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REVIEW

Edaravone: A Possible Treatment for Acute Lung Injury

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Abstract: Despite technological advances in science and medicine, acute lung injury (ALI) is still associated with high mortality rates in the ICU. Therefore, finding novel drugs and treatment approaches is crucial to preventing ALI. Drug repurposing is a common practice in clinical research, primarily for drugs that have previously received approval for use in patients, to investigate novel uses of drugs and therapies. One such medication is edaravone, which is a highly effective free-radical scavenger that also has anti-inflammatory, anti-apoptotic, antioxidant, and anti-fibrotic effects. Both basic and clinical studies have shown that edaravone can treat different types of lung injury through its distinct properties. Edaravone exhibits significant protective benefits and holds promising clinical treatment potential for ALI caused by diverse factors, thereby offering a novel approach to treating ALI. This study aims to provide new insights and treatment options for ALI by reviewing both basic and clinical research on the use of edaravone. The focus is on evaluating the effectiveness of edaravone in treating ALI caused by various factors.

Keywords: acute lung injury, edaravone, oxidative stress, inflammation, apoptosis, fibrosis

Introduction

Overview of Acute Lung Injury

Despite the progress made in medical technology, which has resulted in a decrease in the number of deaths, new cases, and mortality rates related to acute lung injury/acute respiratory distress syndrome (ALI/ARDS), the mortality rate remains at approximately 40%.[1–3] ALI/ARDS represents lung injury or the worsening of respiratory symptoms caused by either pulmonary or extrapulmonary factors.[4] Pulmonary factors include pneumonia, pulmonary contusion, fat embolism, drowning, inhalation injury (hyperoxia, smoke), and lung transplantation, and extrapulmonary factors include sepsis, severe traumatic shock, medications, blood transfusions, burns, and disseminated intravascular coagulation.[5] There are also additional factors that can increase the risk of ALI, such as virulence, race, environmental influences (alcoholism, smoking), age factors (>65 years), acute exacerbations of chronic obstructive pulmonary disease (AECOPD), and inappropriate mechanical ventilation.[6–8] Lung injuries can be categorized into many types based on their underlying causes, including hyperoxic acute, smoke inhalation, septic, paraquat poisoning, acute drug-induced, ischemia-reperfusion, acute pancreatitis, seawater drowning lung injuries, and other factors-induced acute lung injuries (Figure 1).[5–7] The etiology of ALI remains incompletely elucidated, with current theories encompassing hypoxia,[8] excessive oxidative stress,[9] inflammatory reaction,[7] cell apoptosis,[10] and autophagy.[11] Oxidative stress is closely related to ALI as it triggers the release of large amounts of reactive oxygen species (ROS) during ALI. This in turn leads to lipid peroxidation, DNA damage, activation of transcription factors, pulmonary edema, and the activation of polymorphonuclear leukocytes, thereby exacerbating the lung injury.[12–14] Therefore, inhibiting oxidative stress in the lungs and identifying suitable antioxidants is important for alleviating ALI. Although the understanding of the course and treatment of ALI/ARDS has improved significantly in the past decades, its mortality rate is still very high in clinical practice.

