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Review Article

N-Acetylcysteine in Lung and Liver Health: A Comprehensive Review

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Abstract

N-Acetylcysteine (NAC) is a synthetic derivative of the sulfur-containing amino acid L-cysteine that has been widely used as a mucolytic agent and as the standard antidote for acetaminophen-induced hepatotoxicity. In recent years, its therapeutic potential has expanded considerably because of its antioxidant, anti-inflammatory, and cytoprotective properties. The primary mechanism of NAC involves replenishing intracellular glutathione (GSH), the body's major endogenous antioxidant, thereby restoring cellular redox balance and protecting tissues against oxidative stress. In addition to enhancing GSH synthesis, NAC directly scavenges selected reactive oxygen and nitrogen species, reduces disulfide bonds within mucin glycoproteins to improve mucus clearance, preserves mitochondrial function, and modulates redox-sensitive signaling pathways involved in inflammation. This review provides a comprehensive overview of the chemistry, physicochemical properties, pharmacokinetics, pharmacodynamics, and molecular mechanisms of NAC, with particular emphasis on its role in maintaining lung and liver health. The review also discusses the relationship between oxidative stress and the pathogenesis of respiratory and hepatic diseases, highlighting how NAC prevent oxidative damage through multiple complementary mechanisms. Current evidence supporting the therapeutic use of NAC in chronic respiratory diseases, including chronic obstructive pulmonary disease, chronic bronchitis, and cystic fibrosis, as well as in liver disorders such as acetaminophen-induced hepatotoxicity, non-alcoholic fatty liver disease, alcoholic liver disease, and drug-induced liver injury, is summarized. Furthermore, the safety profile, clinical limitations, and future therapeutic prospects of NAC are discussed.

Keywords: N-Acetylcysteine; Glutathione; Oxidative Stress; Antioxidant; Lung Disease; Liver Disease; Mucolytic Agent; Reactive Oxygen Species

Abbreviations

NAC: N-Acetylcysteine; GSH: Glutathione; GSSG: Oxidized Glutathione; ROS: Reactive Oxygen Species; RNS: Reactive Nitrogen Species; NAPQI: N-Acetyl-p-benzoquinone Imine; COPD: Chronic Obstructive Pulmonary Disease; CF: Cystic Fibrosis; ARDS: Acute Respiratory Distress Syndrome; NAFLD: Non-Alcoholic Fatty Liver Disease; ALD: Alcoholic Liver Disease; SOD: Superoxide Dismutase; GR: Glutathione Reductase; NF-κB: Nuclear Factor-kappa B; MAPK: Mitogen-Activated Protein Kinase; TNF-α: Tumor Necrosis Factor-alpha; NADPH: Nicotinamide Adenine Dinucleotide Phosphate (Reduced Form); IL: Interleukin; ATP: Adenosine Triphosphate.

Introduction

N-Acetyl-L-cysteine (NAC) is a synthetic N-acetyl derivative of the naturally occurring sulfur-containing amino acid L-cysteine and has been extensively investigated for its diverse pharmacological properties [3,5,8]. Initially it is known for its mucolytic activity, because it breaks disulfide bonds within mucin glycoproteins [9,21], it is also known as antidote for acetaminophen induced hepatotoxicity, because it restores intracellular glutathione (GSH) levels [2,5,14]. That GSH helps to neutralize the toxin metabolite N-acetyl-p-benzoquinone imine (NAPQI), which is metabolically changed form of paracetamol [2,14]. Over the past several decades, accumulating experimental and clinical evidence has demonstrated that the therapeutic potential of NAC extends far beyond these conventional indications [2,3].

Rather than functioning solely as a precursor of glutathione, NAC is now recognized as a multifunctional pharmacological agent capable of modulating oxidative stress, inflammatory signaling, mitochondrial homeostasis, and cellular redox balance, thereby influencing the pathogenesis of a broad spectrum of acute and chronic diseases [5,17,19]. Because of these concepts NAC is used as attractive therapeutic compound in disorders where oxidative damage and inflammation is the central mechanism of tissue injury [17,21].

