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REVIEW

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Antioxidants as adjuvant therapy in the treatment of community-acquired pneumonia

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Abstract

Background Community-acquired pneumonia remains a major health concern, characterized by significant morbidity and mortality. The underlying pathophysiology of community-acquired pneumonia involves substantial oxidative stress and inflammation, which contribute to lung tissue damage and impaired immune function.

Main body Variations in oxidative metabolism contribute to the inflammatory cascade which triggers pneumonia to commence and evolve, whereas oxidative stress as well as inflammatory processes is strongly related. Understanding the underlying immunological dysregulation and unbalanced redox that heighten vulnerability to a variety of illnesses has improved over the past several decades attributable to research. One of the key strategies for addressing oxidative stress is to lower the reactive oxygen species creation in the mitochondrion which is one of the main sites of their generation by using antioxidants, where they prevent oxidants from transferring electrons to other molecules. Consequently, antioxidants either directly or indirectly reduce the risk of damage and preserve the redox equilibrium. Therefore, antioxidants, due to their ability to neutralize reactive oxygen species and modulate inflammatory processes, have been explored as potential adjuvant therapies to enhance the treatment outcomes of community-acquired pneumonia. Where recent research has explored the potential of antioxidants as adjuvant therapy in the treatment of community-acquired pneumonia, aiming to mitigate these detrimental effects. Antioxidants such as N-acetylcystein, vitamin C, vitamin E, astaxanthin, and zinc have shown promising results in both preclinical and clinical studies.

Conclusion Outcomes of several in vitro as well as in vivo antioxidant studies have demonstrated the antioxidants' promising potential as an adjunct pneumonia therapy. For an assessment of its effectiveness in this therapeutic context, more research involving humans will be required.

Background

Pneumonia is a major public health concern globally due to its high morbidity and death rates. It is caused by a number of pathogens, including bacteria, viruses, and fungi [1]. Despite advances in medical care, pneumonia remains a primary cause of hospitalization and mortality, especially among vulnerable groups such as the very young, the elderly, and those with preexisting health issues [2]. The worldwide burden of pneumonia is high, with millions of cases recorded each year and significant healthcare expenses associated with treatment and management. Furthermore, pneumonia causes long-term morbidity, frequently leading in chronic respiratory diseases, and a worse quality of life [3]. Pneumonia is categorized into different types based on the context and conditions in which it is acquired, with the two most common being community-acquired pneumonia (CAP)

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and hospital-acquired pneumonia (HAP) [4]. Another prominent category is ventilator-associated pneumonia (VAP), a subgroup of HAP that develops in individuals who have been on mechanical breathing for at least 48 h. In addition, healthcare-associated pneumonia (HCAP) refers to infections in individuals who have had considerable healthcare contact, such as those in nursing homes, getting home wound care, or undergoing dialysis [5].

Community-acquired pneumonia

CAP affects those who have not recently been hospitalized or had considerable healthcare interaction. It is usually caused by infections such as Streptococcus pneumoniae, Haemophilus influenzae, and respiratory viruses [6]. CAP is a primary cause of morbidity and death globally, particularly among vulnerable groups such as the elderly, babies, and those suffering from concomitant illnesses such as chronic obstructive pulmonary disease (COPD), diabetes, and cardiovascular disease. The economic burden of CAP is significant, covering both direct medical expenditures, such as hospital admissions and treatments, and indirect costs associated with lost productivity and long-term health implications [7].

Incidence and mortality of CAP

The overall incidence of CAP varies greatly between people and locations, depending on factors such as age, socioeconomic position, concomitant conditions, and environmental exposures. The yearly incidence of CAP varies from 5 to 11 cases per 1000 people, with greater rates found in the elderly, where it can surpass 30 cases per 1000 individuals aged 65 years and more [8]. CAP that necessitates intensive care unit (ICU) care accounts for 10% to 30% of all CAP hospitalizations. Patients with severe CAP have a high risk of complications, hospitalization, and death [9].

The mortality rate for CAP is high, especially among hospitalized patients and those with severe diseases. Overall death rates among hospitalized patients range between 5 and 15%, with greater rates seen in ICUs. Mortality rates for older people and those with substantial comorbidities can surpass 20% [10].

In Egypt, CAP is a major public health concern, with a high prevalence and large healthcare costs. The prevalence of CAP in Egypt follows worldwide trends but is impacted by regional factors such as socioeconomic position, environmental conditions, and access to healthcare [11].

Where CAP is frequently exacerbated by high smoking rates and exposure to air pollution, both of which aggravate respiratory problems and increase susceptibility to infections. Furthermore, the high incidence of antibiotic resistance in Egypt poses a substantial barrier to the treatment and management of CAP [12].

Pathophysiology of CAP

CAP is characterized by acute inflammation of the lung parenchyma caused by pathogens such as bacteria, viruses, and fungi. CAP pathogenesis occurs when bacteria surpass the host's first defensive systems, such as mucociliary clearance of the respiratory tract and alveolar macrophages. Once these bacteria enter the lower respiratory system, they cling to and penetrate epithelial cells, causing an inflammatory reaction [13]. CAP frequently elicits a robust immunological response marked by a cytokine storm and oxidative stress, both of which significantly contribute to disease severity and patient prognosis [14].

Oxidative stress and cytokine storm in CAP

Oxidative stress contributes significantly to the pathogenesis of CAP. In CAP, oxidative stress is caused by an imbalance in the generation of reactive oxygen species (ROS) and the body's ability to detoxify or repair the associated damage [15]. Several mechanisms are involved in the oxidative stress process; the pathogen-induced ROS production includes direct production by pathogens where many pathogens, such as bacteria and viruses, may generate ROS directly during their metabolic activities, consequently this causes activation of the host's immunological response, specifically neutrophils, and macrophages. ROS (such as superoxide anion, hydrogen peroxide, and hydroxyl radicals) are produced by activated immune cells as part of the respiratory burst that kills pathogens [16].

The oxidative damage affects cell membranes, including those found in the respiratory epithelium and endothelial cells. Additionally, oxidative changes can deactivate enzymes and structural proteins, limiting cell activity. Furthermore, ROS may induce oxidative damage to DNA, resulting in strand breakage, nucleotide changes, mutations and, if the DNA damage is severe enough, it can cause cell death [17].

Moreover, the infection causes an inflammatory response, including the production of cytokines and the inflammation promotes the recruitment and activation of extra immune cells to the infection site, hence boosting ROS generation which is known as the cytokine storm [18].

The cytokine storm is a serious and sometimes lethal consequence of CAP, caused by an overactive and dysregulated immune system. CAP infection causes the secretion of pro-inflammatory cytokines, including interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α). These cytokines are required for a successful immune response, but excessive production can cause a cytokine storm, leading to widespread of inflammation and tissue damage [19].

Throughout a cytokine storm, elevated amounts of cytokines attract extra immune cells to the site of infection, exacerbating the inflammatory response. This hyper inflammatory condition can harm lung tissues, causing increased vascular permeability, edema, and poor gas exchange. The ensuing acute respiratory distress syndrome (ARDS) is a common and severe symptom of this process, sometimes needing urgent medical intervention. The cytokine storm in CAP is not restricted to the lungs; it can have systemic consequences, causing numerous organ failures. Elevated cytokine levels in the circulation can cause systemic inflammatory response syndrome (SIRS), which can result in septic shock and organ failure [20].