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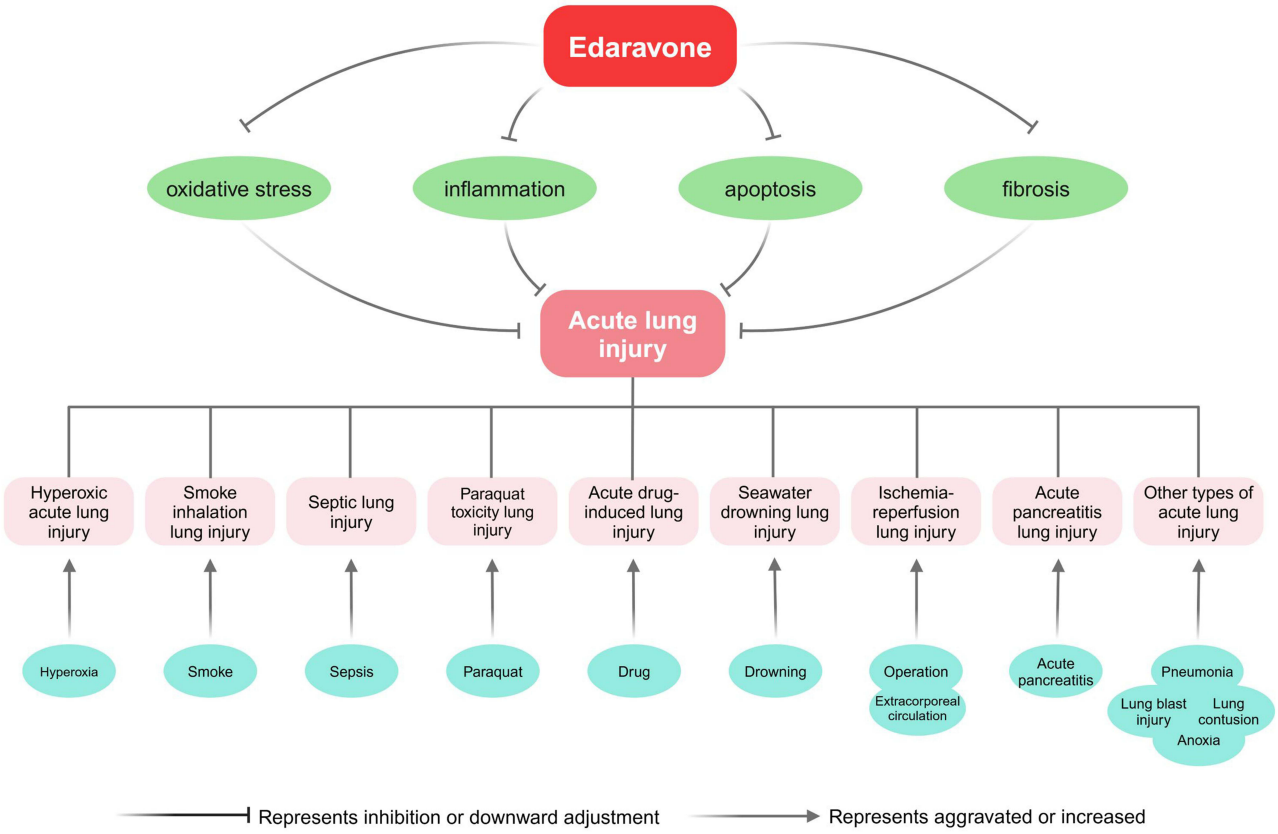
Graphical Abstract



Currently, the treatment available for ALI is limited, with the main available treatments being oxygen therapy, ventilator-assisted ventilation, fluid replacement, anti-infection, anticoagulation, antioxidant and anti-inflammatory treatments, prevention of stress ulcers, prone ventilation, and other symptomatic supportive treatments,[15–17] but their efficacy is poor. However, the effectiveness of these treatments is limited, and no individual drugs have a large and consistent effect on ALI/ARDS.[15,18] As a result, the discovery of new drugs and the continued research into innovative uses of existing drugs is required for the treatment of ALI/ARDS.

Properties of Edaravone

Edaravone is a classical free-radical scavenger. It is lipophilic and has a high safety profile with low toxicity and few side effects. This compound, with the chemical formula $C_{10}H_{10}N_2O$ and a molecular weight of 174.199, is an organic substance capable of crossing the blood-brain barrier and offering protection to brain cells.[19] Furthermore, edaravone has various properties and can inhibit lipid peroxidation and free-radical generation while providing direct scavenging of hydroxyl radicals by enhancing the activity of superoxide dismutase (SOD) and maintaining mitochondrial structure and oxidative phosphorylation levels, thus counteracting oxidative stress.[20–22] In an in vivo model of amyotrophic lateral sclerosis (ALS), edaravone was found to preserve motor neurons by increasing SOD1 activity in the spinal cord, reducing the deterioration in muscular and motor function.[23] In addition, in an in vitro ALS model, edaravone reduced reactive oxygen species generation, neuronal cytotoxicity, and mortality.[24] A study conducted by Zeng et al also demonstrated that edaravone mitigates inflammation in mouse lungs in a mouse model of ambient particulate matter (PM)-induced pneumonitis by reversing mitochondrial dysfunction caused by oxidative stress.[25]