The expanding clinical relevance of NAC is closely linked to the understanding of oxidative stress and redox biology. The body's normal redox balance is maintained by a balance between the production of reactive oxygen species (ROS) and the endogenous antioxidant defense system, in which Glutathione (GSH) is the main non-enzymatic antioxidant inside cells that helps protect them from oxidative damage [16,17,21]. Under pathological conditions, excessive ROS production and depletion of reserves antioxidant can disrupt this equilibrium, and leading to oxidative modification of lipids, proteins, nucleic acids, and mitochondrial components, that ultimately promoting cellular dysfunction and tissue injury [16,21]. NAC restores this disturbed redox environment primarily by supplying cysteine, which is the rate-limiting substrate for glutathione biosynthesis, as a result it will enhances intracellular antioxidant capacity [3,5]. NAC is also directly interacting with selected reactive oxidants species, reduces protein disulfide bonds, preserves protein thiol homeostasis, modulates redox-sensitive transcription factors such as nuclear factor-kappa B (NF- κB), and attenuates the production of pro-inflammatory cytokines [5,17,19]. So, NAC has antioxidant and anti-inflammatory effects that collectively contribute to cellular protection under conditions of oxidative stress [5,19].

Oxidative stress is an important factor in the development and progression of many lung and liver diseases [11,16]. Body's respiratory system is continuously challenged by inhaled oxidants, airborne pollutants, cigarette smoke, infectious agents, and inflammatory mediators, all of which contribute to increasing in ROS generation and decreasing in reserves pulmonary glutathione. Similarly, the liver serves as the principal metabolic and detoxifying organ. But continuous exposure to xenobiotics, drugs, alcohol, metabolic intermediates, and inflammatory stimuli creates a highly oxidative microenvironment, which is capable of triggering hepatocellular damage [14,18].

Within this context, NAC has emerged as a particularly promising therapeutic molecule because its pharmacological properties target several interconnected mechanisms involve in hepatic and pulmonary injury [5,17]. In respiratory system, NAC has the capacity to reduce mucus viscosity by breaking disulfide bonds within mucin glycoproteins while simultaneously reducing the oxidative stress and inflammatory responses associated with chronic respiratory diseases [6,11,19]. In hepatic disorders, it has established role in treating acetaminophen-induced hepatotoxicity. Its use has also been studied in other liver conditions, like non-acetaminophen acute liver failure, non-alcoholic fatty liver disease (NAFLD), drug-induced liver injury, and other diseases caused by oxidative stress and inflammation [7,14,15].

Although N-Acetyl-L-Cysteine has been used in medicine for many years, its therapeutic potential continues to grow as researchers gain a better understanding of oxidative stress and redox biology. Many studies have examined its effects in different lung and liver diseases. However, these findings are spread across different research studies and clinical settings. Therefore, reviewing all the available evidence together is important to better understand how NAC protects the lungs and liver, where it is currently used, and where it may be useful in the future. This information can help researchers and healthcare professionals develop better ways to prevent or reduce tissue damage caused by oxidative stress.

Therefore, this review provides a comprehensive overview of the chemistry, pharmacokinetic and pharmacodynamic properties, molecular mechanisms, and current therapeutic evidence supporting the role of N-acetyl-L-cysteine in lung and liver health.

Oxidative stress in lung and liver injury

Oxidative stress is a condition in which the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) increases into the body and resulting in disruption of cellular redox homeostasis. This imbalance leads to oxidative damage of cellular macromolecules and contributes to the initiation and progression of various respiratory and hepatic diseases.

Generation of reactive oxygen species and reactive nitrogen species

Under normal physiological conditions, ROS and RNS are continuously generated as natural by-products of aerobic metabolism and play essential roles in regulating various cellular functions [21]. At controlled concentrations, these reactive molecules act as important signaling mediators involved in cell proliferation, differentiation, immune defense, apoptosis, and intracellular communication [16,17]. Therefore, ROS should not be regarded solely as harmful molecules, as they are essential for maintaining normal cellular physiology. The harmful effects of ROS arise only when their production becomes excessive or when antioxidant defense mechanisms become insufficient, resulting in disruption of the cellular redox balance [17,21].

Reactive oxygen species (ROS) like Superoxide, hydrogen peroxide, and hydroxyl radicals are the main free radicals that involved in oxidative tissue damage. And the reactive nitrogen species (RNS) like nitric oxide and peroxynitrite, are also play important roles in both normal body functions and disease. Most ROS are produced naturally during energy production in the mitochondria. They are also generated by enzymes such as NADPH oxidase, xanthine oxidase, and cytochrome P450, as well as by immune cells like neutrophils and macrophages to fight infections [16,17,21].

Environmental and lifestyle factors, including cigarette smoke, air pollution, alcohol, heavy metals, certain drugs, ultraviolet radiation, and infections, can increase the production of ROS [11,12,16]. Under normal conditions, the body's antioxidant system neutralizes these harmful molecules and maintains balance. However, when ROS production becomes excessive or antioxidant defenses become weak, oxidative stress occurs. This can damage cells and tissues and contribute to the development of diseases, especially those affecting the lungs and liver [11,16].