Treatment of CAP

The treatment of CAP is comprehensive, encompassing antibiotic medication, supportive care, and preventative measures including vaccination and smoking cessation. The infections to be treated, the patient's clinical condition, and local antimicrobial resistance trends all influence antibiotic selection. Empirical therapy for mild CAP often comprises a macrolide, in locations with high rates of macrolide resistance, particularly in patients with comorbidities, a respiratory fluoroquinolone or a combination of a beta-lactam and a macrolide is suggested [21].

Antibiotics

Antibiotics, the main course of treatment for pneumonia, should be administered as soon as CAP is diagnosed where managing a cytokine storm entail attacking the underlying infection with antibiotics. Despite breakthroughs in antibiotic medicines and supportive care, CAP remains a primary cause of mortality, especially among vulnerable groups. Antibiotic resistance, rising comorbidity rates, and an aging population all contribute to the worldwide burden of CAP [22].

Adjuvant therapy for CAP

Adjuvant therapies for CAP are continuously being developed. Several adjuvant treatments for pneumonia are now being proposed where they help in modifying the immune response. Corticosteroids, statins, macrolides, and toll-like receptor antagonists are all promising therapy possibilities [23].

Antioxidants

Another important adjuvant therapy that is recently a point of concern and research in CAP are antioxidants as they can play an important role in boosting the effectiveness of conventional therapy for CAP by reducing oxidative damage and modifying immunological responses, thereby resulting in improved patient outcomes and lower healthcare expenses [23].

The role of antioxidants in CAP

During CAP, the requirement for antioxidants rises to counterbalance the increased ROS levels. Chronic infection and inflammation can deplete endogenous antioxidants such as glutathione, catalase, and vitamins C and E, resulting in amplification for the oxidative stress and cellular damage, and this may have negative effect by causing damage to the alveolar-capillary membrane which causes increased permeability, pulmonary edema, decreased gas exchange, and prolonged oxidative stress causing inflammation, fibrosis, and long-term lung damage. Impaired antioxidant defenses compound the damage, causing tissue injury and malfunction therefore, antioxidants are essential for neutralizing ROS and promoting tissue repair [24].

The mechanism of action of antioxidants in CAP

Antioxidants are important adjuvant therapies in the treatment of CAP because of their potential to reduce oxidative stress and improve immunological function. In CAP patients, the inflammatory response causes the generation of ROS and pro-inflammatory cytokines. Such substances can harm lung tissues and weaken the immune system. Antioxidants prevent this by scavenging ROS and thereby protecting cellular components from oxidative stress and reducing the cytokine storm associated with severe pneumonia [25].

Additionally, antioxidants might impact immunological function. They improve macrophage phagocytic activity and neutrophil bactericidal activity, resulting in better pathogen clearance from the lung. Therefore, antioxidants reduce oxidative stress, which helps preserve the integrity of the epithelial barrier in the lungs, avoiding subsequent infections and facilitating speedier recovery [26].

Recent research has also demonstrated the importance of antioxidants in modulating metabolic pathways during infection. Severe CAP is characterized by dysregulated metabolism and increased inflammation. Antioxidants can assist restore metabolic equilibrium, promoting cellular energy generation and minimizing the negative effects of metabolic perturbations on lung function [10].

In summary, antioxidants provide a multimodal approach to management of CAP by lowering oxidative stress, regulating the immunological response, and correcting metabolic imbalances, which collectively enhance clinical outcomes in afflicted people [26].

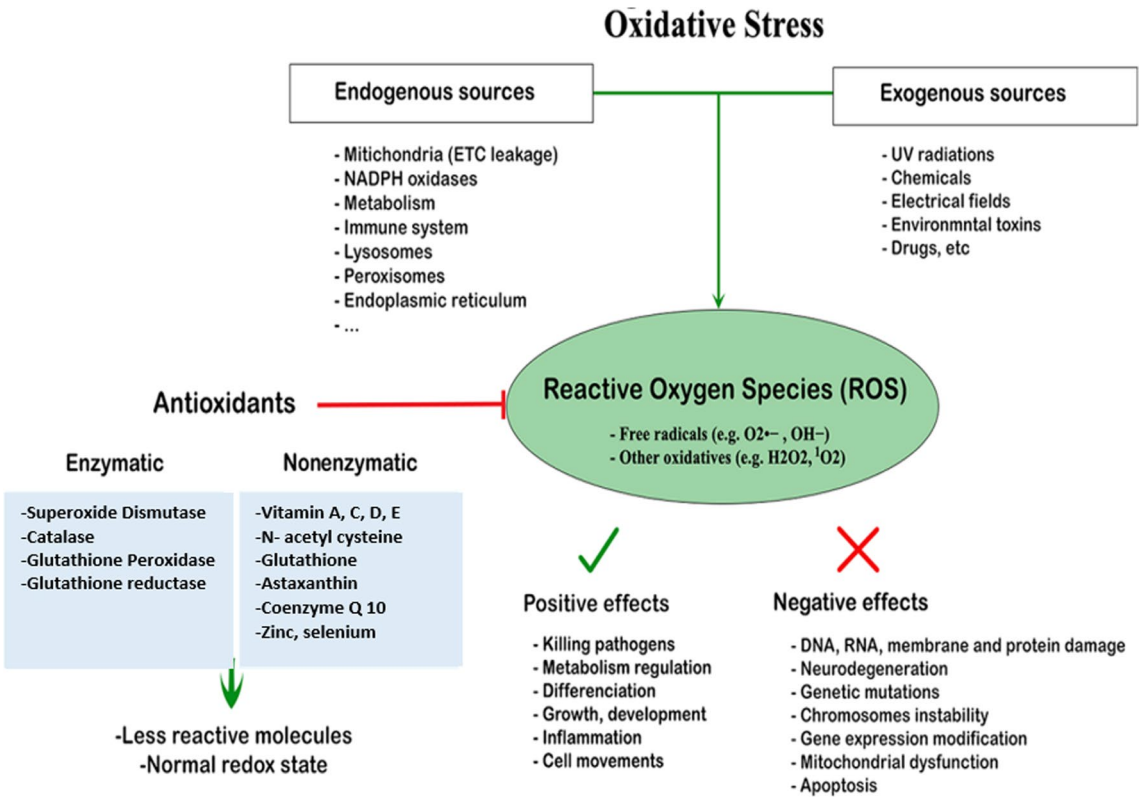

Fig. 1 Schematic presentation of the action of the antioxidant defense mechanism and the classification of antioxidants [31]

Classification of antioxidants used in CAP

Antioxidants used as adjuvant therapy in the treatment of CAP and which serve an important function in reducing the detrimental effects of ROS of both endogenous and exogenous sources as shown in Fig. 1, fall into two groups based on their type and method of action: enzymatic antioxidants and nonenzymatic antioxidants. Each kind is essential for reducing oxidative stress and strengthening the body's defensive mechanisms against oxidative damage caused by CAP [27].

Enzymatic antioxidants

Enzymatic antioxidants are proteins or enzymes that help remove ROS via biochemical processes. They are crucial for maintaining cellular redox equilibrium and protecting tissues from oxidative damage. Examples of the enzymatic antioxidants include: superoxide dismutase, catalase, and glutathione peroxidase [28].