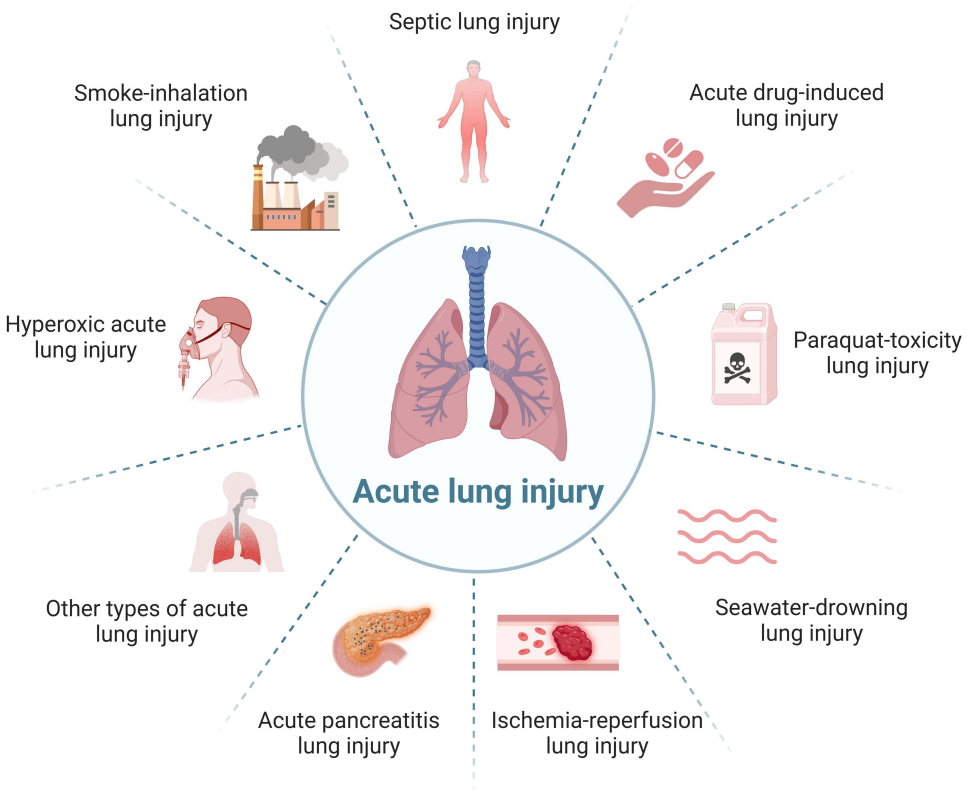


Figure 1 Classification of Acute Lung injury.

In terms of anti-inflammatory effects, edaravone can neutralize free radicals, regulate the activity of Nrf2 and NF-κB, inhibit the release of inflammatory factors, and reduce the inflammatory response.[26] In a mouse model of brain injury involving ischemia-reperfusion, edaravone can modulate the expression of inflammation-related proteins (such as TNF-α, IL-1β, IL-4, IL-10) by activating the Nrf2/HO-1 pathway. This effect contributes to the suppression of the inflammatory response, resulting in a reduction in brain nerve injury in mice.[27] Furthermore, investigations have suggested that edaravone can regulate the activities of Nrf2 and NFκB, therefore reducing the release of inflammatory factors in a rat model of cyclophosphamide (CP)-induced hemorrhagic cystitis. This, in turn, reduces the inflammatory damage caused by CP.[28]

Edaravone can inhibit the loss of mitochondrial membrane potential and down-regulate the line apoptotic pathway and pro-apoptotic protein expression, thus exerting anti-apoptotic properties.[29,30] In a mouse model of ischemia-reperfusion kidney injury, edaravone has shown promising results in reducing kidney damage by preserving mitochondrial membrane potential and decreasing the expression of apoptotic proteins (such as Bax and caspase-3). Moreover, studies have indicated that edaravone can activate the PI3K/Akt/mTOR signaling pathway to modulate neuronal apoptosis and autophagy. This action leads to a decrease in the levels of pro-apoptotic proteins, ultimately enhancing cognitive functions in rats with neurovascular dementia.[31]

Edaravone possesses anti-inflammatory and antioxidant capabilities, which enable it to impede the growth of tumor cells and induce anti-tumor effects. Furthermore, it may impede the occurrence of side effects and unfavorable responses induced by anti-neoplastic drugs.[32] Edaravone demonstrates inhibitory effects on a range of cancer cells, including liver cancer, gastric cancer, and breast cancer. It functions by disrupting the cell cycle of tumor cells, inducing cancer cell apoptosis, and ultimately impeding tumor cell proliferation, thus demonstrating anti-tumor properties.[32] Moreover, numerous cisplatin effectively reduces the adverse reactions associated with anti-tumor medications.[33–35]

Furthermore, edaravone also has antiviral,[36] immunomodulatory,[37] anti-fibrosis,[38] and other effects. Because of its multiple properties, edaravone has been used as a first-line drug for a variety of diseases, such as acute cerebral

infarction,[39,40] amyotrophic lateral sclerosis (ALS),[41] and acute intracerebral hemorrhage,[42,43] and its effects are remarkable.

