REVIEW ARTICLE

A Review on N-acetylcysteine: A Versatile Adjuvant in Respiratory Diseases

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ABSTRACT

N-acetylcysteine (NAC), the acetylated variant of the amino acid L-cysteine and precursor of glutathione, has several therapeutic uses and has been used worldwide for over 50 years. It is used as an antidote for paracetamol poisoning, for treating neurological illnesses and substance use disorders, and as a mucolytic, antibiofilm, antioxidant, and anti-inflammatory agent in various respiratory diseases. Therefore, NAC exhibits promising therapeutic potential and may be an effective choice for add-on therapy. This review aims to establish the benefits of NAC beyond its mucolytic and antibiofilm actions and highlights the utility of its antioxidant as well as anti-inflammatory activity not only in chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD) and bronchiectasis, but also in respiratory infections, such as tuberculosis, pneumonia, and coronavirus disease 2019 (COVID-19). The review will be of interest to physicians as it summarizes the advantages of using NAC in the treatment of various respiratory disorders in their clinical practice.

Keywords: N-acetylcysteine, antioxidants, oxidative stress, respiratory diseases, chronic obstructive pulmonary disease, exacerbations

N-acetylcysteine (NAC) has gained immense popularity over the past six decades and is listed as an essential drug by the World Health Organization (WHO). It is an acetylated precursor of L-cysteine and is an exceptional source of sulfhydryl-containing compounds[1]. PubMed has listed approximately 29,500 articles with NAC featured in the titles and abstracts as of May 2024, which is indicative of its wide popularity. However, this might not reflect true numbers and these figures could be much higher. Nevertheless, NAC is a molecule of interest to researchers around the globe. The diverse therapeutic uses of NAC are highlighted in Fig. 1[2].

Since its discovery, NAC has been widely used as a mucolytic agent and this property is, perhaps, the most discussed. However, the agent has many other relatively less highlighted applications of clinical relevance.

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BIOLOGICAL ACTIONS OF NAC

Mucolytic Properties

NAC was first noted in the 1960s for its role in replenishing cellular glutathione (GSH), a vital antioxidant, and its potential to reduce respiratory mucus viscosity[3]. In the 1970s, clinical studies explored the mucolytic properties, particularly in conditions with thick mucus, such as chronic bronchitis and cystic fibrosis (CF). By the 1980s, NAC had gained recognition as an effective mucolytic agent, breaking disulfide bonds in mucoproteins to reduce mucus viscosity. It became integral in treating respiratory disorders, such as chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis. From the 1990s to the present, NAC's role as a mucolytic persists in various respiratory conditions, including COPD and acute respiratory distress syndrome (ARDS)[4].

Mucus hypersecretion is a risk factor for increased morbidity for patients with COPD, asthma, and CF. In the case of obstructive lung disorders, excessive mucus production accompanied by inadequate mucus clearance may further hinder air passage by clogging the already obstructed airways.

NAC is an effective mucolytic agent that breaks the three-dimensional network of mucus through the reduction

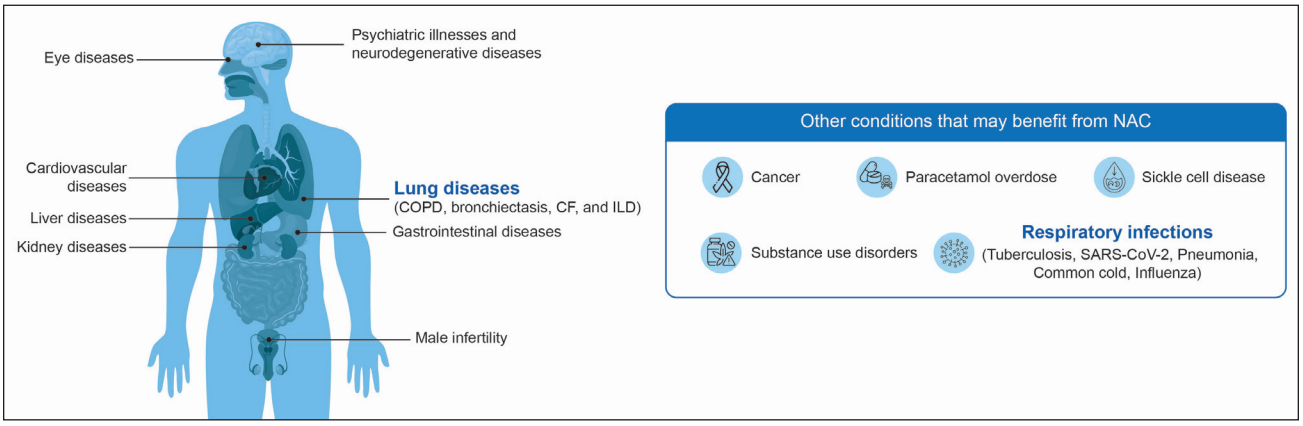


Figure 1. Therapeutic uses of NAC[2].

CF = Cystic fibrosis; COPD = Chronic obstructive pulmonary disease; ILD = Interstitial lung disease; NAC = N-acetylcysteine; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2.

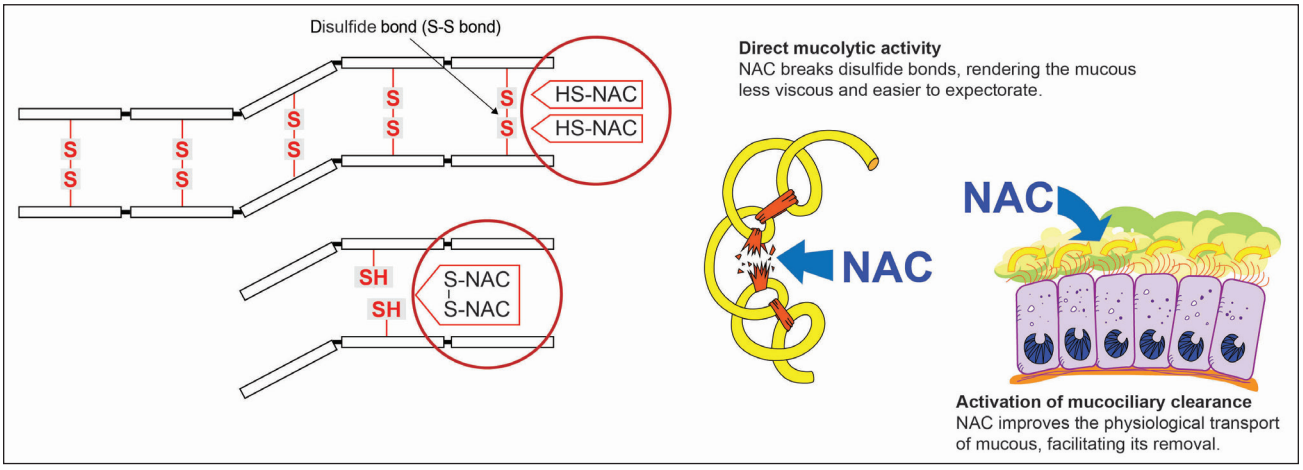


Figure 2. Action of NAC on mucus[5].