Nonenzymatic antioxidants

Nonenzymatic antioxidants are very small substances that either directly scavenge ROS or indirectly regulate oxidative stress via other mechanisms. They supplement the function of enzymatic antioxidants by offering further protection against oxidative damage. Examples include: vitamin C, vitamin E, carotenoids, flavonoids, coenzyme Q10, and polyphenols [29].

In conclusion, enzymatic antioxidants typically serve as components of complicated enzymatic systems that detoxify ROS and regenerate other antioxidants, whereas nonenzymatic antioxidants are smaller molecules capable of directly neutralizing free radicals. Both kinds are necessary for protecting the body from oxidative damage and promoting general health [30].

The current review aims to critically evaluate the efficacy of antioxidants as adjuvant therapy in the management of CAP. It focuses on their impact on oxidative stress markers, inflammatory responses, and clinical outcomes by reviewing findings from both clinical and preclinical studies.

Materials and methods

A comprehensive review of preclinical and clinical studies was conducted, assessing various antioxidants, including N-acetylcysteine (NAC), vitamin C, vitamin E, zinc, and other antioxidants used in combination with standard antibiotic therapy for CAP. The primary endpoints analyzed were reductions in oxidative stress parameters, inflammatory markers, and clinical symptoms, as well as improvements in lung function and overall recovery.

The current review was conducted following a search of the literature on antioxidants and their effect on pneumonia. The search, carried out in the PubMed database, featured publications published from 2000 to March 2024 and included the following keywords: pneumonia, community-acquired pneumonia, antioxidants, adjuvant, ROS, oxidative stress, cytokine storm, enzymatic antioxidants, nonenzymatic antioxidants. The scientific articles were selected from research published in English.

Main text

Antioxidants' overview

While this manuscript focuses on the effect of antioxidants as adjuvant therapy in patients with CAP, it is important to note that the available studies specifically addressing CAP are limited. Consequently, some of the included studies were conducted on other types of pneumonia to provide a comprehensive evaluation of the potential benefits of antioxidant therapy, and the following are some of the antioxidants reported in the literature to have positive effect on pneumonia and other respiratory diseases.

Nonenzymatic antioxidants

Coenzyme Q10

Coenzyme Q10 (CoQ10) also known as ubiquinone, is a fat-soluble, vitamin-like molecule present in most eukaryotic cells, particularly in the mitochondria. It is essential for the synthesis of energy (ATP) through the electron transport chain during cellular respiration, and also it is a key component of electron transport in mitochondria that possesses antioxidant characteristics [32]. Its deficits interfere with mitochondrial activity, which leads to amplification of oxidative stress and cellular damage. By switching between its three redox states—completely oxidized ubiquinone, semiquinone, and fully reduced ubiquinol—CoQ10 can function as a transporter of one or two electrons. It was reported before that reducing the expression of nuclear factor Kappa B (NF-κB), TNF-α, and IL-6 by CoQ10 is caused due to its anti-inflammatory effects [33].

As a nonenzymatic antioxidant, CoQ10 directly scavenges free radicals, which reduces oxidative stress in cells, it also aids in the regeneration of other antioxidants such as Vitamin E, ensuring that the body's total antioxidant network remains intact, and it contributes to the integrity and fluidity of cell membranes, which can be impaired by oxidative stress [34].

There are limited studies on the use of CoQ10 for CAP patients, although it appears promising where it acts as an antioxidant, which may help lower oxidative stress in the lungs, which is increased during pneumonia. Furthermore, it may help reduce inflammation associated with CAP which may lead to improved clinical outcomes and also CoQ10 has been linked to improved immunological function, which may help the body fight infections more efficiently [35].

Overall, it can aid in the cellular function and recovery all of which are important in controlling and recovering from pneumonia, and following are some of the studies of CoQ10:

CoQ10 supplementation has been proven to enhance outcomes in older individuals with CAP, where a randomized controlled trial studying the effect of CoQ10 supplementation on 150 elderly patients diagnosed with CAP reported positive clinical outcomes including quicker defervescence and shorter stays in the hospital in the CoQ10 supplemented group compared to placebo [36].

Another study finding suggests that the redox state of CoQ10 can accurately predict the oxidative stress load in CAP patients [37].

Moreover, CoQ10 had been reported to have positive impact on other chronic respiratory diseases, where in a randomized study, DeBenedetto et al. [38] found that 2 months of supplementation with QTer® (a formulation for CoQ10) and creatine significantly improved exercise capacity, body composition, dyspnea, and daily activities, as well as positive changes in the plasma metabolic profile in COPD patients on long-term oxygen therapy.

Overall, while CoQ10's antioxidant and anti-inflammatory qualities are promising, and its particular function and effectiveness in treating CAP require more clinical studies to be carried out.

Vitamin E

Vitamin E, a powerful antioxidant, has recently received attention for its possible involvement in the treatment and prevention of CAP. This fat-soluble vitamin is well-known for its capacity to neutralize free radicals and minimize oxidative stress, which can boost the immune system and regulate inflammatory processes. According to research, appropriate vitamin E levels might strengthen the body's defense systems, potentially reducing the occurrence and severity of respiratory infections like CAP. In the setting of CAP, vitamin E's anti-inflammatory characteristics may aid in reducing lung inflammation and thereby improve patient outcomes. Furthermore, its immunomodulatory properties may lead to a stronger and more effective immune response, allowing for faster recovery [39].

A research was done to determine the effectiveness of vitamin E supplementation in lowering the prevalence of CAP among older male smokers. The trial population consisted of male smokers aged 50 to 69 years who were given an intervention of 50 mg/day of vitamin E

for 5–8 years. The primary outcome was the incidence of hospital-treated CAP. The results showed a considerable reduction in the incidence of pneumonia, with the vitamin E group having a 72% lower incidence than the control group. These findings indicate that vitamin E administration may provide significant advantages in lowering the incidence of CAP among high-risk elderly male smokers [39].

A study which was carried out to ascertain the impact of vitamin E and other antioxidant supplementation on resistance to influenza infection, as well as the role of cytokines in vitamin E-induced increase in resistance to influenza infection reported that vitamin E reduced the oxidative stress and improved the immune response [40].

The effects of vitamin E on human lung epithelial cells' reactivity to the pro-inflammatory signal TNF-α were investigated in an in vitro investigation. It has been shown that exogenously administered vitamin E downregulates the expression of cell adhesion molecules in both untransformed primary cells and the A549 and BEAS-2B cell lines and suppresses the synthesis of the neutrophil chemoattractant IL-8 [41].

While more thorough clinical studies are needed to develop definite guidelines, growing data suggests that vitamin E supplementation might be effective as a supplemental therapy in the prevention and treatment of CAP.

Vitamin C

Vitamin C, a powerful antioxidant, is important in the treatment and prevention of CAP. This water-soluble vitamin is crucial for immune system health and response to infections. Vitamin C helps preserve lung tissue by scavenging free radicals, lowering oxidative stress, and moderating the inflammatory response. Studies have shown that high vitamin C levels can improve respiratory infection outcomes by reducing the severity and length of symptoms. Moreover, numerous studies found that individuals with severe illnesses, such as sepsis, had decreased plasma vitamin C concentrations, they also revealed a connection between this decline and the beginning of multiple organ failure [42–45].