Cellular effects of oxidative stress

When production of reactive oxygen species increases than body's antioxidant defense, oxidative stress occurs [16,21]. These harmful molecules damage important parts of the cell, including lipids, proteins, DNA, and mitochondria. As a result, normal cell functions are disturbed, and that leads to inflammation, cell death, tissue damage, and at the end loss of organ function.

- **Lipid Peroxidation:** One of the first effects of oxidative stress is lipid peroxidation, where ROS attack the fats present in the cell membrane. This produces harmful compound such as malondialdehyde and 4-hydroxynonenal. These compound damage the cell membrane, increase its permeability, and reduce its ability to function properly [17].
- **Protein Oxidation:** ROS can also damage proteins by changing their structure. This affects the activity of enzymes, receptors, and other important proteins, that leading to poor cell function and reduced ability of cells to respond to stress [17].
- **DNA Damage**: High levels of ROS can damage both nuclear DNA and mitochondrial DNA. This may cause changes in the genetic material and interfere with normal cell growth and repair. If damage is severe, the cell may stop dividing or undergo programmed cell death (Apoptosis) [16,17].
- **Mitochondrial Dysfunction:** Mitochondria are responsible for producing energy (ATP) for the cell. Oxidative stress damages the mitochondria, reducing energy production and increase the formation of more ROS. This create a cycle of continuous oxidative damage and can eventually lead to cell death [5,6,21].
- **Inflammation and Tissue Remodeling**: Oxidative stress activates inflammatory pathways such as NF-κB and MAPK, which increase the production of inflammatory molecules like TNF-α, IL-1β, and IL-6. Long term inflammation causes excessive collagen deposition and tissue remodeling, which can lead to Fibrosis and permanent damage to organs such as the lungs and liver [7,18].

Oxidative stress in the lung

The lungs are highly exposed to the oxidative stress because they come in direct contact with oxygen and harmful substances such as cigarette smoke, air pollution, allergens, and microorganisms [11,12]. These factors increase the production of ROS in lung cells. Normally, antioxidants protect the lungs from this damage. However, when ROS levels become too high, they damage the airway lining, reduce the ability to remove mucus and harmful particles, increase mucus production, and promote inflammation. Over time, this can cause scarring and structural changes in the lungs, contributing to diseases such as chronic obstructive pulmonary disease (COPD), asthma, acute respiratory distress syndrome (ARDS), and idiopathic pulmonary fibrosis (IPF) [6,11,12].

Oxidative stress in the Liver

The liver is susceptible to oxidative stress because it is responsible for metabolism, detoxification, and the breakdown of drugs and other chemicals [14,16]. During these processes, reactive oxygen species (ROS) are naturally produced. Under normal conditions, antioxidants such as glutathione (GSH) neutralize these harmful molecules. when ROS production becomes excessive, glutathione levels decrease, mitochondria become damaged, and lipid peroxidation occurs, leading to liver cell injury [14,16,18]. At the same time, immune cells in the liver increase inflammation and collagen production, which can cause fibrosis (scarring). These changes play an important role in the development of acetaminophen-induced liver toxicity, drug-induced liver injury, non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease, and acute liver failure [7,14,15].

Antioxidant defense system

The human body have an efficient antioxidant defense system that protects cells from the harmful effects of reactive oxygen species while maintaining redox homeostasis [5,16,17]. This antioxidant defense contains enzymatic antioxidants, like Superoxide dismutase (SOD), Catalase, Glutathione peroxidase and Glutathione reductase. And also, it contains non-enzymatic antioxidants such as glutathione (GSH), Vitamin C and E, and Uric acid and other endogenous antioxidants [5,17]. These components function properly to regulate intracellular ROS levels, and preventing oxidative damage.

Among the enzymatic antioxidants, SOD acts as the primary defense against superoxide radicals by catalyzing it into hydrogen peroxide (H_2O_2) and molecular oxygen. And this H_2O_2 is rapidly detoxified by catalase into water and oxygen or by glutathione peroxidase into water using reduced glutathione as an electron donor [16,17]. During this reaction, GSH is oxidized to glutathione disulfide (GSSG). Subsequently, glutathione reductase regenerates GSH from GSSG in an NADPH-dependent reaction, thereby maintaining intracellular glutathione levels and maintain the cellular antioxidant capacity [5,16].