NAC = N-acetylcysteine.

of the disulfide bonds (S-S) to a sulfhydryl bond (-SH) (Fig. 2)[5]. Beyond the mucolytic property, NAC plays a mucoregulatory role as it acts on mucus elasticity as well as modulates its production and secretion[6]. A study by Van Overveld et al[7] reported a decrease in neutrophil chemoattractant properties in the sputum of patients with COPD after 8 weeks of treatment with NAC at 600 mg/day. Shen et al[8] reported that NAC administration exerts its mucolytic effect and can help reduce the incidence of exacerbations in patients with COPD (relative risk [RR] = 0.59, 0.47-0.74, 95% confidence interval [CI], $p < 0.001$). Another study showed that the use of oral NAC (200 mg twice daily) resulted in a change in sputum compositions and patients reported reduced sputum volume and cough severity[9]. It has been found effective for reducing sputum viscosity in both CF and COPD, essential for facilitating the removal of pulmonary secretions. Intracellular reactive oxygen species (ROS) mediate mucin MUC5AC production induced by pyocyanin, a redox-active toxin causing oxidative stress (OS) in the host cell. MUC5AC release is prevented by the intracellular antioxidant NAC[10]. Moreover, oral NAC prevents bacterial stimulation of mucin production and hence, mucus hypersecretion[6].

Biofilm Inhibition

Bacterial biofilm formation specially produced by *Pseudomonas aeruginosa* may be involved in pulmonary diseases, including ventilator-associated pneumonia (VAP), CF, bronchiectasis, bronchitis, diffuse panbronchiolitis, and upper respiratory airway infections[11,12].

Biofilms pose a challenge to antibiotic effectiveness due to their protective matrix and reduced metabolic activity. Bacteria in biofilms are 2- to 1,000-fold more resistant than the corresponding planktonic form[12]. Given the limited effectiveness of antibiotics against

biofilms, the focus has shifted toward the use of nonantibiotic therapies. NAC has been found to inhibit biofilm formation by both Gram-positive and Gram-negative bacteria; it also reduces the production of extracellular polysaccharide (EPS) matrix while disrupting mature biofilms. Zhao et al[11] demonstrated the inhibitory effects of NAC on biofilms produced by *Pseudomonas aeruginosa*. NAC was able to detach and disrupt *P. aeruginosa* biofilms at concentrations of 0.5 mg/mL and 10 mg/mL, respectively, suggesting that the biofilm disruption was directly proportional to NAC concentrations. The production of EPS by *P. aeruginosa* also decreased by 27.64% and 44.59% at NAC concentrations of 0.5 mg/mL and 1 mg/mL, respectively[11]. Qu et al[13] evaluated the role of NAC on VAP caused by biofilms in endotracheal tubes. Biofilm culture positive rate and incidence of VAP decreased in the study group compared with the control group (65% [37/57] vs. 80% [48/60], $p < 0.05$; 11% [6/57] vs. 32% [19/60], $p < 0.01$). Studies highlighting the activity of NAC as an antibiofilm of different species and as an antibacterial have been presented in Table 1[14-25].

Table 1. *In vitro* NAC Activity Against Biofilms[14-25]

Bacteria strains	Effective NAC concentration	Outcomes	References
Gram-negative bacteria			
Escherichia coli	2 mg/mL and 4 mg/mL; 0.007-8 mg/mL	NAC has good antibacterial properties and can interfere with biofilm formation and disrupt them.	El-Feky et al, 2009[14]; Marchese et al, 2003[15]
Klebsiella pneumoniae	2.5 mg/mL	NAC can be used in the treatment of catheter-associated infections.	Mohsen et al, 2015[16]
Pseudomonas aeruginosa ATCC 10145	0.5 mg/mL, 2 mg/mL, and 4 mg/mL	Biofilm reduction growth by 89.52%, 20.87%, and 19.42% at 4 mg/mL, 2 mg/mL, and 0.5 mg/mL NAC concentration.	Guerini et al, 2020[17]
Pseudomonas aeruginosa ATCC 10145	2.5 mg/mL	NAC when combined with NSAIDs displayed a greater inhibitory effect in bacterial adherence.	Mohsen et al, 2015[16]
Pseudomonas aeruginosa ATCC 15692	6 mg	NAC in combination with bone cement can improve the ciprofloxacin effect.	Onger et al, 2016[18]
Proteus spp.	2.5 mg/mL	NAC can be used in the treatment of catheter-associated infections.	Mohsen et al, 2015[16]
Stenotrophomonas maltophilia and *Burkholderia cepacia* complex (Bcc)	8 mg/mL, 16 mg/mL, and 32 mg/mL	NAC was able to significantly inhibit biofilm formation against most of the strains.	Pollini et al, 2018[19]
Pseudomonas mendocina and *Acinetobacter baumannii*	0.25-2 mg/mL	NAC affects growth, extracellular polysaccharide production, and bacterial biofilm formation on solid surfaces.	Olofsson et al, 2003[20]
Prevotella intermedia	0.375-3 mg/mL	NAC can be used for the prevention of biofilm formation by *P. intermedia*.	Moon et al, 2015[21]
Gram-positive bacteria			
Enterococcus faecalis ATCC 29212	1.56-12.5 mg/mL	The use of NAC eliminated both biofilm and planktonic forms of *E. faecalis*.	Quah et al, 2011[22]
Staphylococcus aureus	20 mg/mL	NAC demonstrated good antibacterial activity and a high disruptive effect on mature biofilms.	Mohsen et al, 2015[16]
Staphylococcus aureus	6-24 mg/mL	NAC can be used in the treatment of orthopedic prosthetic infections.	Drago et al, 2013[23]
Staphylococcus epidermidis	4 mg/mL and 40 mg/mL	NAC can be used to combat infections caused by *S. epidermidis* biofilms, namely as a catheter lock solution therapy.	Leite et al, 2013[24]
Staphylococcus epidermidis	0.5-32 mg/mL	NAC and ethanol alone or in combination with antibiotics may be used to salvage infected catheters.	Venkatesh et al, 2009[25]

NAC = N-acetylcysteine; NSAID = Nonsteroidal anti-inflammatory drug.

Antioxidant and Anti-inflammatory Properties

Oxidative stress, an imbalance between ROS production and antioxidant defenses, has an established role in lung diseases, such as bronchial asthma, COPD, ARDS, acute lung injury, and pulmonary fibrosis[26]. Chronic infections (e.g., bronchiectasis, tuberculosis [TB], and pneumonia) and microbial colonization inside the lung tissues can also cause activation of the immune system, subsequently leading to the production of ROS and reactive nitrogen species (RNS)[27]. Endogenous antioxidants, such as sulfhydryl (thiol)-containing tripeptide GSH, maintain oxidant-induced lung epithelial cell dysfunction and control proinflammatory processes and its depletion or alteration in alveoli and lungs are a central feature of many inflammatory lung diseases[28]. NAC is one of the most widely used antioxidants (~2,26,000 results in a Google Scholar search for 'antioxidant and NAC'); the *in vivo* antioxidant capacity can be either direct or indirect. The direct effect is mediated by the presence of a free sulfhydryl group that can act as a ready source of reducing equivalents and as a scavenger of ROS. The indirect effect is through replenishment of intracellular GSH levels due to its ability to act as a source of cysteine (Cys). It has been reported to lower endogenous oxidant levels and to protect cells against a wide range of pro-oxidative insults[29]. As a result, NAC helps in breaking the 'vicious cycle' of OS and inflammation[2].

Several reviews have highlighted multiple properties of NAC compared to other mucolytics, such as erdosteine and carbocisteine (Fig. 3; Table 2)[2,30-33]; however, this review will focus particularly on the antioxidant effects of NAC in respiratory diseases and lung health. This is because its antioxidant mechanism has sparked great interest in recent years. This review will help the researchers analyze the drug from a new perspective and learn more about its role as an important antioxidant.