Vitamin C has been proven in the setting of CAP to boost the activity of numerous immune cells, including neutrophils, lymphocytes, and phagocytes, which are critical in the fight against bacterial and viral infections. Vitamin C supplementation may thereby lower the occurrence and course of pneumonia, especially in people with weakened immune systems or high oxidative stress levels [45]. Vitamin C is mostly present in the epithelial lining of the respiratory tract, where it functions as an immune-stimulating agent, helping ameliorate symptoms of upper respiratory tract infections [46]. Viral and bacterial infections can potentially decrease vitamin C levels because they generate reactive oxygen and nitrogen species through leukocyte activation that lead to oxidation of extracellular vitamin C [47]. Also, changes in vitamin C metabolism due to respiratory infections suggest that vitamin C may have a beneficial effect for people with pneumonia [48].

Results from a randomized, double-blind clinical trial involving eighty critically ill patients with severe pneumonia showed that giving them an intravenous dose of vitamin C is safe and can lower inflammation, lengthen the time they need for mechanical ventilation, and decrease their use of vasopressors without having a significant impact on death [49].

In another research, intravenous vitamin C or placebo were administered to patients with moderate and severe CAP who were receiving antibiotic therapy, and the findings of this research revealed that the concentration of C-reactive protein and vitamin C had an inverse relationship [50].

Furthermore, another study showed that giving vitamin C in addition to antibiotics considerably shortened the average hospital stay for children with pneumonia who were between the ages of two months and five years, when compared to placebo [51].

While further studies are needed to create solid therapeutic guidelines, present data suggests that vitamin C is effective as an additional therapy in the prevention and treatment of CAP.

Vitamin D

Vitamin D's immunomodulatory and anti-inflammatory effects make it essential for the prevention and treatment of CAP. It boosts the innate immune response by encouraging the development of antimicrobial peptides like cathelicidins and defensins, which help fight respiratory infections. Furthermore, vitamin D regulates the adaptive immune system, lowering the risk of chronic inflammation and lung tissue damage. Epidemiological studies have revealed that vitamin D deficiency increases the chance of getting respiratory infections, including CAP. Vitamin D supplementation has been linked to a lower incidence of CAP, improved clinical outcomes, and lower death rates, particularly in high-risk populations including the elderly and those with chronic conditions. Maintaining proper vitamin D levels allows the immune system to work more efficiently, thereby lowering the intensity and length of CAP and improving overall patient recovery [52].

Notably, pneumonia risk is increased in those with low vitamin D levels, according to several research [53–55].

Where a single high-dose oral vitamin D3 supplementation in conjunction with antibiotic treatment was found

to be effective in reducing the occurrence of repeated pneumonia episodes in a double-blind, placebo-controlled trial involving 453 children aged 1–36 months who were diagnosed with either non-severe or severe pneumonia at an inner-city hospital in Kabul [56].

In contrast, 200 children with severe pneumonia, aged 2 to 5 years, who participated in a different randomized, double-blind, placebo-controlled experiment were given oral vitamin D once daily for five days following enrollment. The findings showed that oral vitamin D supplementation for a brief period of time has no therapeutic impact on the recovery of severe pneumonia in children younger than five years [57].

Another randomized control trial was conducted where one hundred patients with pneumonia were treated with antibiotics and vitamin D concurrently, and another hundred patients were treated with antibiotics only. The study findings indicated that giving children diagnosed with pneumonia a single dose of vitamin D supplement significantly lowered the likelihood of new episodes of pneumonia occurring within a month of discharge [58].

In a different trial, a total of 46 patients with vitamin D insufficiency and VAP were randomized to receive either medication or a placebo. Intramuscular vitamin D (300,000 units) was administered to the treatment group. At baseline and seven days following the intervention, serum procalcitonin and vitamin D levels were assessed. Ultimately, the results showed that vitamin D supplementation can significantly reduce procalcitonin levels in VAP patients which may indicate a low risk of developing sepsis and progression to severe sepsis and/or septic shock and therefore need to be considered as a therapeutic or preventative measure in pneumonia patients [59].

On the other hand, a study involved 154 children between the ages of 2 months and 5 years who were hospitalized for an acute lower respiratory infection. The children were randomly assigned to receive either standard care therapy alone or standard care therapy for the respiratory infection plus a single oral dosage of 100,000 IU of vitamin D3, the children in the supplemented group did not experience a reduction in hospital stay duration, mortality, or ICU admission when compared to standard therapy alone [60].

Also, a double-blind, randomized, placebo-controlled study was carried out to examine the impact of extra vitamin D supplementation on patients admitted to the hospital due to CAP. Individuals were allocated to either receive a placebo or 200,000 IU of vitamin D3 orally. Six weeks after therapy, the study revealed that vitamin D supplementation may considerably lower the pro-inflammatory IL-6 and consequently vitamin D should be used as a supplement in the treatment of pneumonia patients [61].

Another randomized controlled trial included 100 children under five who had pneumonia. Two groups of children were assigned: one group received conventional therapy plus 300,000 IU of vitamin D, while the other group received the standard therapy alone. During a one-year period of observation, the children were observed for signs of upper respiratory tract infections, lower respiratory tract infections, vitamin D toxicity, and deficiency. According to the study's findings, children under the age of five can avoid recurrent pneumonia episodes due to oral vitamin D supplementation [62].

N-acetylcysteine

NAC has emerged as a viable supplementary therapy for CAP due to its strong antioxidant and anti-inflammatory characteristics. NAC works by refilling intracellular glutathione levels, which is an important antioxidant that decreases oxidative stress and cellular damage. This approach is especially useful in CAP, where oxidative stress and inflammation play important roles in the disease's pathology. Clinical investigations have shown that NAC can considerably reduce oxidative stress indicators while improving inflammatory profiles in CAP patients. Furthermore, NAC has been demonstrated to increase mucociliary clearance, which aids in the elimination of mucus and pathogens from the respiratory system. NAC reduces oxidative and inflammatory damage, which not only helps to alleviate symptoms but may also decrease hospital stays and improve overall results in CAP patients. These findings suggest the inclusion of NAC as an important component of comprehensive CAP control regimens [63].

From August 2016 to March 2017, eligible patients with CAP were randomly allocated to one of two groups: NAC or non-NAC group. The NAC group got standard pneumonia treatment augmented with 1200 mg/day of NAC, whereas the non-NAC group received only conventional therapy. The key endpoint indications were changes in oxidative stress markers following treatment in the NAC group vs the non-NAC group. The difference in computed tomography (CT) scores after treatment between the two groups served as the secondary endpoint indication. The study's findings suggested that NAC medication may considerably reduce oxidative and inflammatory damage in pneumonia patients, implying that NAC supplementation might be a useful complement to conventional therapy in controlling CAP [64].

Another prospective, randomized, double-blind, placebo-controlled research was carried out on 60 mechanically ventilated patients at high risk of acquiring VAP. Participants were randomly allocated to either the NAC or control group. In addition to usual care, the NAC group got 600 mg of NAC twice a day via a nasogastric

tube, whereas the control group received a placebo via the same method. The study's findings showed that NAC is both safe and effective at preventing and delaying the start of VAP. Furthermore, NAC dramatically increased the full recovery rate in this high-risk ICU group. These findings suggest NAC's potential as a helpful therapeutic adjuvant in managing individuals at high risk for VAP [65].