Among the non-enzymatic antioxidants, Glutathione (GSH) is considered the most effective intracellular antioxidant and plays a key role in maintaining cellular redox homeostasis [5,16]. It acts as a substrate for glutathione peroxidase and also, it directly scavenges reactive oxygen species and participates in the detoxification of electrophilic compounds. Then water-soluble antioxidants like Vitamin C neutralizes free radicals in the aqueous environment and regenerates oxidized Vitamin E, whereas lipid soluble Vitamin E protects biological membranes by interrupting lipid peroxidative chain reactions [16,17]. Together, these antioxidant system function synergistically to protect cells from oxidative damage. Since GSH is essential for protecting cells from oxidative damage, a decrease in GSH levels is considered an important sign of oxidative stress. Therefore, increasing GSH levels has become an important strategy to reduce oxidative damage. N-acetylcysteine (NAC) supports this process by supplying cysteine, the amino acid required for GSH synthesis [3,5,21].

The coordinated action of enzymatic and non-enzymatic antioxidants maintains cellular redox homeostasis through a series of interconnected reactions. The major antioxidant defense pathway and glutathione redox cycle are illustrated in Figure 1.

Chemistry of N-Acetylcysteine (NAC)

Chemical structure and physicochemical properties

N-Acetylcysteine (NAC) is the N-Acetyl derivative of the naturally occurring amino acid L-Cysteine [5,8,9]. The acetylation of the amino group improves the chemical stability of Cysteine while maintain its biological activity, making NAC a suitable therapeutic agent for both oral and intravenous administration [9,19,21]. Because of its unique structure, NAC has been used as a mucolytic agent, an antidote for acetaminophen poisoning, and an antioxidant precursor in various clinical conditions associated with oxidative stress [2,5,9,21].

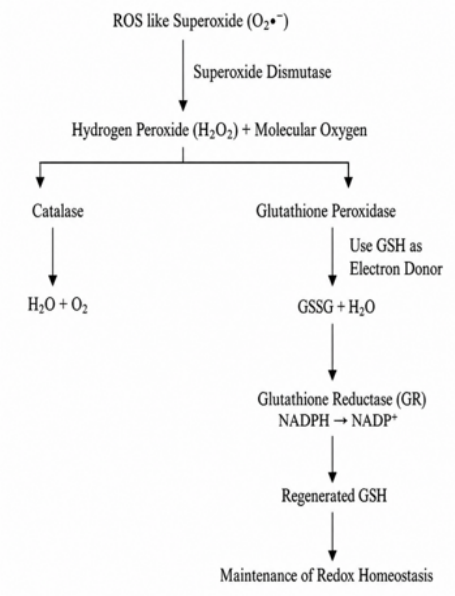

Figure 1: The major antioxidant defense pathway showing the detoxification of ROS by Superoxide dismutase, catalase and glutathione peroxidase, and the glutathione redox cycle involving glutathione peroxidase-mediated oxidation of reduced GSH and glutathione reductase-mediated regeneration of GSH using NADPH.

The chemical and Physicochemical properties of NAC are summarized in Table 1, highlighted its chemical structure, name, molecular composition, functional groups, and the characteristics that influence its antioxidant activity and therapeutic applications.

Property	Description
Chemical name	N-Acetyl-L-cysteine
Molecular formula	$C_5H_9NO_3S$
Molecular weight	163.19 g/mol
Chemical class	N-Acetyl derivative of the amino acid L-cysteine
Appearance	White to slightly off-white crystalline powder
Solubility	Soluble in water
Key functional group	Acetyl group (-$COCH_3$), Thiol (-SH), and Carboxyl (-COOH) groups
Biologically active group	Thiol (-SH) group responsible for antioxidant and mucolytic activity
Chemical stability	Susceptible to oxidation in aqueous solution, leading to disulfide formation
Major metabolic conversion	Deacetylated to L-cysteine, the precursor of glutathione synthesis

Table 1: Chemical and Physicochemical Properties of N-Acetylcysteine.