NAC IN CHRONIC RESPIRATORY DISEASES

COPD

COPD is a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production, and exacerbations) due to inflammation or hypersecretion of the airways (bronchitis and bronchiolitis) and/or destruction of alveoli (emphysema). COPD can cause persistent, often progressive, airflow obstruction[34] often admixed with systemic inflammation and symptoms. Evidence suggests that OS is the major driving factor for the pathogenesis of COPD (Fig. 4)

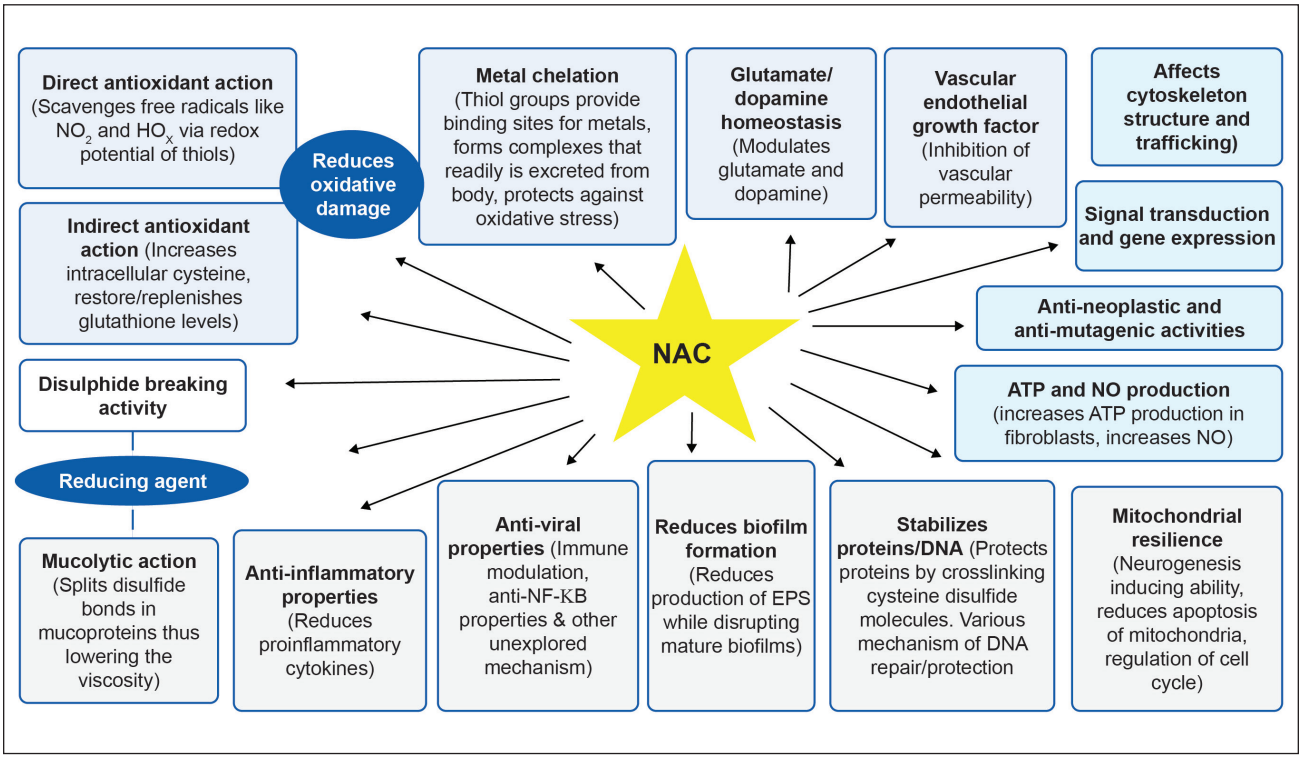


Figure 3. Various Effects of NAC[2,30,31].

ATP = Adenosine triphosphate; DNA = Deoxyribonucleic acid; EPS = Extracellular polysaccharide matrix; HO_x = Hydrogen oxide radicals; NF-κB = Nuclear factor-Kappa B; NO = Nitric oxide; NO_2: = Nitrogen dioxide.

Table 2. Various other Activities of NAC[32,33]

Mucolytic activity	Reduced viscosity of mycoprotein solutions
	Reduced bronchial secretions
	Increased mucociliary clearance
Antioxidant activity	Reduced pro-oxidant profile
	Increased antioxidant profile
Anti-inflammatory activity	Reduced neurogenic inflammation
	Reduced cytokine release
	Reduced proteinase synthesis
	Reduced levels of proinflammatory proteins and activation of transcription factors
Direct and indirect antibacterial activity	Increased neutrophil-killing activity
	Bacteriostatic effect
	Reduced bacterial adhesion on epithelium
	Reduced biofilm formation
	Viral replication and infectivity
Direct antiviral activity	Disintegrates the spike protein structures of SARS-CoV-2 (coronavirus)

NAC = N-acetylcysteine; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2.

following long-term environmental exposure to cigarette smoke, biomass fuels, and industrial pollution. OS drives COPD through various mechanisms. It activates pro-inflammatory pathways, such as nuclear factor-Kappa B (NF-κB) and p38 mitogen-activated protein kinase (MAPK). Additionally, it leads to the generation of autoantibodies targeting carbonylated proteins, reduces the expression of sirtuin-1, induces DNA damage, decreases histone deacetylase (HDAC)-2 expression, impairs antiprotease activity, and enhances the release of transforming growth factor-beta (TGF-β). These interconnected processes contribute to inflammation, tissue damage, and structural changes in the airways, further highlighting the central role of OS in COPD pathogenesis[35].

The inherent antioxidant defenses in the lung work in tandem to neutralize ROS production. However, these defenses may be impaired and/or overwhelmed by the presence of ROS[35]. A study suggested that decreased levels of antioxidants may deteriorate the pulmonary function in COPD and dietary antioxidant intake may be associated with reduced carbonyl stress[36].