Astaxanthin

Astaxanthin (ASX), a powerful antioxidant carotenoid, has demonstrated encouraging results in the treatment of CAP due to its various pharmacological characteristics. ASX 's capacity to neutralize ROS and reduce oxidative stress makes it a promising choice for reducing inflammation and preserving lung tissue during CAP. Furthermore, ASX has anti-inflammatory characteristics that can help regulate the immune response and reduce the inflammatory cascade associated with CAP. Preclinical research has shown that ASX supplementation can improve lung function, minimize lung damage, and strengthen host defense systems against respiratory infections. In addition, ASX has been demonstrated to enhance clinical outcomes and reduce mortality in animal models of pneumonia [66–68].

In several preclinical studies, ASX has been shown to have an indirect antioxidant effect by activating the transcription factor nuclear factor erythroid 2-related factor 2 and increasing the expression of its antioxidant target genes, including phase II biotransformation enzymes [69–74].

Rationale for use of astaxanthin as potential adjunctive supplement in pneumonia patients

The microalgae Haematococcus pluvialis produces natural ASX, a new bioactive substance with numerous medical and physiological advantages. It is suggested that natural ASX, which the microalga H. pluvialis accumulates in response to unfavorable conditions, has a wide range of potential therapeutic and nutritional benefits as an antioxidant, immune booster, anti-inflammatory, neuroprotective, immunomodulatory, antiproliferative, antiaging, antibacterial, and antiapoptotic. Previous research has also demonstrated that natural ASX can play important roles in regulating immunity and disease etiology [66, 74, 75].

As a potent antioxidant and anti-inflammatory with established medical and physiological benefits, natural ASX is anticipated to work well as a co-adjunctive supplement for patients with pneumonia. Neither the antiviral nor the efficacy of ASX against pneumonia has been documented. Nonetheless, a sufficient body of published research points to its possible application in the management of cytokine release syndrome and associated conditions. Though further clinical evidence is required, there are indications that it may be a useful as a co-adjunctive supplement for pneumonia [76].

Recent reviews have synthesized a growing body of research that highlights the therapeutic potential of ASX across a range of health conditions, where an article reviewed the wide effects of ASX on a variety of respiratory diseases. The review cited multiple research that demonstrated ASX's capacity to modify immunological responses, decrease oxidative stress, and enhance lung function in various respiratory illness models [77].

Furthermore, another review reported that the anti-inflammatory properties of ASX are discussed in relation to neurological illnesses, diabetes, gastrointestinal diseases, hepatic and renal diseases, as well as eye and skin problems. In addition to the protective effects of ASX in various chronic and acute diseases, we also summarize recent advances for the inconsistent roles of ASX in infectious diseases, and give our opinion that the exact function of ASX in response to different pathogen infection and the potential protective effects of ASX in viral infectious diseases should be important research directions in the future [78].

These findings collectively show that astaxanthin, with its high antioxidant characteristics, can be used as an adjuvant treatment in a variety of respiratory disorders, including pneumonia and COVID-19, by lowering oxidative stress and modifying inflammatory responses. More clinical trials are needed to determine the therapeutic effectiveness of astaxanthin in human patients with various respiratory diseases.

Vitamin A

Vitamin A (retinol) is important in the treatment and prevention of CAP because of its effects on the immune system and epithelial integrity. Vitamin A is an important element that helps to preserve the integrity of mucosal barriers, which are the first line of defense against respiratory infections. It improves immune cell activity, such as T cells and B cells, and promotes antibody synthesis, which is essential for combating infections. Vitamin A also has anti-inflammatory effects that assist to regulate the immune response, minimizing excessive inflammation and lung tissue damage during CAP. Clinical investigations have found that vitamin A deficiency is linked to an increased risk of respiratory infections, including pneumonia. Vitamin A treatment can considerably enhance clinical results in CAP patients by boosting immunological activity and preserving epithelial integrity, allowing for speedier recovery and lower mortality rates [23, 79].

Additionally, vitamin A, stops the spread of free radical damage in biological membranes and is a potent peroxyl radical scavenger and chain-breaking antioxidant [80].

A randomized controlled study was conducted to treat children with pneumonia using vitamin A supplements. There was no significant reduction concerning the mortality due to pneumonia in the group comprising of the children who were supplemented with vitamin A when compared to the other group who didn't receive vitamin A. Moreover, no statistical significant difference was reported regarding the duration of stay in the hospital. However, supplementing with vitamin A considerably decreased the recurrence rate of bronchopneumonia [81].

Another prospective cohort study that enrolled forty pneumonia diagnosed hospitalized children with the ages ranging from six months to five years demonstrated that after recovering from pneumonia, and serum retinol levels were much higher after recovery than they were during the acute stage which denotes the positive correlation between serum retinol levels and decrease in inflammatory disease state [82].

Additionally, a study was carried out between the years 2015 and 2018 where 122 children were enrolled; fifty-two patients had severe Mycoplasma pneumoniae pneumonia and seventy had non-severe Mycoplasma pneumoniae pneumonia. The serum levels of vitamins A, D, and E were measured and compared. The results of the investigation showed a connection between severe Mycoplasma pneumoniae pneumonia and vitamin A deficiency which denotes the importance of supplementing vitamin A to severe pneumonia patients to improve their disease state and lead to better clinical outcomes [83].

Zinc

Zinc's key immune system activities and capacity to moderate inflammatory responses make it essential for the prevention and treatment of CAP. Zinc, an important trace element, plays a role in a variety of cellular activities such as DNA synthesis, cell division, and protein synthesis, all of which are critical for immunological competence. Zinc improves the activity of immune cells such as neutrophils, macrophages, and natural killer cells, strengthening the body's defenses against respiratory infections. Furthermore, zinc has been proven to have antiviral capabilities, which can prevent the reproduction of viruses that cause respiratory illnesses [84, 85].

In a research, a total of 75 children diagnosed with CAP in the pediatric ICU underwent a comparative, randomized, open label, controlled trial in which they were randomly assigned to three groups. Group 1 received zinc in addition to the usual therapy, Group 2 received vitamin A, and Group 3 simply received the standard therapy. The length of hospital stays and recovery rates of the three groups were compared. Supplementing with zinc or vitamin A was found to be beneficial as an adjuvant therapy for CAP, as it shortened hospital stays and decreased the duration of pneumonic effusion in children under five years old [86].

On the other hand, a randomized, double-blind, placebo-controlled study carried out in Tanzania which enrolled pneumonia hospitalized children with ages ranging from six to thirty-six months comparing a group supplemented with zinc (daily 25 mg) as an adjunct to antibiotic therapy for pneumonia and the other group received placebo. The study revealed that no specific benefit from zinc supplementation was identified regarding the clinical outcomes of pneumonia [87].

There is a pressing need for further research to comprehensively study the effects of zinc on pneumonia, as current evidence is limited and more robust clinical trials are required to establish its efficacy and optimal usage.

Selenium

Se, an essential trace element, is important in the body's antioxidant defense system, chiefly through its integration into selenoproteins, which have strong antioxidant and anti-inflammatory effects. Selenium-dependent enzymes, such as glutathione peroxidases (GPXs) and thioredoxin reductases, are crucial in lowering oxidative stress because they neutralize ROS and protect cell membranes from lipid peroxidation. Se deficiency is one of the causes of many human illnesses. Thus, it is important to prevent Se deficiency [88].

Se's antioxidant action can be especially advantageous in cases of CAP's pathogenesis as it includes oxidative stress and inflammation, and Se's function in dampening these effects can help reduce the disease's severity and development. Selenoproteins play an important role in detoxifying cellular peroxides, lowering oxidative damage and perhaps boosting immunological responses to infections like CAP [89].