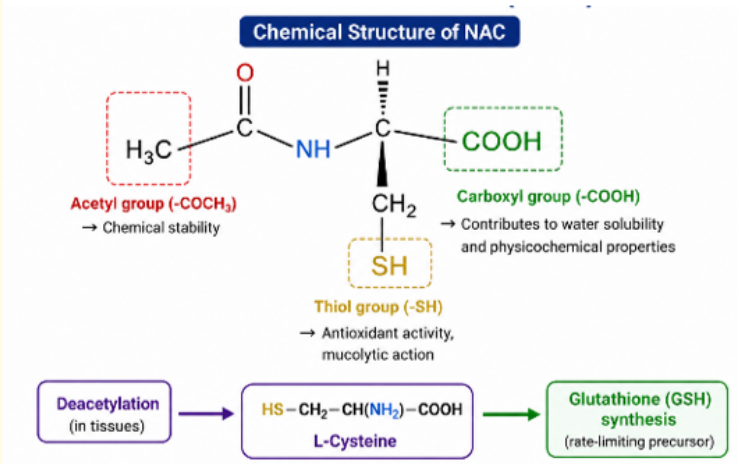

Figure 2: Chemical structure of NAC highlighting its major functional groups and their biological significance.

Among the functional groups present in NAC, the thiol (-SH) group is considered the most biologically important because it participates in redox reactions and interacts with reactive oxygen species (ROS) and electrophilic compounds [9,19]. In water-based solutions, the thiol (-SH) group of NAC can easily react with oxygen, leading to the formation of disulfide-linked dimers. Therefore, NAC should be properly formulated and stored to maintain its stability and effectiveness [21]. After administration, NAC is converted into L-cysteine, which is the main building block required for the production of glutathione (GSH) [5,8,9], one of the body's most important antioxidants. By increasing glutathione levels, NAC helps protect cells from oxidative stress and supports its therapeutic effects in various lung and liver disorders [5,17,21].

Functional groups and chemical reactivity

The biological activity of N-acetylcysteine (NAC) is mainly attributed to its three functional groups: the thiol (-SH), acetyl ($-COCH_3$), and carboxyl (-COOH) groups, as illustrated in Figure 2 [9,19]. Among these, the thiol (-SH) group is the most important, as it participates in redox reactions, scavenges reactive oxygen species (ROS), and breaks disulfide bonds in mucus, thereby reducing mucus viscosity and improving its clearance [21]. The acetyl group enhances the chemical stability of NAC and facilitates the delivery of L-cysteine for glutathione synthesis after deacetylation. The carboxyl group contributes to the molecule's water solubility and physicochemical properties. Together, these functional groups are responsible for the antioxidant, mucolytic, and cytoprotective properties of NAC [5,9].

The unique chemical characteristics of NAC influence its absorption, distribution, metabolism, and elimination, which ultimately determine its therapeutic efficacy. Therefore, understanding the pharmacokinetic and pharmacodynamic properties of NAC is essential for explaining its clinical applications.

Pharmacokinetics of N-Acetylcysteine (NAC)

NAC has pharmacokinetic properties that make it useful for treating various diseases. It can be taken orally, intravenously, or by inhalation, and each route affects how the drug is absorbed, distributed, and utilized in the body [5,8,10]. Although oral NAC has low bioavailability due to extensive first-pass metabolism, it is still effective because it is converted into L-cysteine, which is required for the glutathione synthesis, major intracellular antioxidant [3,5,10]. As a result, most of the therapeutic effects of NAC occur through increased glutathione production rather than the direct action of NAC itself. Intravenous NAC rapidly reaches therapeutic plasma concentrations and is mainly used in emergencies such as acetaminophen overdose, while inhaled NAC acts directly in the lungs to reduce mucus with minimal systemic absorption [2,5,10].

Absorption

After oral administration, NAC is rapidly absorbed from the small intestine, and peak plasma concentration are usually reached within 1-2 hours [5,8]. The peak plasma concentration means the maximum amount of drug present into the blood after administration. However, NAC has low oral bioavailability, typically less than 10% [5,9]. This is because of major first-pass metabolism of the liver. First-pass metabolism is the process in which drug is break down in the liver before it reaches the main blood circulation. During this process, NAC is converted into L-cysteine, which is then used to produce glutathione. Therefore, only a small amount of unchanged NAC enters the circulation, but regular oral administration effectively maintains intracellular glutathione levels and antioxidant protection [5,9,10].

Intravenous administration bypasses the intestine and liver, resulting in rapid and high plasma concentrations [10,18]. This route is preferred in emergency conditions, especially acetaminophen poisoning, where quick restoration of glutathione is required. Inhalational NAC is delivered directly to the lungs, where it helps break down thick mucus while producing minimal systemic effects. Because its action in the airways is relatively short, repeated doses may be needed in patients with chronic respiratory diseases [6,11].