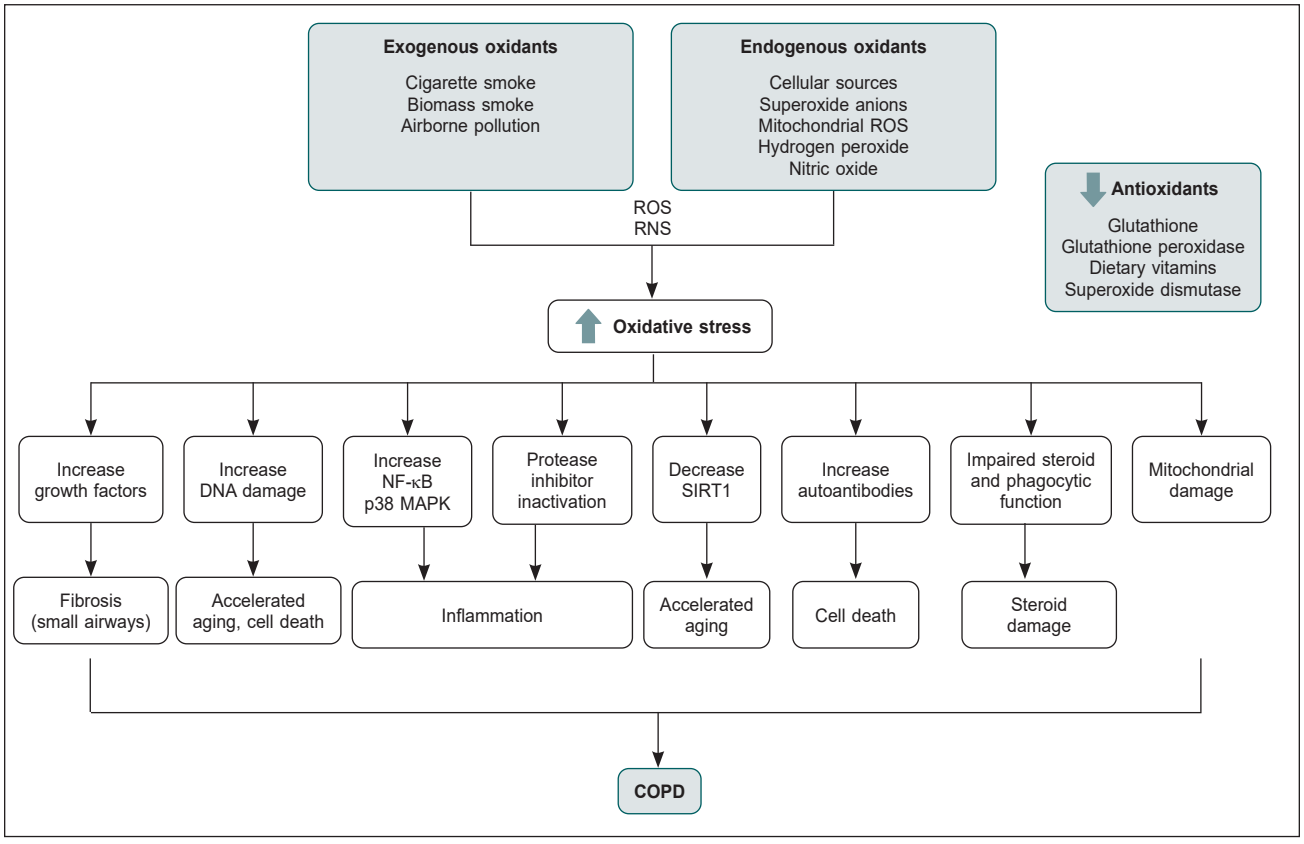


Figure 4. Mechanism for the development of COPD driven by OS[35].

COPD = Chronic obstructive pulmonary disease; DNA = Deoxyribonucleic acid; NF-κB = Nuclear factor-Kappa B; p38 MAPK = p38 mitogen-activated protein kinase; RNS = Reactive nitrogen species; ROS = Reactive oxygen species; SIRT1 = Sirtuin 1.

Furthermore, a 10-year follow-up study showed that antioxidant supplementation may bring about a 10% reduction in the risk of chronic lung disease[37]. Another study demonstrated that a 2-month oral NAC treatment significantly decreases hydrogen peroxide levels in exhaled air condensate of clinically stable patients with COPD, highlighting its potential as an effective intervention to alleviate OS in the airways[38]. Singh et al[39] demonstrated in their study that in COPD, OS intensifies with disease severity, as evidenced by significantly lower antioxidant enzyme activities (superoxide dismutase, catalase, GSH peroxidase, and GSH reductase) and elevated lipid peroxidation (malondialdehyde [MDA] levels). These findings underscore the critical role of oxidant–antioxidant imbalance in COPD progression, suggesting that interventions aimed at reducing OS through antioxidants or enhancing endogenous antioxidants may prove beneficial in treating COPD[40].

Of all environmental factors, cigarette smoke is considered the major contributor to OS as it promotes a huge influx of neutrophils and is associated with an increased release of oxidants, such as superoxide, in smokers as compared to nonsmokers[41]. A study showed that GSH concentrations in bronchoalveolar lavage (BAL) fluid decrease as inflammatory activity increases in smokers. Montuschi et al[42] assessed OS in the lungs of patients with COPD and healthy smokers using 8-isoprostane concentrations in breath condensate. Results revealed a 1.8-fold increase in 8-isoprostane in COPD ex-smokers and current smokers compared to healthy smokers, with an acute 50% rise observed after smoking. These findings highlight elevated free radical production in COPD and underscore the immediate impact of smoking on OS[42]. Increasing the circulating levels of GSH can be of therapeutic benefit in smokers[43]. NAC displays significant improvement in the phagocytic activity of alveolar macrophages and a reduction in ROS production[44,45]. Inflammatory markers, such as lactoferrin and antichymotrypsin, in BAL fluid and concentrations of myeloperoxidase (MPO) and elastase in serum/plasma have also been found to decrease in response to NAC administration[46]. A study by Lu et al[47] demonstrated that NAC exerts a positive effect on the microcirculatory flow during smoking. NAC treatment of 200 mg thrice a day for 2 weeks resulted in a significant reduction in the relative smoking-induced decrease in capillary flow velocity in healthy male and female volunteers with varied smoking habits ($p = 0.0016$)[45,47]. Oral treatment with NAC in smokers affects the content and composition of cells in BAL fluid. In a study, healthy smokers with a mean cigarette consumption of 14.5 ± 2.8 pack-years treated with NAC displayed an increased proportion of lymphocytes in the BAL fluid ($p < 0.05$). Therefore, it can be concluded that smoking leads to reduced phagocytic capacity, and treatment with oral NAC leads to the reduction of superoxide radicals[45].

NAC is useful in reducing the risk of exacerbations in patients with COPD and this has been investigated in several trials, such as the Bronchitis Randomized on NAC Cost-Utility Study (BRONCUS), the Effect of High Dose NAC on Air Trapping and Airway Resistance of Chronic Obstructive Pulmonary Disease (HIACE), and the Placebo-controlled study on efficAcy and safety of N-acetylcysTeine High dose in Exacerbations of chronic Obstructive pulmoNary disease (PANTHEON), which used NAC at different doses in several target populations, justifying its utility in a variety of clinical settings[48-50]. The details of the trials have been summarized in Table 3[38,48-55].

Post-hoc analysis of the PANTHEON study evaluated that NAC reduces the rate of COPD exacerbations mainly in patients with a smoking history ($p < 0.0001$)[56]. The prevention of exacerbations started at 6 months and increased thereafter, suggesting NAC maintenance therapy should be provided regularly and for a long time.

The effect of NAC on exacerbations has also been evaluated in several other studies. In a study by Pela et al[57], patients with COPD were randomly assigned to standard therapy plus NAC (600 mg/day orally) or standard therapy alone for 6 months. The results indicated that the group of patients receiving NAC plus standard therapy experienced a 41% reduction in the number of exacerbations in comparison to standard therapy alone. In addition, the number of patients with two or more exacerbations was lower in the NAC and standard therapy group (26%) than in the standard therapy group alone (49%). The adverse events reported were comparable to those of the placebo group[57].

A systematic review of 11 relevant and valid trials (2,011 patients, published 1976-1994) demonstrated that with treatment periods of 12 to 24 weeks, oral NAC significantly reduces the risk of exacerbations (relative benefit 1.56) and improves symptoms (relative benefit 1.78) in chronic bronchitis patients compared to placebo[58]. A meta-analysis of double-blind, placebo-controlled trials on the use of oral, long-term NAC in chronic bronchopulmonary (CB) disease showed a statistically significant effect size of −1.37 (95% CI, −1.5 to −1.25) for NAC compared with placebo. These findings

Table 3. Summary of Randomized Controlled Trials on the Usage of Oral NAC in COPD[38,48-55]

