TCRM.S273700

[12] Poe FL, Corn J.N-Acetylcysteine: A potential therapeutic agent for SARS-CoV-2. Med Hypotheses. Published online 2020. doi: 10.1016 / j.mehy.2020.109862

[13] Suhail S, Zajac J, Fossum C, et al. Role of Oxidative Stress on SARS-CoV (SARS) and SARS-CoV-2 (COVID-19) Infection: A Review.Protein J. Published online 2020. doi: 10.1007 / s10930-020-09935-8

[14] Ibrahim H, Perl A, Smith D, et al. Therapeutic blockade of inflammation in severe COVID-19 infection with intravenous N-acetylcysteine.Immunol Clin. Published online 2020. doi: 10.1016 / j.clim.2020.108544

[15] 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 (10): 13185-13193. doi: 10.1096 / fj.202001807

[16] Andreou A, Trantza S, Filippou D, Filippou D, Sipsas N, Tsiodras S. COVID-19: The potential role of copper and N-acetylcysteine (NAC) in a combination of candidate antiviral treatments against SARS-CoV-2. In Vivo (Brooklyn). Published online 2020. doi: 10.21873 / invivo.11946

[17] Goodnough R, Canseco K. Truncated IV acetylcysteine treatment duration has potential to safely preserve resources during the COVID-19 pandemic. Clin Toxicol. Published online 2020. doi: 10.1080 / 15563650.2020.1758327