A prospective, placebo-controlled, randomized, single-blind phase II trial was conducted in a multidisciplinary university hospital's ICU where two groups of patients with systemic inflammatory response syndrome aged more than 18 years were randomized to receive either placebo or intravenous Se as a bolus-loading dosage of 2000 μg Se followed by a continuous infusion of 1600 μg Se per day for ten days, the study revealed that Se supplementation improved illness severity, and reduces the risk of VAP [90].

On the contrary, ninety-nine mechanically ventilated patients were randomly assigned to receive either Se or isotonic saline infusions for ten days. One of the clinical outcomes was the development of VAP or death. Despite the boosting antioxidant activity of Se, however, its administration didn't reduce the incidence of VAP and the probability of developing VAP or death within 30 days of ICU admission remained the same in both treatment and control groups [91].

Glutathione

Glutathione, an important intracellular antioxidant, aids in the fight against oxidative stress in individuals with CAP. As a tripeptide made up of glutamine, cysteine, and glycine, glutathione directly neutralizes ROS, protecting lung tissues from oxidative injury. In CAP, the inflammatory response frequently causes increased ROS generation, exacerbating lung damage and impairing immunological function. Glutathione not only scavenges these dangerous free radicals, but it also regenerates additional antioxidants like vitamins C and E, which improves the total antioxidant defense system. Furthermore, glutathione controls the immune response by preserving redox equilibrium inside immune cells, allowing them to operate optimally [92].

A research examines the epidemiology, transmission, and clinical presentation of COVID-19, with an emphasis on etiology and the potential use of liposomal GSH as an adjuvant therapy to current treatment methods in COVID-19 patients. Based on evidence that GSH can inhibit viral replication and lower IL-6 levels in HIV and tuberculosis patients, as well as GSH's beneficial effects on other pulmonary disease processes, we believe liposomal GSH could be beneficial in COVID-19 patients. This paper examines the epidemiology, transmission, and clinical presentation of COVID-19, with an emphasis on its etiology and the potential use of liposomal GSH as an adjuvant treatment to the current treatment methods in COVID-19 [93].

In a clinical study, patients presented with pneumonia were administered a trial dose of 2 g of glutathione alleviated their respiratory symptoms. These findings suggest that glutathione, its precursors (such as NAC), and alpha-lipoic acid may offer a novel therapeutic approach for mitigating NF-κB activation, thereby addressing "cytokine storm syndrome" and respiratory distress in patients with pneumonia. This novel treatment strategy holds promise in enhancing patient outcomes by effectively managing the severe inflammatory responses associated with COVID-19 [94].

Enzymatic antioxidants

Catalase

Catalase plays an important role in the treatment of CAP by reducing oxidative stress and inflammation in the respiratory system. Catalase, a vital antioxidant enzyme, catalyzes the breakdown of hydrogen peroxide into water and oxygen, protecting lung tissue from oxidative damage. Catalase aids in the preservation of lung function and immunological response in CAP, where inflammation and oxidative stress are major factors to lung damage. In preclinical research, recombinant catalase has been demonstrated to prevent oxidative stress, enhance lung histology, and lower inflammatory markers in pneumonia models. These protective benefits are linked to improve scavenging of ROS, which reduces cellular damage and promotes recovery. Catalase's capacity to lower oxidative stress and inflammation shows its potential as a therapeutic agent in the treatment of CAP, which might lead to better clinical results and reduced disease severity [95, 96].

While there aren't enough studies to evaluate the benefits of catalase on pneumonia, research has shown that it helps with other respiratory ailments. Catalase has been proven in studies to reduce inflammation and improve lung function in a variety of respiratory disorders, including COPD and asthma. These encouraging findings imply that more study is needed to investigate catalase's therapeutic effects in pneumonia, which might provide a unique way to controlling this prevalent and dangerous infection [97].

A preclinical investigation found that recombinant human catalase greatly reduces acute oxidative damage in lung tissues after influenza-induced pneumonia. Mice infected with the influenza virus H1N1 were administered recombinant human catalase (50,000 U/kg) by inhalation. The therapy significantly improved the survival time and rates of mice with H1N1-induced pneumonia. Furthermore, protective benefits were seen in lung histology, antioxidant markers, pulmonary pathology, and virus titers in the lungs. The therapeutic advantages were linked to increased serum superoxide and hydroxyl radical anion scavenging capabilities. These data indicate that recombinant human catalase has potential as a therapeutic method for treating H1N1 influenza-induced pneumonia [98].

Another preclinical research found that catalase supplementation increases specific enzyme activity while decreasing hydrogen peroxide levels in the airways, providing significant protection against respiratory syncytial virus (RSV)-induced clinical sickness and airway pathology. In this study, mice supplemented with catalase

demonstrated significant decreases in airway blockage, neutrophil elastase levels, and inflammation. Furthermore, catalase supplementation reduced airway hyper responsiveness after viral inoculation. The medication also dramatically reduced inflammatory cytokines and chemokines in RSV-infected mice's bronchoalveolar lavage fluid while not enhancing viral replication in the lungs. These data indicate that catalase supplementation may be a potential pharmacological strategy for preventing or treating respiratory infections in people [99].

Superoxide dismutase

SOD is an important enzyme in the fight against oxidative stress in CAP. SOD is an important antioxidant enzyme that catalyzes the dismutation of superoxide radicals into oxygen and hydrogen peroxide, decreasing oxidative damage in lung tissues. In the case of CAP, the inflammatory response frequently leads in an excess of ROS, aggravating lung damage and compromising pulmonary function. By reducing superoxide radicals, SOD protects alveolar cells from oxidative damage and contributes to lung integrity. New study reveals that increasing SOD activity may enhance clinical outcomes in CAP patients by lowering oxidative stress and inflammation. Although more research is needed to fully grasp its therapeutic potential, SOD's involvement in controlling oxidative stress emphasizes its relevance in the etiology and possible therapy of CAP [100].

A multicenter, randomized, placebo-controlled pilot trial was done to determine the safety and effectiveness of 40 or 80 mg dosages of SOD in patients with progressive idiopathic interstitial pneumonias. The findings showed that SOD medication was safe and improved blood indicators including lactate dehydrogenase and surfactant protein-A in individuals with advanced idiopathic interstitial pneumonias and severe respiratory dysfunction. These data indicate that SOD has therapeutic potential in these individuals, necessitating more investigation into the consequences and advantages of long-term SOD therapy [101].