Study and year	Study type	Study duration	Trial design	Study outcomes
Zuin et al, 2005[51]	Randomized controlled trial	10 days	123 patients with a history of COPD with at least two exacerbations in the previous 2 years. No. of patients: Patients were randomly assigned, using a randomization list for 6-patient blocks, to one of three treatment groups: NAC 1,200 mg/day (n = 41), 600 mg/day (n = 39), or placebo (n = 42) administered once daily for 10 days.	Both NAC 600 mg/day and 1,200 mg/day were associated with a significantly higher proportion of patients achieving normalized CRP levels compared with placebo (52% and 90% vs. 19% of patients; $p \leq 0.01$). Treatment with NAC 1,200 mg/day was more efficacious than NAC 600 mg/day in reducing IL-8 levels and difficulty of expectoration.
De Backer et al, 2013[52]	Randomized crossover trial	3 months	Eligible patients were to have documented COPD and meet the following inclusion criteria: a smoking history of at least 10 pack-years; compatible symptoms, including dyspnea, cough, and sputum production; a decreased Tiffeneau index (FEV_1/FVC) <0.7; age ≥40 years; cessation of smoking for at least 1 month; moderate to severe COPD with an FEV_1 of 30%-80% of predicted (GOLD stages II and III). No. of patients: 12 patients with GOLD stage II COPD were randomized to receive NAC 1,800 mg or placebo daily for 3 months and were then crossed over to the alternative treatment for a further 3 months.	Significant correlations were found between image-based resistance values and GSH levels after treatment with NAC ($p = 0.011$) and GSH peroxidase at baseline ($p = 0.036$). Decreased hyperinflation was observed in NAC responders.
De Benedetto et al, 2005[38]	Clinical trial	2 months	55 patients (48 males and 7 females), mean age 65.93 ± 9.3 years (range: 41-75 years), nonsmokers or ex-smokers for at least 5 years, affected by moderate COPD (FEV_1 ≥50 <70% of predicted) were recruited. No. of patients: 55 patients were randomly allocated to group A (usual therapy plus oral NAC 600 mg BID for 2 months, n = 32) or group B (usual therapy plus placebo BID for 2 months, n = 23).	Reduced H_2O_2 in exhaled air condensate was observed at 15 days, 30 days, and 60 days compared to baseline (no change in the placebo group).
Sinojia et al, 2014[53]	Randomized, double-blind, parallel-group study	15 days	Moderate to severe stable COPD subjects, on stable doses of both inhaled beta-2 agonist and antimuscarinic agents with or without inhaled steroids for at least the last 3 months, visiting an outpatient clinic were enrolled in the study. No. of patients: 15 patients with COPD received NAC treatment, while 9 patients with COPD received placebo treatment for 15 days.	15 days of treatment with 1,200 mg/day NAC significantly enhanced the potential of ipratropium bromide to reduce functional residual capacity by nearly three fold.
Decramer et al, 2005 (BRONCUS study)[48]	Double-blind, randomized, placebo-controlled, parallel	3 years	Eligible patients aged 40-75 years with smoking-related COPD; post-bronchodilator FEV_1 of 40%-70% of predicted were included in the study from 50 centers across 10 European countries.	There was no difference in the yearly rate of decline in FEV_1 (54 mL vs. 47 mL; 95% CI −25-10) and the number of exacerbations per year between the two groups (1.25 [SD 1.35] vs. 1.29 [SD 1.46]; HR 0.99 [95% CI 0.89-1.10, $p = 0.85$]).

Table 3. Summary of Randomized Controlled Trials on the Usage of Oral NAC in COPD[38,48-55]

Study and year	Study type	Study duration	Trial design	Study outcomes
			No. of patients: 523 patients were allocated to receive either NAC (256 patients; 600 mg daily) or placebo (267 patients; 600 mg daily).	The risk of exacerbation was lower in patients on NAC (especially in those who were not taking any inhaled steroids) compared to those on placebo (0.96 [SD 1.36] vs.1.29 [1.46]; HR 0.79 [95% CI 0.631-0.989], p = 0.040).
Tse et al, 2013 (HIACE study)[49]	Double-blind, randomized, placebo-controlled	12 months	Patients aged 50-80 years, with stable COPD and post-bronchodilator spirometry FEV_1/FVC ratio <0.7 were included in the study (Hong Kong). No. of patients: 133 patients* were allocated to receive either NAC (58 patients; one 600-mg tablet BID) plus standard therapy or placebo (62 patients; 1 tablet BID). *13 patients excluded	1-year treatment with high-dose NAC (600 mg BID) resulted in significantly improved small airway function in patients with stable COPD. Significant improvement in forced expiratory flow 25%-75% (p = 0.037), a significant reduction in COPD exacerbation frequency (0.96 vs. 1.71 times/y, p = 0.019), and a reduction in admission rates (0.5 times/y vs. 0.8 times/y, p = 5.196).
Zheng et al, 2014 (PANTHEON study)[50]	Prospective, randomized, double-blind, placebo-controlled, parallel	12 months	Patients aged 40-80 years with moderate to severe COPD at 34 hospitals in China were enrolled. No. of patients: Eligible patients (1,006) were allocated in a 1:1 ratio to receive either NAC (504 patients; one 600-mg tablet BID) or placebo (502 patients; 1 tablet BID) in addition to existing individual therapy according to GOLD guidelines.	NAC treatment was more effective in patients with GOLD II (moderate) disease than in those with GOLD III (severe) disease (p = 0.0077) suggesting early intervention is beneficial. The exacerbation frequency reduced in 1.16 vs. 1.49 per patient-year, (p = 0.0011; RR 0.78, 95% CI 0.67-0.90; p = 0.0011). Long-term use of NAC 600 mg BID in patients with moderate to severe COPD prevents exacerbations and hospital readmissions.
Stav et al, 2009[54]	Randomized, double-blind, crossover study	14 weeks	24 eligible patients >40 years of age with a diagnosis of COPD were included in the study. No of patients: 24 patients were allocated in a 1:1 ratio to receive either NAC (1,200 mg) or placebo orally.	Treatment with NAC 1,200 mg/day for 6 weeks in patients with stable, moderate to severe COPD has a beneficial effect on physical performance, probably due to a reduction in air trapping.
Salve et al, 2016[55]	Randomized, parallel-group, open-labeled, placebo-controlled trial	10 weeks	Patients diagnosed as stable COPD on basis of FEV_1 according to (GOLD guidelines 2010) of age 40 years to 70 years were enrolled in the study. No. of patients: 50 patients were enrolled in a study group and control group each. The study group was treated with NAC 600 mg OD combined with daily physical activity in addition to standard treatment. The control group patients were treated with a placebo and standard treatment.	Significant improvement in quality of life in patients treated with NAC (p < 0.05).

BID = Bis in die (twice a day); BRONCUS = Bronchitis Randomized on NAC Cost-Utility Study; CI = Confidence interval; COPD = Chronic obstructive pulmonary disease; CRP = C-reactive protein; FEV_1 = Forced expiratory volume in 1 second; FVC = Forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HIACE = The Effect of High Dose NAC on Air Trapping and Airway Resistance of Chronic Obstructive Pulmonary Disease; GSH = Glutathione; H_2O_2 = Hydrogen peroxide; HR = Hazard ratio; IL-8 = Interleukin-8; NAC = N-acetylcysteine; PANTHEON = The Placebo-controlled study on efficAcy and safety of N-acetylcysTeine High dose in Exacerbations of chronic Obstructive pulmoNary disease; OD = Once a day; SD = Standard deviation.

suggested that prolonged administration of oral NAC prevents acute exacerbations of CB and contributes to decreased morbidity and health care costs[59]. In another observational study, the decline in forced expiratory volume in 1 second (FEV_1) in patients with COPD was lesser in the NAC group compared to the reference group, and the effects were particularly apparent in patients over 50 years of age[60]. A systematic review encompassing 20 randomized controlled trials and 4,044 patients investigated the impact of oral NAC treatment at doses ranging from 400 mg to 3,600 mg daily for a duration of at least 2 months up to 3 years. The analyses distinguished between patients with chronic bronchitis with no reported spirometric abnormalities (CB/pre-COPD group) and those with COPD and/or CB with clear evidence of airflow obstruction (COPD group). The findings indicate that NAC is more likely to improve symptoms and quality of life in the CB/pre-COPD group, demonstrating an odds ratio of 3.47 (95% CI 1.92-6.26), and to reduce the total number of exacerbations with an incidence rate ratio of 0.81 (95% CI 0.69-0.95). For the COPD group, NAC showed a significant effect in reducing the incidence of exacerbations with an incidence rate ratio of 0.76 (95% CI 0.59-0.99). Overall, this meta-analysis suggests that oral NAC treatment holds promise in improving respiratory symptoms and reducing exacerbations, particularly in CB/pre-COPD patients[56].