Applications of Edaravone

The FDA (Food and Drug Administration) in the US has approved edaravone as a clinical drug for the treatment of diseases such as acute ischemic stroke and ALS.[44,45] It has a noteworthy therapeutic effect on neurological conditions. Previous research and clinical experience have demonstrated that edaravone is beneficial not only for neurological disorders but also for significant improvements in respiratory (lungs),[46,47] digestive (liver, intestines, and pancreas),[48–50] urinary (kidneys and bladder),[28,30] reproductive (testes),[51] cardiovascular (heart) disorders,[52] and especially on ALI (Figure 2).[53,54] There are obvious advantages to using edaravone instead of drugs for ALI. Edaravone plays a broader role, as it can suppress oxidative stress, inflammation, apoptosis, fibrosis, and other pharmacological effects (Figure 2).[41] This can compensate for the limitations of the current ALI treatment and have a preventive impact on ALI, completing the demand for ALI preventive drugs.[25,55] Meanwhile, the most important thing is that edaravone has a stable effect and high safety in the process of long-term clinical application. In a clinical trial investigating the use of edaravone for the treatment of ALS, patients were administered a daily oral dose of 105 mg for 48 consecutive weeks. No adverse reactions were observed, and no new safety concerns were identified.[56] Similarly, in a Phase I clinical study, volunteers demonstrated good tolerance and safety when administered either a single or multiple doses of edaravone.[57] Furthermore, a multicentre, propensity score-matched cohort study of edaravone also demonstrated that edaravone was well tolerated and safe in patients treated with long-term intravenous edaravone for ALS.[58]

This article provides a comprehensive analysis of the latest scientific studies on the effectiveness of edaravone in treating ALI caused by different factors. The objective is to identify a novel therapeutic drug for this condition.