Antioxidant	Dosage	Year	Species	Measured outcomes	Summary of findings	Reference
Nonenzymatic antioxidants						
Coenzyme Q10	200 mg/d	2014	Human	Clinical cure at days 3 and 7 Hospital stay in intervention group compared with the placebo group Adverse events in two groups	Coq10 administration has no serious side effects and can improve outcome in hospitalized elderly CAP; therefore, they recommend it as an adjunctive treatment in elderly patients	[36]
		2011	Human	Plasma was extracted from blood samples on day 1 before the antimicrobial treatment, and either at day 8 or day 15, after treatment Both oxidized and reduced forms of coenzyme Q10 were measured and%coq10 was defined as the percentage of plasma level of the oxidized form to total coenzyme Q10	Coq10 can well indicate the oxidative stress burden on CAP patients	[37]
	160 mg Coenzyme + 170 mg Creatine	2018	Human	At baseline and after 2 months of therapy, the patients underwent spirometry, 6-min walk test (6MWT), bioelectrical impedance analysis, and activities of daily living questionnaire (ADL)	The results show that dietary supplementation with coq10 and creatine improves functional performance, body composition, and perception of dyspnea. A systemic increase in some anti-inflammatory metabolites supports a pathobiological mechanism as a reason for these benefits	[38]

Antioxidant	Dosage	Year	Species	Measured outcomes	Summary of findings	Reference
Vitamin E	50 mg/d of vitamin E	2016	Human	The outcome was the incidence of hospital-treated, CAP by the age at the follow-up	Although the evidence of benefit from vitamin E against pneumonia in elderly males is strong in this analysis, the overall findings about vitamin E have been complex. Further research on vitamin E in nonsmoking elderly males is warranted	[39]
	800 mg dl-alpha-tocopheryl acetate	2000	Mice& Human	Effects of antioxidants on cytokine production	Vitamin E Supplementation significantly decreases influenza virus titer following influenza infection in young and old mice. There is also evidence for the beneficial effect of antioxidants in other viral infections	[40]
	Cells were exposed to various concentrations of α-tocopherol for 45 min in a concentration range of 25–100 μM	2007	A human type II alveolar epithelial cell line	The supernatants were separated by centrifugation, and the concentration of IL-8 was measured Expression of cell adhesion molecules in both untransformed primary cells and the A549 and BEAS-2B cell lines was observed	The action of vitamin Eon activated epithelium can protect cells from oxidative stress and excessive inflammation by inhibition of signal transduction pathways	[41]
Vitamin C	60 mg/kg/day vitamin C	2021	Human	Serum levels of vitamin C were noted at baseline and 48 h after vitamin C administration. Duration of mechanical ventilation, ICU length of stay, pao2/fio2, and mortality rate were noted for all patients till the 28th day. Any complications related to the vitamin C administration were recorded	Results showed that the intravenous administration of a relatively high dose of vitamin C to critically ill patients with severe pneumonia was safe and could decrease the inflammation, duration of mechanical ventilation, and vasopressor use without any significant effect on mortality	[49]
	Intravenous vitamin C (2.5 g per 8 h) before moving to oral vitamin C (1 g three times daily)	2023	Human	Blood samples were collected at baseline and then daily while in the hospital. Vitamin C concentrations were determined. The inflammatory and infection biomarkers, C-reactive protein, and procalcitonin were measured	Patients with moderate-to-severe CAP have inadequate plasma vitamin C concentrations for the duration of their hospital stay. The administration of intravenous or oral vitamin C, titrated to match the antimicrobial formulation, provided saturating plasma vitamin C concentrations while in the hospital	[50]

Antioxidant	Dosage	Year	Species	Measured outcomes	Summary of findings	Reference
	125 mg daily	2008	Human	Venous blood was collected for estimation of serum level of five micronutrients from all the samples before starting treatment by standard procedures	Chest indrawing and fast breathing disappeared earlier in the intervention group suggesting that supplementation of micronutrients decrease the morbidity and duration of hospital stay of children suffering from pneumonia	[51]
Vitamin D	100,000 IU of vitamin D (3)	2010	Human	Number of days to recover between the vitamin D (3) and placebo arms The risk of a repeat episode of pneumonia within 90 days of supplementation	A single high-dose oral vitamin D (3) supplementation to young children along with antibiotic treatment for pneumonia could reduce the occurrence of repeat episodes of pneumonia	[56]
	Oral vitamin D (1000 IU for < 1 year and 2000 IU for > 1 year)	2012	Human	Primary: time to resolution of severe pneumonia. Secondary: duration of hospitalization and time to resolution of tachypnea, chest retractions, and inability to feed	Short-term supplementation with oral vitamin D (1000–2000 IU per day for 5 days) has no beneficial effect on resolution of severe pneumonia in under-five children	[57]
	Oral or intramuscular high-dose (300,000 units for children of 2 to 12 months and 600,000 units for age 12 to 60 months) vitamin D	2016	Human	The duration of the hospital stay was noted. They were followed up for next 90 days after discharge from hospital and any new episode of pneumonia was noted and recorded	Vitamin D supplementation in a single dose to the children diagnosed as pneumonia significantly reduces the occurrence of new episodes of pneumonia within one month of discharge	[58]
	300,000 units of intramuscular vitamin D	2017	Human	Levels of procalcitonin and vitamin D along with Sequential Organ Failure (SOFA score) and clinical pulmonary infection score (CPIS) were determined at baseline and on day 7 after intervention	Results indicate that vitamin D supplementation can significantly reduce the procalcitonin in (VAP) patients and must be considered as a preventive and/or therapeutic strategy	[59]
	A single oral dose of 100,000 IU of vitamin D3	2017	Human	The primary outcome measured was the duration of hospital stay. Secondary outcomes measured were mortality, incidence of complications, admission to pediatric intensive care unit (PICU), and recurrence of respiratory infections within 90 days of discharge	Single oral dose of 100,000 IU of vitamin D3 did not lead to reduction in duration of hospital stay, mortality, PICU admission, or complications related to acute lower respiratory tract infection (ALRI) when compared to standard therapy alone in under-five children hospitalized with ALRI but was able to achieve serum vitamin D sufficiency within 72 h of administration	[60]

Antioxidant	Dosage	Year	Species	Measured outcomes	Summary of findings	Reference
	Single oral dose of 200,000 IU vitamin D3	2018	Human	The primary outcome was the complete resolution of chest radiograph infiltrate at 6 weeks post-study treatment Secondary outcomes included length of hospital stay, intensive care admission, and return to normal activity	Adjunctive vitamin D did not have any effect on the primary outcome. However, there was evidence it increased the complete resolution of pneumonia in participants with baseline vitamin D levels < 25 nmol/L. There were no significant effects for any secondary outcome	[61]
	300,000 IU of vitamin D	2019	Human	The children were followed up for 1 y and signs of upper respiratory tract infections (URTI), lower respiratory tract infections (LRTI), vitamin D deficiency, and vitamin D toxicity were recorded	The study highlights that oral vitamin D (300,000 IU bolus dose quarterly) has some beneficial effect in the prevention of recurrent pneumonia in under-five children, although, not to a significant degree	[62]
N-acetylcysteine	1200 mg/d	2018	Human	Malondialdehyde (MDA), SOD, total antioxidant capacity (TAOC), TNF-α, and CT images were evaluated at baseline and after treatment	Treatment with NAC may help to reduce oxidative and inflammatory damage in pneumonia patients	[64]
	600 mg/twice daily	2018	Human	The study aimed to examine the effect of NAC in preventing VAP in patients hospitalized in ICU	NAC is safe and effective to prevent and delay VAP, and improve its complete recovery rate in a selected, high-risk ICU population	[65]
Vitamin A	Doses range from 100,000 IU to 200,000 IU	2005	Human	To determine whether adjunctive vitamin A is effective in infants and children diagnosed with non-measles pneumonia	The evidence did not suggest a significant reduction with vitamin A adjunctive treatment in mortality, measures of morbidity, or an effect on the clinical course of pneumonia in children with non-measles pneumonia	[81]
		2005	Human	They evaluated plasma retinol level during the acute phase and after recovery	Serum retinol levels were significantly higher after recovery than during the acute phase of pneumonia	[82]
		2020	Human	The serum levels of vitamins A, D, and E were measured and compared	The results of the investigation showed a connection between severe Mycoplasma pneumoniae pneumonia and vitamin A deficiency	[83]
Zinc	10 mg once daily for children aged less than 1 year, or 20 mg once daily for children aged over 1 year to 5 years	2022	Human	The study compares the effects of zinc and vitamin A, as two elements of micronutrient agents, on the recovery rate of children suffering from CAP aged from 6 months to 5 years. The length of hospital stays was also investigated	The administration of zinc or vitamin A supplementation reduced the length of hospital stay and the duration of pneumonic effusion in pneumonic children less than 5 years of age	[86]