Distribution

After absorption, NAC is distributed throughout the body's fluids, and slightly reaches to the tissue such as liver, lungs, and kidney, where it helps to protect cells from oxidative stress [5,21]. In bloodstream, NAC exists in different form, like free NAC, protein-bound NAC, and oxidized forms, which together help maintain the body's redox balance [9,10]. The volume of distribution of NAC is about 0.33 – 0.47 L/kg, that indicates that it remains preliminary restricted to the extracellular water space of the body rather penetrating deeply into intracellular tissue or fat [10,18]. Another important point is that NAC binds effectively to blood proteins, particularly Albumin. Around 66-97% of NAC is protein-bound [5]. Protein binding indicates the drug's affinity for blood

proteins. Here, bound drugs are considered inactive and free drugs considered active in the body. This binding allows NAC to stay longer in bloodstream and release slowly when needed. Although NAC is rapidly removed from the bloodstream, its beneficial effects continue because it is converted into L-cysteine, which helps produce glutathione (GSH) [5,9,10]. Its distribution to the liver supports its use in acetaminophen poisoning, while its delivery to the lungs contributes to its antioxidant and mucus-thinning effects in respiratory diseases [5,18].

Metabolism

NAC extensively metabolized after absorption [5,9]. Its main metabolic pathway is the conversion of NAC into L-cysteine, which is the key precursor required for glutathione synthesis. In the liver, NAC is first deacetylated to produce L-cysteine and with the help of enzyme Glutamate-Cysteine ligase, cysteine reacts with L-glutamate and then glycine is added with the help of enzyme glutathione synthetase, and at the end glutathione is generated [5,17,21]. The increased production of glutathione strengthens the body's antioxidant defense and protects cells from oxidative damage.

Excretion or elimination

NAC and its metabolites are mainly excreted through the kidneys in the urine [5,10]. Renal excretion occurs mainly in the form of inorganic sulfate, cysteine, cystine, and other sulfur-containing metabolites, while only a small proportion of unchanged NAC is excreted in urine. Urine excrete around 13-38%, while feces excreted very low around 3% of NAC [5]. NAC has half life around 5-6 hours, which means half of the drug (NAC) is eliminated from the body during this time [5]. That time is depending on the formulation, route of administration, and physiological condition of the individual. So, in the patients having liver or kidney disorders, the half time of NAC may increase because removal of NAC is slower [10].

Pharmacodynamics and molecular mechanism of action of NAC

Pharmacodynamics describes the biochemical and physiological effects of a drug and the molecular mechanism responsible for its therapeutic actions [9,21]. Unlike other antioxidants that primarily scavenge free radicals directly, NAC shows its effects through multiple complementary mechanisms [17,19,21]. Although only a small amount of orally administered NAC reaches the bloodstream unchanged, because of the first-pass metabolism, it is quickly converted into L-cysteine, an amino acid needed for the production of glutathione. Since glutathione is one of the body's most important antioxidants, increasing its level is considered the main mechanism by which NAC protects cells from oxidative damage [5,9,21].

Apart from increasing glutathione levels, NAC can also directly neutralize certain reactive oxygen species (ROS) because of its free sulfhydryl (-SH) group [9,19]. It helps reduce inflammation by lowering the production of inflammatory molecules and regulating redox-sensitive signaling pathways. In the lungs, NAC acts as a mucolytic agent, breaking the disulfide bonds in mucus proteins, which makes mucus thinner and easier to remove [6,9,21]. NAC also supports normal mitochondrial function, helping cells produce energy and reducing cell damage caused by oxidative stress.

Because NAC works through several different mechanisms rather than a single pathway, it is effective in many diseases associated with oxidative stress and inflammation, particularly chronic respiratory diseases and liver disorders [5,17,18].

Enhancement of Glutathione (GSH) Synthesis

The most important pharmacological action of N-acetylcysteine (NAC) is its ability to increase the synthesis of glutathione (GSH), the body's major intracellular antioxidant [3,5,21]. Under conditions of oxidative stress, inflammation, or toxin exposure, GSH levels decrease, reducing the cell's ability to neutralize reactive oxygen species (ROS). NAC acts as a precursor of L-cysteine, the rate-limiting amino acid required for GSH synthesis, thereby restoring intracellular glutathione levels [5,9,21].

After administration, NAC is rapidly converted into L-cysteine, which combines with glutamate and glycine to synthesize glutathione through the γ-glutamyl cycle, as illustrated in Figure 3. The increased GSH then detoxifies hydrogen peroxide and other reactive oxygen species with the help of glutathione peroxidase, while glutathione reductase (GR) regenerates GSH from its oxidized form (GSSG). This continuous recycling helps maintain the cellular antioxidant defense system and protects cells from oxidative injury [5,17,21].