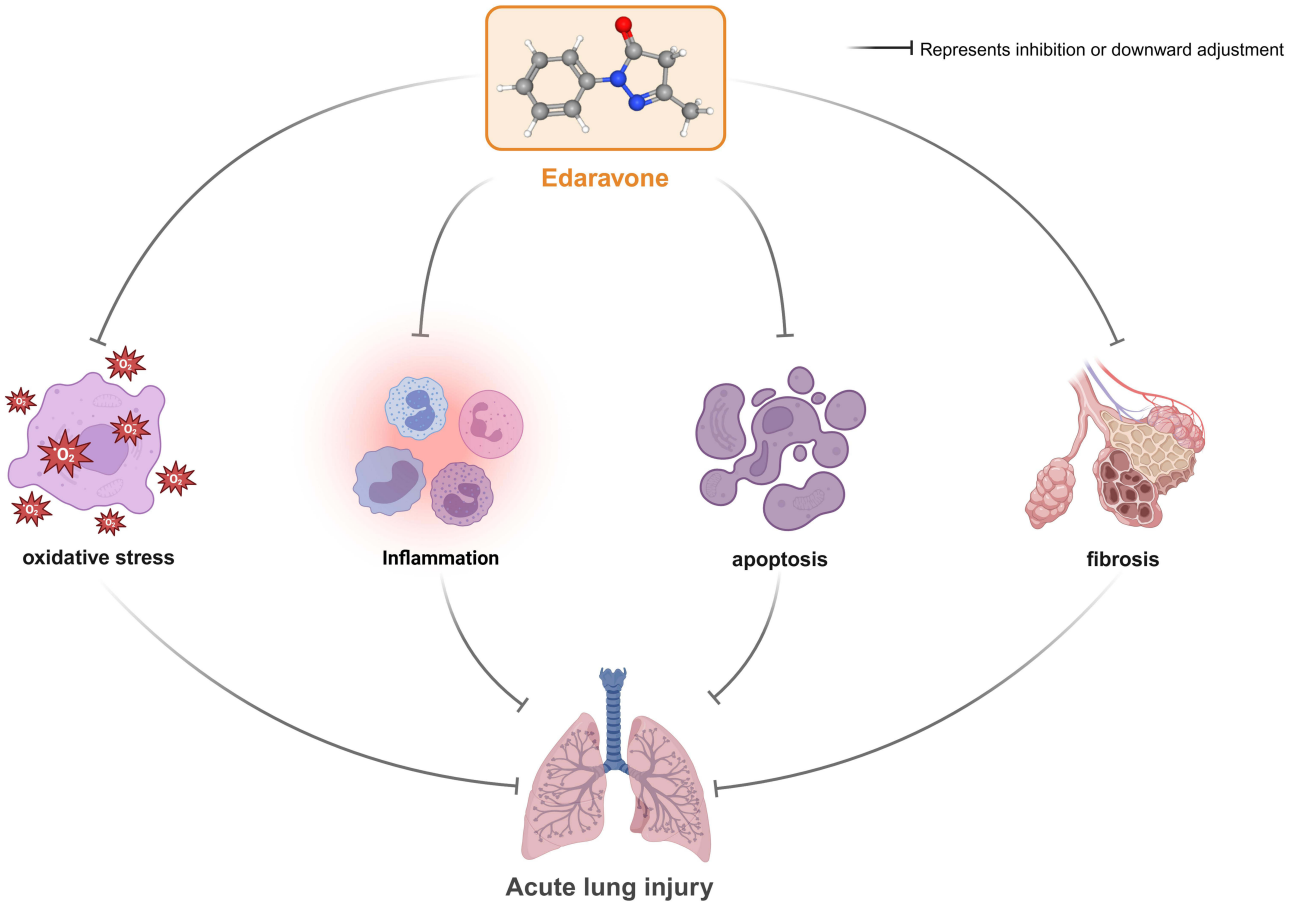


Figure 2 Pathways of edaravone to reduce lung injury.

The Use of Edaravone for Treating Various Types of Acute Lung Injury

Hyperoxic Acute Lung Injury

Hyperoxic acute lung injury (HALI) is an ALI resulting from the inhalation of high concentrations of oxygen over a prolonged time.[59] The severity of HALI is directly related to oxidative stress and inflammation levels in the lungs.[60,61] Bao et al[62] discovered that edaravone decreased the levels of pro-apoptotic (cleaved-caspase3) and inflammatory (IL-1β) proteins and suppressed the hyperoxia-induced inflammatory response and apoptosis in the lungs of a mouse model of HALI. Furthermore, edaravone reduced both the dry and wet specific gravity in the lungs, mitigated pathological alterations related to lung injury, and decreased lung compliance in the mice. Meanwhile, it was found that after hyperoxia-treated human alveolar epithelial cells and rats were given edaravone, edaravone reduced apoptosis, cellular lipid peroxidation, and oxidative DNA damage in lung epithelial cells; Edaravone significantly improved lung biochemical parameters and reduced mortality in hyperoxic injury models. Han et al[63] also showed that in rat HALI models, hyperoxia promotes the generation of large amounts of reactive oxygen species (ROS), leading to the activation of necrotic apoptosis. Additionally, administration of edaravone can decrease oxidative stress and apoptosis in the lungs by reducing the levels of malondialdehyde (MDA) in lung tissues and serum, enhancing the activity of SOD in lung tissues, decreasing the expression of necrotic apoptosis-associated proteins (RIP1, RIP3, MLKL), and inhibiting the interaction between RIP1 and RIP3. As a result, this treatment mitigates the characteristic alterations linked to lung injury. The findings indicate that edaravone effectively prevents the development of ALI caused by hyperoxia.

Smoke-Inhalation Lung Injury

Smoke-inhalation lung injury refers to the inhalation of hazardous gasses released during the combustion of toxic materials. These small molecules travel through the air passages and enter the lungs, causing harm to the lung tissue and leading to the buildup of significant quantities of protein-rich substances and inflammatory agents in the alveolar space. This finally results in the development of pulmonary edema and ALI.[64] The death of lung cells, heightened production of inflammatory agents, and oxidative stress characterize smoke inhalation lung injury. Inhibiting these pathways can effectively mitigate the severity of lung injury caused by smoke inhalation. Guo et al[65] found that edaravone combined with flumethasone reduced the expression of apoptosis-related proteins (caspase-3, caspase-9) and the cleavage of poly ADP-ribose polymerase (PARP) in lung tissues, together with inhibiting smoke-induced apoptosis of lung cells and reversing smoke-induced mitochondrial dysfunction in the lungs, as well as ROS generation, loss of the mitochondrial membrane potential and cytochrome C, and the early release of apoptosis-inducing factors, thereby reducing smoke-induced lung injury in the rats. Xiao et al[66] constructed a rat model of smoke inhalation lung injury for control experiments. It was discovered that the level of miR-320 expression in the serum decreased significantly following advanced nebulization and inhalation of edaravone. There is a positive relationship between the levels of miR-320 and the production of the inflammatory factor TNF-α in the lungs. When miR-320 is down-regulated, it can prevent the release of inflammatory factors from the lungs. As a result, this reduces the serum inflammatory oxidative stress indices that were elevated due to smoke inhalation and improves overall lung function. Furthermore, the application of edaravone resulted in notable enhancements in the lung damage of rats exposed to smoke inhalation, as demonstrated by the hematoxylin and eosin (HE) staining. This indicates that edaravone has the potential to serve as a prophylactic medication for smoke inhalation-induced lung injury. A recent study has demonstrated that edaravone effectively decreases the release of inflammatory factors and oxidative stress in the lungs of rats by inhibiting the Notch pathway. This leads to improved lung function and relief from lung injury induced by inhaling smoke.[67]