Based on the available evidence, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend that mucolytics, such as NAC, may reduce exacerbations and modestly improve health status in patients with COPD not receiving inhaled corticosteroids[34]. The joint American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines recommend the use of an oral mucolytic agent for patients with COPD who have moderate or severe airflow obstruction and experience exacerbations despite optimal inhaled therapy, aiming to prevent future exacerbations[61]. In a meta-analysis conducted by Cazzola et al[62] in 2015, it was concluded that NAC should be administered at a dose of ≥1,200 mg/day to prevent exacerbations in patients with an objective confirmation of airway obstruction. However, for patients with chronic bronchitis without airway obstruction, a regular treatment of 600 mg/day seems to be sufficient.

Bronchiectasis

Bronchiectasis is a chronic lung disease associated with a permanent alteration of the bronchi and bronchioles. It is characterized by chronic and indolent or progressive remodeling of bronchi from ongoing inflammation leading to destruction and distortion. As a result, a patient may have hypersecretion, recurrent mucopurulent infection, and destruction of the lungs[63]. The patients may present with cough, hemoptysis, shortness of breath, wheezing, chest pain, and occasionally systemic symptoms[64,65]. Recurrent infection is often a challenging problem in patients with bronchiectasis. Bronchiectasis involves a harmful cycle where bacterial colonization of damaged airways leads to chronic inflammation, causing further tissue damage and providing a favorable environment for bacterial growth. This cycle is accompanied by OS, where oxidative damage triggers airway inflammation through factors like NF-κB and activator protein-1. This inflammation, in turn, exacerbates OS. Bacterial infection is also followed by an uncontrolled and exaggerated neutrophil response and results in the production of ROS (superoxide and hydrogen peroxide) and RNS, which collectively play a crucial role in the development of OS[66]. Evidence suggests that bronchiectasis patients exhibit increased ROS levels in their plasma[67]. Olveira et al[68] also found that the total antioxidant capacity and the activity of superoxide dismutase were decreased and the OS biomarkers (superoxide anion and hydrogen peroxide) of bronchiectasis patients were significantly elevated in both cellular and plasma extracts (total leukocytes, lymphocytes, monocytes, and neutrophils) suggesting that OS plays an important role in the pathophysiological changes of bronchiectasis. NAC as a classic mucolytic agent with antioxidant and anti-inflammatory properties can be effective in the treatment of bronchiectasis (Table 4)[64,69].

Based on the evidence generated from trials, the Spanish guidelines published by the Spanish Society of Pulmonology (SEPAR), British Thoracic Society (BTS) guidelines, and the ERS guidelines recommend the use of mucoactive agents (such as NAC) for the treatment of bronchiectasis[70-72].

The SEPAR guidelines state that patients with COPD presenting with bronchiectasis can be treated with mucolytics, such as acetylcysteine (400-1,800 mg/day), as these can reduce exacerbations[70]. The BTS guidelines recommend that oral mucolytics can improve sputum expectoration and recommend treatment with mucoactive agents for bronchiectasis patients who have difficulty in sputum expectoration[71]. The ERS guidelines state that mucolytics alter mucus viscosity and/or enhance mucociliary clearance. The ERS guidelines recommend long-term treatment with mucoactive agents (≥3 months) in adult patients with bronchiectasis who have difficulty in expectorating sputum and a

Table 4. Summary of Oral NAC in the Treatment of Bronchiectasis[64,69]

Study and year	Study type	Study duration	Trial design	Study outcomes
Qi et al, 2019 (BENE study)[64]	Prospective, randomized, controlled trial	12 months	Patients aged between 18 and 80 years having at least two exacerbations were selected from general hospitals in China. No. of patients: 161 patients were eligible. 81 patients were allocated to receive NAC (600 mg BID) and 80 patients received placebo (600 mg BID).	• Administration of oral NAC 600 mg twice daily was associated with significantly lower exacerbations compared to the control group (1.31 vs. 1.98 exacerbations per patient-year; risk ratio, 0.41; 95% CI, 0.17-0.66; p = 0.0011). • The sputum volume was significantly reduced in the NAC group (t = −3.091, p = 0.002). • The quality of life substantially improved in the NAC-treated group (t = −2.57, p = 0.011). • NAC helped in reducing the elasticity and viscosity of sputum and displayed excellent antioxidant and anti-inflammatory properties, which helped in alleviating the symptoms.
Chowdhury et al, 2018[69]	Randomized, prospective, single-blind study	12 months	A total number of 70 patients above 18 years were selected. No. of patients: 28 patients were allocated to receive NAC (600 mg BID) and 30 patients received a placebo (600 mg BID).	• The mean FEV_1 increased from 0.925 L to 1.103 L after 3 months (p < 0.001) in the NAC-treated group. • The mean CAT scores decreased significantly more in the NAC group than in the placebo group. • At the end of the third month, the mean exacerbations were reduced to 0 and 1.03 in the NAC and placebo groups, respectively (p < 0.001).

BID = Bis in die (twice a day); CAT = COPD assessment test; COPD = Chronic obstructive pulmonary disease; CI = Confidence interval; FEV_1: Forced expiratory volume in 1 second; NAC = N-acetylcysteine.

poor quality of life, and in cases where standard airway clearance techniques have failed to control symptoms[72].

Cystic Fibrosis

Cystic fibrosis is a multisystem disorder caused by pathogenic mutations of the CFTR gene (CF transmembrane conductance regulator) particularly affecting the respiratory and intestinal systems. Lung manifestations of CF include chronic bronchitis, abnormal pulmonary function tests, bronchiectasis, atypical asthma, allergic bronchopulmonary aspergillosis, and colonization with *P. aeruginosa*[73]. It is characterized by polymorphonuclear inflammation (PMN), which plays a crucial role in the airway destruction observed in CF. The number of PMNs in the CF airway fluid is 1,000 times more than that in normal airways and is responsible for the increased production of ROS and proteases. The presence of ROS affects the antioxidant balance and interferes with the efflux of GSH into the extracellular lung tissues leading to OS. Being a Cys prodrug, NAC helps restore the cellular levels of GSH, increasing the antioxidant capacity of plasma and reducing the levels of OS markers in CF[74].

Oral treatment with NAC (1,200 mg twice daily) for 4 weeks (short-term) in 21 CF patients significantly increased the level of ascorbic acid (p = 0.037) and decreased the level of dehydroascorbate (p = 0.004) compared to baseline suggesting the antioxidant properties of high-dose NAC. There was an improvement in lung function from baseline in the NAC group vs. control group (FEV_1 [% predicted] mean [95% CI] +2.11 [−1.44; 5.66] vs. −1.4 [−4.7; 1.9]). At high doses, NAC was safe with no significant adverse events. The study underlines the role of GSH and NAC in ascorbate homeostasis. In another study conducted in CF patients (n = 16), high doses of NAC (600-1,000 mg, 3 times a day for 4 weeks) resulted in significantly increased GSH levels in CF blood neutrophils (p = 0.025) and whole blood (0.031). Furthermore, there was a decrease in sputum elastase activity (p = 0.006), which is one of the important predictors of airway dysfunction. The results added to the existing evidence that high-dose oral NAC is an important adjunct to counter redox and inflammatory imbalances in CF patients[75].

The long-term effects of high-dose NAC were evaluated in a randomized, placebo-controlled trial in which 70 patients with CF received either NAC (900 mg 3 times a day for 24 weeks) or placebo. The lung function remained stable (FEV_1 and $FEF_{25\%-75\%}$) or slightly improved in the NAC group compared to

baseline (p = 0.02), whereas a 4% to 6% decrease in the lung function measures was observed in the placebo group (p = 0.02). The study demonstrated a clinically meaningful benefit as it stabilized, if not improved, lung function, which may have a long-term impact on the life expectancy of patients with CF[76].