The restored glutathione detoxifies ROS and helps maintain cellular redox balance. In the lungs, this protects airway cells from oxidative injury, while in the liver it detoxifies harmful metabolites such as NAPQI, preventing hepatocellular damage [5,14,17]. Therefore, enhancement of glutathione synthesis is considered the primary mechanism responsible for the antioxidant and cytoprotective effects of NAC [9,17,21].

Figure 3: Mechanism of NAC-Mediated Glutathione synthesis and Recycling cycle.

Direct antioxidant activity

However, the direct antioxidant effect of NAC is less important than its ability to increase glutathione (GSH) levels. Once GSH levels are restored, it works with enzymes such as glutathione peroxidase to remove reactive oxygen species (ROS) and protect cells from oxidative damage [21]. Therefore, the direct antioxidant action of NAC works together with its glutathione-mediated effect to reduce oxidative stress and protect lung and liver cells [5,21].

Mucolytic activity

N-Acetylcysteine acts as an effective mucolytic agent by breaking the disulfide (-S-S-) bonds present in mucin glycoproteins [6,9,21]. This reduces the viscosity and elasticity of mucus, making it thinner and easier to remove through the normal mucocilliary clearance mechanism [6,9]. As a result, NAC helps clear airway secretions, improves airflow, and reduces airway obstruction. These properties make NAC beneficial in respiratory diseases such as chronic bronchitis, COPD, cystic fibrosis, and bronchiectasis, where excessive mucus production contributes to disease progression [6,11,13,23].

Anti-inflammatory activity

Besides its mucolytic action, NAC also reduces inflammation by lowering oxidative stress and regulating redox-sensitive signaling pathways [5,19]. It inhibits the activation of nuclear factor-kappa B (N F-κB), a key transcription factor involved in inflammation [17,19]. This leads to reduced production of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and interleukin-1β (IL-1β) [19]. By suppressing inflammatory mediators and reducing oxidative injury, NAC help protect lung and liver tissues from chronic inflammation [5,16,17].

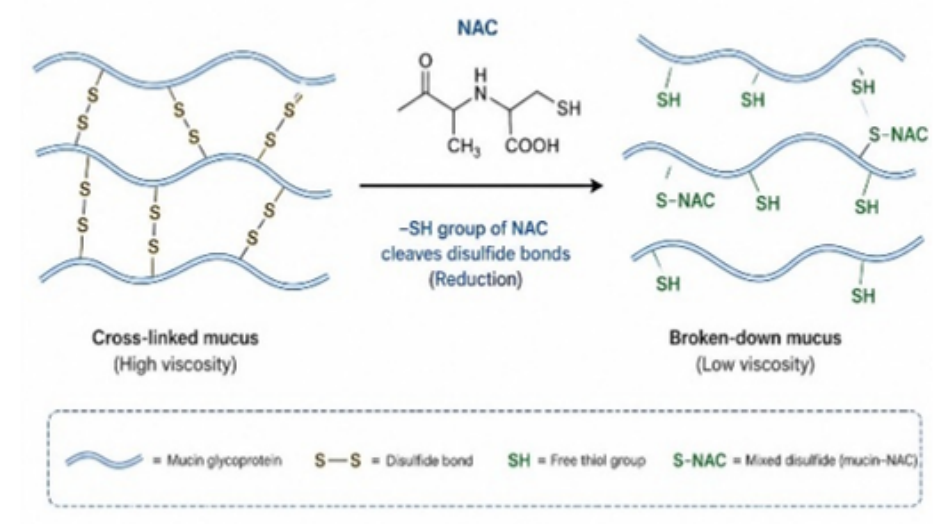

Figure 4: Mucolytic mechanism of N-Acetylcysteine through reduction of disulfide bonds in mucin glycoproteins.

Mitochondrial protection and modulation of cell signaling pathways

- **Mitochondrial protection:** NAC protects mitochondria by restoring intracellular glutathione levels and reducing the accumulation of reactive oxygen species. This helps preserve mitochondrial membrane integrity, maintain ATP production, and prevent oxidative stress-induced apoptosis. By improving mitochondrial function, NAC enhances cell survival and supports tissue repair in both lung and liver diseases [5,17,21].
- **Modulation of Cell Signaling Pathways:** NAC also regulates several redox-sensitive signaling pathways involved in oxidative stress and inflammation [17,19]. It activates the Nrf2 pathway, which increases the expression of antioxidant enzymes, while suppressing the NF-κB and MAPK pathways, leading to reduced inflammation and oxidative damage. Through these mechanisms, NAC maintains cellular redox balance and promotes protection against tissue injury [5,17,21].