Antioxidant	Dosage	Year	Species	Measured outcomes	Summary of findings	Reference
	25 mg	2014	Human	Effect of zinc supplementation on duration of hospitalization	This randomized trial provided no evidence for a beneficial effect of zinc supplementation adjunct to antibiotics for hospitalized children	[87]
Selenium	Intravenous selenite as a bolus-loading dose of 2000 µg Se followed by continuous infusion of 1600 µg Se per day for 10 days	2011	Human	Blood samples were analyzed before randomization (day 0) then at days 3, 7, and 10. Clinical outcome was assessed by Assessment SOFA score. HAP including VAP, adverse events, and other safety parameters were monitored as secondary endpoints	Daily infusion of 1600 µg Se (as selenite), following an initial bolus of 2000 µg, is novel and did not cause any short-term adverse events. High-dose parenteral selenite significantly increases Se status, improves illness severity, and lowers incidence of HAP including early VAP for patients in ICU	[90]
	2 mg bolus on day one followed by daily infusion of 1.6 mg for 9 days	2018	Human	The primary endpoint was serum glutathione peroxidase-3 (GPX-3) activity and secondary endpoints were development of VAP or death, ICU stay, and vasopressor requirement	Despite increasing the antioxidant activity, selenium supplementation did not affect the incidence of VAP in critically ill patients. The risk of developing VAP or death within 30 days of ICU admission remained the same in the treatment and the controls	[91]
Glutathione	2 g of PO or IV glutathione	2020	Human	They evaluated the effects of using high-dose oral and/or IV glutathione in the treatment of 2 patients with dyspnea secondary to COVID-19 pneumonia	Oral and IV glutathione, glutathione precursors (NAC) and alpha-lipoic acid may represent a novel treatment approach for blocking NF-κb and addressing "cytokine storm syndrome" and respiratory distress in patients with COVID-19 pneumonia	[94]
Enzymatic antioxidants						
Catalase	50,000 U/kg by inhalation	2010	Mice	The survival time and survival rates were observed Protective efficacy of catalase, antioxidant parameters, pulmonary pathology, and influenza viral titer in lungs in mice all were observed and measured	This study strongly indicated that recombinant catalase might be a potential therapy for H1N1 influenza-induced pneumonia	[98]
	2.84 mg/kg 24 h prior to RSV inoculation and a second dose 2.84 mg/kg 24 postinfection	2020	Mice	Airway obstruction, neutrophil elastase, inflammation and Airway hyperresponsiveness were observed in mice that received catalase as a treatment post-viral inoculation In addition, inflammatory cytokines and chemokines were observed	Catalase supplementation may represent a novel pharmacologic approach to be explored in human for prevention or treatment of respiratory infections caused by RSV	[99]

Antioxidant	Dosage	Year	Species	Measured outcomes	Summary of findings	Reference
Superoxide dismutase	40 or 80 mg lecithinized superoxide dismutase	2014	Human	The primary endpoint of forced vital capacity and the secondary endpoints of lactate dehydrogenase, surfactant protein-a, surfactant protein-d, and krebs von den lungen-6 levels were measured in the serum	Treatment with lecithinized superoxide dismutase is safe and improves the levels of serum markers such as lactate dehydrogenase and surfactant protein-a in patients with advanced idiopathic interstitial pneumonias with severe respiratory dysfunction	[101]

Conclusion

In conclusion, our review shows that the use of antioxidants as adjuvant therapy in CAP shows promising potential in reducing oxidative stress and inflammation, thereby improving clinical outcomes, where according to our findings, antioxidants can reduce pneumonia's inflammatory components while also preventing oxidative damage. As a result, supplementary antioxidant therapy, when combined with standard treatment, may assist pneumonia patients experience less oxidative and inflammatory damage, improving clinical outcomes.

However, there are some limitations in our review including that the studies included in the review may vary significantly in terms of study design, sample size, and population characteristics, making it difficult to draw consistent conclusions; moreover, many studies may focus on the short-term effects of antioxidants, while the long-term impact on CAP outcomes and overall health may not be well-documented and also the quality of the studies included in the review may vary, with some studies having methodological limitations such as lack of randomization, blinding, or control groups, which can affect the reliability of the results.

Future research should aim for standardized methodologies, including similar study designs, antioxidant dosages, and administration routes, to facilitate better comparison and synthesis of results and it is required to conduct larger, well-designed randomized controlled trials to provide more robust and generalizable evidence on the efficacy of antioxidants in treating CAP. Also, it is essential to implement longitudinal studies to assess the long-term effects of antioxidant use in the prevention and treatment of CAP, including potential benefits and risks as well as encourage comprehensive reporting of study results, including negative and inconclusive findings, to reduce publication bias and provide a more balanced view of the evidence.

Finally, by addressing these limitations and following these recommendations, future research can provide more definitive insights into the role of antioxidants in the management of CAP, where the integration of antioxidants into the treatment regimen for CAP holds potential for significantly improving patient outcomes by reducing oxidative stress and inflammation, thereby enhancing the overall effectiveness of conventional therapies.

Abbreviations

CAP	Community-acquired pneumonia
HAP	Hospital-acquired pneumonia
VAP	Ventilator-associated pneumonia
HCAP	Healthcare-associated pneumonia
COPD	Chronic obstructive pulmonary diseases
ICU	Intensive care unit
ROS	Reactive oxygen species
DNA	Deoxyribonucleic acid
IL-6	Interleukin-6
IL-8	Interleukin-8
IL-1 β	Interleukin-1 βeta
TNF-α	Tumor necrosis factor alpha
ARDS	Acute respiratory distress syndrome
SIRS	Systemic inflammatory response syndrome
NAC	N-acetylcysteine
CoQ10	Coenzyme Q10
ATP	Adenosine triphosphate
NF-KB	Nuclear factor kappa B
A549 cell lines	Adenocarcinomic human alveolar basal epithelial cells
BEAS-2B	Human non-tumorigenic lung epithelial cell line derived from a human lung tissue
COVID-19	Severe acute respiratory syndrome coronavirus 2 (SARS-cov-2)
CT	Computed tomography
ASX	Astaxanthin
Se	Selenium
GPX1	Glutathione peroxidase
RSV	Respiratory syncytial virus
SOD	Superoxide dismutase
6MWT	6-Minute walk test
ADL	Activities of daily living questionnaire
ICAM-1	Intercellular adhesion molecule-1
SOFA score	The sequential organ failure assessment score
CPIS	Clinical pulmonary infection score
PICU	Pediatric intensive care unit
ALRI	Acute lower respiratory tract infection
URTI	Upper respiratory tract infection
LRTI	Lower respiratory tract infection
MDA	Malondialdehyde
TAOC	Total antioxidant capacity
nsMPP	Non sever mycoplasma pneumoniae pneumonia
sMPP	Sever mycoplasma pneumoniae pneumonia

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Declarations

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