Septic Lung Injury

Septic lung injury occurs when several pathogenic bacteria invade and multiply in the lungs, causing an acute inflammatory reaction. Inflammation in the pulmonary vasculature leads to increased permeability and decreased osmolality of the plasma, resulting in the leakage of significant quantities of inflammatory exudates from the lungs. This leads to the formation of pulmonary edema, which can result in respiratory failure or, in severe cases, the death of the patient.[68] Zhang et al[54] found that both edaravone and compound edaravone reduced the production of interleukin-6

(IL-6) and expression of cyclooxygenase-2 (COX-2) in lipopolysaccharide (LPS)-induced murine monocyte-macrophage leukemia cells (RAW264.7 cells) in in vitro experiments. In contrast, the results of animal experiments showed that intravenous injection of compound edaravone after intratracheal instillation of LPS in mice reduced LPS-induced lung injury, including histological abnormalities associated with polymorphonuclear leukemia. Daravon attenuated LPS-induced lung injury, including lung histological abnormalities, polymorphonuclear leukocyte infiltration, and exudation, and suppressed LPS-induced elevation of TNF-α and IL-6 in the serum and bronchoalveolar lavage fluid (BALF), as well as the activation of NF-κB and COX-2 expression in mouse lung tissue. Tajima et al[69] discovered that edaravone reduced the levels of albumin, pro-inflammatory factors, keratinocyte-derived chemokine (KGF-2), and macrophage inflammatory protein (MIP-2) in the BALF and suppressed inflammatory responses in the lungs in a mouse model of septic lung injury. Furthermore, in an in vitro cellular assay, co-incubation of mouse alveolar macrophages (MH-S cells) with edaravone decreased the secretion of IL-6 (MH-S cells). These findings suggest that edaravone can prevent ALI by inhibiting the production of inflammatory factors by lung macrophages. Hence, the suppressive impact of edaravone on septic lung injury is apparent.

Paraquat-Toxicity Lung Injury

Paraquat-toxicity lung injury is a condition in which patients who have accidentally or deliberately ingested paraquat (PQ) develop acute pulmonary fibrosis and lung injury, potentially resulting in death due to respiratory failure.[70] The presence of the inflammatory response in the lung, along with pulmonary fibrosis and oxidative stress, are significant factors contributing to mortality caused by paraquat.[71] Shokrzadeh et al[72] discovered that edaravone effectively prevented the production of ROS generated by PQ in A549 cells. Moreover, it protects against oxidative stress damage and cytotoxicity. In animal studies, edaravone mitigated the PQ-induced reduction in lung mitochondrial viability, and reduced ROS production in isolated lung mitochondria, thereby reducing the toxic effects of PQ on the lung. An in vitro model was created in a study where A549 cells were treated with PQ. The study indicated that PQ caused an increase in oxidative stress in the cells, which was accompanied by lipid peroxidation. Edaravone effectively scavenged ROS, hence reducing the lung injury caused by paraquat. Meanwhile, an evaluation of edaravone efficacy in the rat paraquat toxic lung-injury model showed that the drug could reduce the levels of MDA, interleukin-6, TNF-α, and hydroxyproline (HYP) in both the lung tissue and BALF of the rats, together with increasing the levels of the antioxidants SOD and glutathione peroxidase (GSH-PX), reducing interstitial edema and inflammatory cell infiltration in the lungs, and halting the process of acute pulmonary fibrosis, thus alleviating the PQ-induced acute progressive lung injury.[73] A recent retrospective study involving 44 cases of paraquat poisoning demonstrated that edaravone effectively postponed the development of acute pulmonary fibrosis, diminished the histological alterations linked to lung injury, and extended the life periods of poisoned patients at 7 and 14 days. Collectively, these findings indicate that edaravone has the potential to impede lung injury caused by paraquat.[38]