Fibrotic Interstitial Lung Disease

Due to its antioxidant effects, NAC can be used in the treatment of patients with fibrotic-interstitial lung disease (f-ILD). Studies have suggested that NAC helps in slowing the deterioration of lung function, particularly forced vital capacity (FVC). NAC therapy further aids in improving the 6-min walking distance test and decreases the percentage of predicted vital capacity (VC)[77,78].

NAC IN RESPIRATORY INFECTIONS

Tuberculosis

Pulmonary TB is an air-borne, chronic infection caused by *Mycobacterium tuberculosis* (MTB) and is a significant public health problem[79]. Patients with active TB disease experience fever, fatigue, and weight loss, and those with pulmonary disease can have persistent cough and hemoptysis in advanced stages[80]. Infection with MTB triggers the production of ROS and RNS from phagocytic cells during inflammatory responses. Patients with TB have low GSH levels, indicating reduced antioxidant capacity[81]. A study suggested significantly lower concentrations of the antioxidant vitamins C, E, and A in TB patients. Furthermore, TB patients with higher OS levels are likely to have a severe form of the disease[82].

NAC demonstrates potent antimycobacterial effects, potentially restraining MTB infection and disease. This action may be attributed to its ability to suppress the host's oxidative response and exert direct antimicrobial activity[83]. The potential use of NAC as an adjunct therapy has been evaluated in 39 patients with human immunodeficiency virus (HIV)-associated TB through a phase II randomized clinical trial (RIPENACTB). The study groups (RIPE and RIPENAC) received anti-TB treatment with RIPE (rifamycin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg, and ethambutol 275 mg) for 8 weeks and the RIPENAC group received NAC (600 mg twice a day) for 8 weeks, additionally. Treatment with NAC was associated with a greater increase in the total antioxidant status (p = 0.04) compared to standard anti-TB treatment alone. GSH levels were improved only in the NAC group compared to baseline (p = 0.03) and were higher in the NAC group compared to anti-TB treatment at 60 days (p = 0.03). Treatment with NAC was more efficient in increasing the GSH levels (two fold increase vs. anti-TB treatment alone) and the total antioxidant status (1.5-fold increase vs. anti-TB treatment alone). Furthermore, TB patients receiving NAC exhibited a significant reduction in lipid peroxidation (p < 0.001) and DNA oxidation levels (p = 0.048)[84]. Another randomized, double-blind study from India evaluated the efficacy of NAC as an add-on treatment to the Directly Observed Therapy Short-I (DOTS-I) regimen. Forty-eight newly diagnosed, sputum-positive TB patients taking a standard anti-TB regimen were randomized to receive either 600 mg NAC daily (n = 24) or placebo (n = 24) for 2 months. Approximately 95.83% (n = 23) of patients in the NAC-treated group achieved sputum negativity in 3 weeks, whereas this was achieved in 14 patients in the placebo group. A significant clearing of infiltration and reduction in cavity size was observed at 6 months in the NAC group compared to baseline (p < 0.01). Patients treated with NAC displayed improvement in weight, GSH peroxidase levels, and other associated symptoms, such as appetite loss, fever, and fatigue. This can be correlated with a reduction in the level of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) by NAC[85]. The evidence further confirms the utility of NAC as an add-on regimen in patients with TB.

Apart from an elevation of GSH, NAC also exhibits direct antimycobacterial effects and acts via immunomodulation[82]. OS in TB mediates the occurrence of adverse effects due to anti-TB drugs, such as hearing loss. NAC has been shown to reduce drug-associated hearing loss by scavenging free radicals and inhibiting downstream apoptotic pathways induced by OS.

Severe Acute Respiratory Syndrome Coronavirus/ Coronavirus Disease 2019

Coronavirus disease 2019 (COVID-19), the highly contagious infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has a clinical spectrum that can vary from asymptomatic to common symptoms such as fever, cough, and shortness of breath to clinical illness characterized by acute respiratory failure requiring mechanical ventilation, septic shock, and multiple organ failure[86].

OS is thought to be related to the pathogenesis, progressivity, and clinical severity of SARS-CoV-2 infection. SARS-CoV-2 stimulates the exaggerated release of proinflammatory cytokines/chemokines (IL-8, CXCL10, CCL5, and IL-6), collectively known as a cytokine storm.

This results in the oxidation of proteins and lipids and ultimately leads to cell death. It not only affects the respiratory tract but can also infect other organs, such as the heart, liver, and kidneys. Decreased GSH levels and increased ROS production are the most ideal conditions for the SARS-CoV-2 virus to replicate.

Several mechanisms have been implicated in the role of NAC against SARS-CoV-2. Based on the evidence presented, NAC has shown promising potential in the early stages of COVID-19 for prevention and treatment. Debnath et al[33] have demonstrated conformational perturbation in the spike protein of SARS-CoV-2, which may play a role in the process of prevention and containment of COVID-19 infection[33,87]. NAC, due to its excellent properties, may be helpful in the treatment and prevention of SARS-CoV-2 by decreasing the cytokine storm[88]. To further explore the ability of NAC to combat cytokine storm, a cross-sectional study was performed in Kolkata, India, involving 164 patients hospitalized due to COVID-19. Patients with mild COVID-19 received oral NAC 600 mg once daily and moderate to severe patients received intravenous NAC (1 g) thrice daily along with standard therapy. The average length of stay was reduced from 16 days to 12 ± 1.5 days in patients with moderate to severe COVID-19 treated with NAC therapy. Dependency on oxygen therapy was reduced (12 days to 8 days) and increased discharge rate and reduced transfer to critical care facilities were observed in patients treated with NAC therapy. This may be linked to the direct and indirect antioxidant properties of NAC[89]. Several studies suggest that the antioxidant, anti-inflammatory, antiviral, and immune-modulating properties of NAC could be contributing to the mitigation of the disease severity[88-91]. Furthermore, NAC can also help in blocking excessive production of angiotensin II and reducing pulmonary disease severity[92].

Jorge-Aarón et al[93] proposed NAC as a potential therapeutic or adjuvant against SARS-CoV-2 as it may cleave the disulfide bonds in the E protein of the virus, thus reducing its infectivity. NAC can also elevate the number of CD4+ T cells and, at a high-dose, increase GSH levels, thereby improving adaptive immunity[94]. Various strategies have been employed by researchers to reduce the mortality associated with COVID-19. A retrospective cohort study by Izquierdo et al[95] in hospitalized patients with COVID-19 receiving oral NAC at high doses (600 mg every 8 hours) had significantly lower mortality compared to the placebo group (OR: 0.56; 95% CI: 0.47-0.67). Interestingly, most patients treated with NAC were older with multiple comorbidities, such as hypertension, dyslipidemia, diabetes, and COPD compared to those not on NAC. This suggests that NAC was beneficial in patients with COVID-19 despite a high baseline risk[95].

It is well known that smoking exacerbates the symptoms of COVID-19. Aldehydes present in cigarette smoke deplete total GSH levels, which, in turn, can worsen inflammation and airspace enlargement. Due to its ability to enhance GSH levels, NAC may have the ability to alter several smoking-related endpoints[96].

Cytokine storm also induces sudden mucus hypersecretion in COVID-19. Excessive inflammation in patients with COVID-19 can result in the overproduction of mucus, which obstructs the airway. NAC has served as a mucolytic agent, contributing to the breakdown of mucus in the respiratory tract and keeping the tract moist to decrease irritation[97]. Owing to its multiple benefits, NAC can be an effective adjunct in the treatment of COVID-19. A brief overview of NAC as a therapeutic strategy to combat COVID-19 is displayed in Fig. 5[98].