Therapeutic potential of N-Acetylcysteine in lung and liver diseases

NAC has been extensively used for the management of various lung and liver disorders due to its antioxidant, mucolytic, anti-inflammatory, and cytoprotective properties [5,6,18]. By restoring intracellular glutathione levels, reducing oxidative stress, and modulating inflammatory responses, NAC helps to protect tissues from oxidative injury and supports normal cellular function. These pharmacological properties have expanded its therapeutic use beyond its established role in acetaminophen poisoning to several chronic respiratory and liver diseases [2,5,14].

Therapeutic potential in lung disease

N-acetylcysteine (NAC) has shown therapeutic potential in several chronic respiratory diseases, including chronic obstructive pulmonary disease (COPD), chronic bronchitis, and cystic fibrosis [6,11,13,23]. These conditions are characterized by oxidative stress, chronic inflammation, and excessive mucus production, which contribute to airway obstruction and progressive lung damage [6,11,13]. Due to its antioxidant, mucolytic, and anti-inflammatory properties, NAC helps restore glutathione levels, reduce mucus viscosity by breaking disulfide bonds in mucin glycoproteins, and improve mucociliary clearance [6,11]. Clinical studies have reported that long-term NAC therapy may reduce the frequency of disease, improve sputum clearance, and reduce respiratory symptoms. Although NAC is mainly used as an adjunct therapy and does not replace standard treatment, its ability to reduce oxidative stress and improve airway function makes it a valuable supportive agent in the management of chronic respiratory diseases [1,11.13].

Therapeutic potential in liver disease

The liver is highly susceptible to oxidative damage because of its central role in drug metabolism and detoxification [14,16]. NAC has demonstrated significant therapeutic potential in liver diseases by restoring intracellular glutathione, reducing oxidative stress, and protecting hepatocytes from cellular injury. It is the standard treatment for acetaminophen (paracetamol) overdose, where it replenishes glutathione stores and detoxifies the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI) [2,14,18]. In addition, NAC has shown beneficial effects in non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), and drug-induced liver injury (DILI) by reducing oxidative stress, improving liver function, and limiting inflammation [7,14,15]. Although further large-scale clinical studies are needed, current evidence supports the potential of NAC as an effective adjunctive therapy for several acute and chronic liver disorders [7,14,16].

Safety profile and limitations

N-acetylcysteine (NAC) is generally considered a safe and well-tolerated therapeutic agent with a favorable safety profile [1,2,20]. It has been used for several decades in both acute and chronic conditions, particularly as a mucolytic agent and as the standard antidote for acetaminophen overdose [2,5]. At recommended therapeutic doses, oral NAC is associated with minimal adverse effects, the most common being nausea, vomiting, diarrhea, abdominal discomfort, and its characteristic sulfur-like odor [1,5,20]. Intravenous administration may occasionally cause hypersensitivity or anaphylactoid reactions, which are usually mild and can be managed by slowing or temporarily stopping the infusion [1,14].

Despite its broad pharmacological benefits, NAC has certain limitations. Oral administration is associated with relatively low bioavailability due to extensive first-pass metabolism, which may reduce systemic drug concentrations [5,10,18]. Furthermore, the therapeutic response to NAC can vary depending on the disease, dosage, duration of treatment, and individual patient characteristics. Although numerous experimental and clinical studies have demonstrated its antioxidant and cytoprotective properties, evidence supporting its long-term effectiveness in some chronic lung and liver disorders remains inconsistent [6,7,13]. Therefore, further research is needed to optimize dosing strategies, improve drug delivery systems, and better define its role in the management of chronic diseases [5,17,18].

Conclusion

N-acetylcysteine (NAC) is a multifunctional molecule with well-established antioxidant, mucolytic, and cytoprotective properties that contribute significantly to lung and liver health. By replenishing intracellular glutathione, scavenging reactive oxygen species, reducing mucus viscosity, and modulating inflammatory pathways, NAC helps protect tissues against oxidative damage and supports normal cellular function. Its established use in acetaminophen toxicity, along with its potential benefits in chronic respiratory and liver disorders, highlights its broad therapeutic relevance. Although certain limitations, including low oral bioavailability and variable clinical outcomes, remain to be addressed, NAC continues to be a promising pharmacological agent. Future research focusing on optimized formulations and a better understanding of its molecular actions may further expand its applications in the prevention and management of oxidative stress-related diseases.

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