Acute Drug-Induced Lung Injury

Medication-induced lung injury (MIPI) encompasses several conditions, namely drug-induced acute interstitial fibrosis, drug-induced mechanized pneumonia, and drug-induced hypersensitivity pneumonitis. The primary effect of drug-induced lung injury is the induction of inflammation and oxidative stress in the lungs.[74] Therefore, mitigating drug-induced lung injury involves suppressing inflammation and oxidative stress. In a bleomycin-induced mouse model of drug-induced lung injury, edaravone was found to inhibit ALI by reducing inflammatory cell and hydrogen peroxide production and inhibiting inflammatory factor release and oxidative stress in the mouse BALF.[69] In a bleomycin-induced rabbit model of acute drug-induced lung injury, edaravone attenuated acute inflammation, apoptosis, and pathological changes associated with lung injury resulting from bleomycin-induced production of ROS, suggesting that edaravone can help to prevent ALI induced by the production of ROS.[75] Bayrak et al also showed that in a rat model of ALI generated by valproate, edaravone decreased the level of total antioxidant status and the activities of SOD and GSH-PX in lung tissues. Edaravone's strong antioxidant qualities can effectively decrease the number of free radicals, hence reducing lung injury caused by oxidative stress.[76]

Ischemia-Reperfusion Lung Injury

Ischemia-reperfusion (IR) lung injury is a common clinical problem resulting from various causes, including extracorporeal circulation and lung transplantation.[77] Edaravone was discovered to suppress the inflammatory response and oxidative stress produced during ischemia-reperfusion lung damage. Ito et al[78] developed a rat model to simulate lung injury resulting from intestinal ischemia-reperfusion to conduct a controlled experiment. After edaravone treatment, the model rats showed reduced levels of neutrophil infiltration, membrane lipid peroxidation, and IL-6 mRNA expression in the lungs after intestinal ischemia-reperfusion in the rats, thereby reducing lung injury by inhibiting inflammation. At the same time, the mortality of the rats was reduced. An assessment of the effectiveness of the rabbit ischemia-reperfusion lung injury model revealed that administering edaravone beforehand could decrease the generation of ROS-HR and MDA in lung tissue, enhance the functioning of GSH-PX and SOD in the lungs, and prevent the decrease in mitochondrial membrane potential (from 60% to 14%) and mitochondrial swelling caused by ischemia-reperfusion.[79] Therefore, it can be inferred that edaravone can mitigate lung mitochondrial damage caused by IR in young rabbits. Lung transplantation can be complicated by ischemia-reperfusion injury to the lung during the initial stage of transplantation. An isolated lung injury model was constructed in rats. The early administration of edaravone was found to reduce the wet-dry specific gravity of the lung, as well as protein in the alveolar lavage fluid, and the MPO activity, as well as decreasing ROS production, preventing the activation of PLA2 and its downstream cascade, and suppressing oxidative stress and the inflammatory response in the lung, thus reducing the degree of lung injury.[80] Uchiyama et al[81] demonstrated that edaravone decreased the dry and wet specific gravity and MDA levels in rat lungs. Furthermore, it mitigated lung injury resulting from oxidative stress in the lungs following liver reperfusion. More importantly, edaravone prevented lung injury caused by hepatic ischemia-reperfusion. A recent study also found that in a model of lung injury induced by ischemia-reperfusion in the hindlimbs of adult male rats, edaravone reduced neutrophil infiltration in the lungs, as well as reducing the levels of cyclooxygenase, NF-κB activation, and nitric oxide synthase, thereby reducing the inflammatory response and oxidative stress in the lungs. Edaravone was also observed to reduce the rupture of alveolar structures induced by ischemia-reperfusion and inhibited the development of pathological changes in the lung structure.[53]