Pneumonia

Pneumonia is an inflammation of the parenchyma of one or both lungs with varying symptoms, such as productive cough, dyspnea, pleuritic pain, abnormal vital signs, and abnormal lung examination findings[99]. Both community-acquired pneumonia (CAP) and VAP

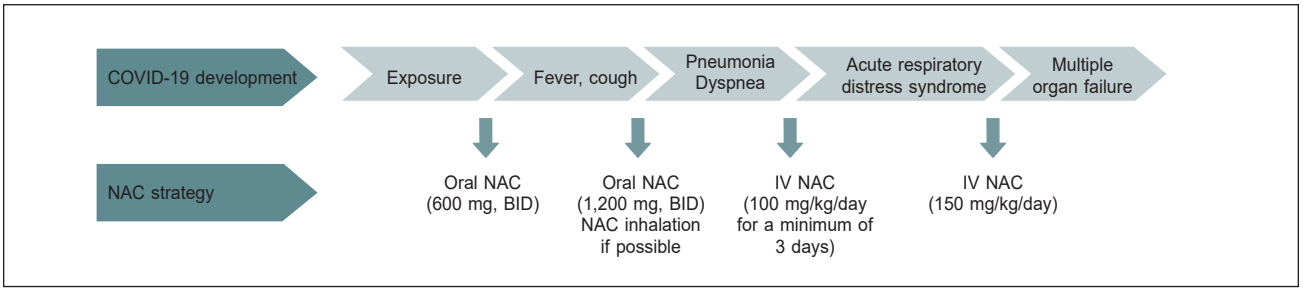


Figure 5. A brief overview of NAC as a therapeutic strategy to combat COVID-19[98].

BID = Bis in die (twice a day); COVID-19 = Coronavirus disease 2019; IV = Intravenous; NAC = N-acetylcysteine.

are associated with downregulation of the antioxidant system, leading to an increase in OS[100,101]. Zhang et al[100] analyzed the effect of NAC (1,200 mg/day) in addition to conventional therapy in CAP patients. The plasma levels of MDA and TNF-α significantly decreased in the NAC group compared to the placebo group ($p < 0.05$; MDA: $p = 0.004$; TNF-α: $p < 0.001$). There was a significant increase in the total antioxidant capacity in the NAC-treated group ($p = 0.005$). Hence, an adjuvant therapy involving NAC is highly beneficial in reducing oxidative and inflammatory damage in CAP patients[100].

In a randomized, double-blind study, Sharafkhah et al[102] compared the effect of NAC (600 mg/twice daily) in preventing VAP in hospitalized patients with a placebo in addition to routine care. Patients on NAC had less chance of developing clinically confirmed VAP than those in the placebo group (26.6% vs. 46.6%; $p = 0.032$). Moreover, patients in the NAC group were associated with fewer intensive care unit (ICU) and hospital stays. Similarly, complete recovery was significantly higher in patients in the NAC group than in the placebo group (56.6% vs. 30%; $p = 0.006$)[102].

The effectiveness of NAC was also observed in patients with moderate COVID-associated pneumonia. The addition of NAC (1,200-1,500 mg NAC/day intravenously) to standard care led to a significant increase in blood oxygen saturation and a rapid reduction in the volume of lung damage. Furthermore, the group receiving NAC showed a significant decrease in the rate of reduction of C-reactive protein (CRP) and the length of hospital stay ($p < 0.001$)[103].

Common Cold and Influenza

Common cold and influenza (flu) are both contagious respiratory illnesses caused by different viruses but present with similar clinical features (runny nose, sneezing, and sore throat). Reduced GSH concentrations suppress the activation of NF-κB, which is an inflammatory mediator of rhinoviral infection. NAC exhibits its anti-inflammatory properties via GSH and is generally used to alleviate symptoms of cold, such as coughing and wheezing. A clinical trial was conducted to evaluate the efficacy of NAC (800 mg 3 times daily) in the treatment of common cold and cough in 70 individuals. The log-transformed total cough count was 6.92 (0.95) and 6.51 (0.83) in the NAC and placebo groups, respectively[104].

The highly pathogenic H5N1 influenza virus is inhibited by NAC, which can be linked to its anti-NF-κB properties along with the inhibition of the MAPK p38 pathway. Depending on the strain pathogenicity, NAC may have a variable effect on viral growth[105,106]. In a double-blind, randomized, placebo-controlled study, patients treated with NAC (600 mg twice daily) for 6 months were less likely to exhibit clinical influenza symptoms ($p = 0.0006$). NAC treatment was well-tolerated and resulted in a significant decrease in the severity of the disease and length of hospital stay. Another study reported that even though NAC did not prevent A/H1N1 virus influenza infection, it significantly reduced the incidence of clinically apparent disease and attenuation of influenza and influenza-like episodes[107].

NAC ADMINISTRATION, DOSAGE, AND SAFETY

NAC can be administered through several routes, such as oral, intravenous, inhaled, and transdermal. Different studies suggest that of all the routes, oral and intravenous administration of NAC is associated with minimum side effects and no serious adverse events. Intravenous and inhaled administration of NAC is generally employed in liver detoxification treatment and forits mucolytic activity in severe respiratory diseases, respectively. The transdermal delivery of NAC is rarely employed and very few studies on it have been reported[17].

The dosage of NAC is directly related to the desired therapeutic effect. The effects of NAC at different doses, such as 600 mg/day, 1,200 mg/day, and >1,200 mg/day, have been studied in various respiratory diseases. Multiple studies have proved the efficacy and tolerability of oral NAC at both high and low doses. The commonly reported serious adverse events reported are upper and lower respiratory tract infections, gastrointestinal pain, epigastric discomfort, pruritus, dizziness, and diarrhea[48,50]. Calverley et al[108] reviewed 41 articles that explicitly reported on the safety of NAC when used at 600 mg and above, up to 3,000 mg/day; the adverse effects profile of NAC at higher than the standard dose in chronic respiratory diseases to establish a risk-benefit ratio in increasing the daily dose were evaluated. Most studies were conducted in patients with COPD, idiopathic pulmonary fibrosis, bronchiectasis, chronic bronchitis, and CF using oral NAC. In general, the safety profile was similar at both the high and standard doses with the oral formulation; gastrointestinal symptoms were reported but they were no more common than in the control group[62,108].

However, researchers believe that NAC may be more effective in reducing fatigue and preventing COPD exacerbations at higher doses[31]. The benefits of NAC at higher doses are linked to its indirect antioxidant and anti-inflammatory mechanisms of action.

CONCLUSION

NAC, a precursor to intracellular Cys, exhibits a potent protective effect against OS under different conditions. Despite being introduced as a mucolytic agent, the antioxidant properties of NAC have been utilized in wide clinical settings. Furthermore, NAC is well-tolerated, has a defined mechanism of action, is inexpensive, and displays no serious adverse events when used as a treatment or as an adjunct to conventional therapy. The most likely benefits of NAC include replenishing endogenous GSH levels, scavenging ROS radicals, and cytokine storm suppression, thereby mitigating inflammation and tissue injury. These manifold properties of NAC have urged researchers to explore its applicability in treating diseases associated with OS and impaired glutamate homeostasis.

This review focuses on the therapeutic effects of NAC in chronic respiratory diseases, such as COPD, bronchiectasis, CF, and acute respiratory infections, such as TB, pneumonia, common cold, and influenza. Its most recent adjunct role in the management of COVID-19 has also been explored. It is undeniable that NAC plays an important role in protecting the lungs against toxic ROS by increasing pulmonary defense mechanisms in respiratory conditions. Researchers can further explore the use of NAC by performing studies to analyze its impact on human health and determine adequate dosage and treatment protocols for different respiratory diseases.

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Informed Consent and Human Research: Not applicable.

Data Availability: The datasets used and/or analyzed in this review article are available from the corresponding author on reasonable request.

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