Acute Pancreatitis Lung Injury

Acute pancreatitis lung injury is a lung injury induced by severe pancreatitis, with both oxidative stress and the inflammatory response being the causative factors of the injury.[82] Thus, inhibition of oxidative stress and the inflammatory response can mitigate this type of lung injury.[83] Yang et al[84] found that edaravone reduced elevated MDA and lung inflammatory factor (IL-6, TNF-α) mRNA levels in the lungs of rat models of acute pancreatitis by reducing both oxidative stress and inflammation and thus reducing lung damage. Meanwhile, a retrospective study conducted by Zhang et al[85] demonstrated that the combination of edaravone and ustekin in the treatment of severe pancreatitis resulted in several positive outcomes. These included a reduction in respiratory symptoms such as chest tightness and difficulty breathing, improvement in respiratory rate and oxygenation index, decrease in serum levels of inflammatory factors, alleviation of lung imaging abnormalities, mitigation of lung injury, and a shorter duration of illness with improved patient tolerability. A recent systematic review of 48 patients with severe pancreatitis combined with ALI also showed that edaravone in combination with temprosan had an overall efficacy rate of 96.4% in the treatment of severe pancreatitis, with edaravone improving the respiratory rate, blood gas index, and oxygenation, and significantly reducing the incidence of ARDS, MODS, and morbidity and mortality.[86]

Seawater-Drowning Lung Injury

In terms of seawater-drowning lung injury, edaravone was found in a rat model of seawater-drowning lung injury to inhibit the infiltration of inflammatory cells in the lungs, down-regulate the expression of pro-inflammatory factors (IL-6, TNF-α) and up-regulate the expression of anti-inflammatory factors (IL-10) in the serum and inhibit inflammatory reactions in the lungs. Edaravone was discovered to prevent the development of pulmonary edema by reducing alveolar capillary permeability, modulating the distribution of water in the lungs, and decreasing the levels of AQP1 and AQP5,

thereby inhibiting the development of pulmonary edema. In conclusion, it can be inferred that edaravone has the potential to prevent ALI, which is the result of water drowning.[87]

Other Types of Acute Lung Injury

Research has demonstrated that edaravone not only protects against the several forms of ALI mentioned before, but it also can treat additional forms of ALI. A clinical systematic review study involving 38 patients with severe COVID-19 found that edaravone effectively decreased the requirement for mechanical ventilation and the duration of intubation in patients with severe COVID-19 after being admitted to the ICU.[88] Furthermore, a recent systematic review found that edaravone, if given on time, could significantly reduce lung, liver, kidney, and other organ damage, as well as the incidence of complications and mortality in critically ill patients with COVID-19.[89]

Wan et al[55] discovered that in a mouse model of lung injury caused by hypoxic pulmonary hypertension, edaravone can decrease the levels of pro-inflammatory cytokines TNF-α and IL-6 in the blood and prevent lung inflammation. Furthermore, it can reduce the thickness of pulmonary artery walls, prevent lung cell death, reduce oxidative stress, and alleviate the pathological changes associated with lung injury. As a result, it effectively reduces lung injury caused by hypoxic pulmonary hypertension.

In terms of traumatic lung contusion, a systematic review of 96 patients with severe lung contusion found that edaravone combined with temprosan reduced the expression of high-mobility group protein B1 (HMGB1), soluble E-selectin (sE-selectin), and soluble leukocyte differentiation antigen 14 (sCD14), thus improving both lung compliance and ventilation, demonstrating significant efficacy in alleviating severe lung contusion.[90] Furthermore, Qiao et al[91] conducted a comprehensive analysis of 100 patients with a traumatic wet lung. They found that edaravone had a significant positive impact on the patient's oxygen metabolism and pulmonary inflammatory response. It also effectively reduced oxidative stress levels and the severity of pulmonary contusion. Moreover, edaravone shortened the deactivation time, decreased the length of ICU stay, and improved the overall prognosis of the patients.

A mouse model of detonation lung injury was utilized to investigate the effects of edaravone. The study found that edaravone was able to decrease both pulmonary edema and damage to the alveolar structure induced by the detonation. Edaravone could inhibit NF-κB signal transduction and the release of pulmonary inflammatory factors and reduce the degree of lung injury. Edaravone can also inhibit ALI caused by knock injuries by mitigating anti-oxidative stress.[92]

Prospects, Summary, and Shortcomings

Despite global progress in diagnosing and treating ALI, effectively managing this condition remains difficult, resulting in an uncertain future and high mortality rates.[1–3] Presently, the main emphasis of therapies is on alleviating symptoms, but this approach fails to tackle the root causes and frequently leads to unsatisfactory therapeutic results.[21] The major obstacle lies in the lack of effective drugs. To tackle this challenge, the strategy of drug repurposing has emerged as a promising method of developing medications for ALI. This method leverages existing drugs with established clinical use, high safety profiles, and widespread acceptance, potentially reducing drug development time and research costs.

Edaravone is a thoroughly investigated therapeutic drug that has demonstrated promising results in the treatment of neurological diseases such as acute stroke and amyotrophic lateral sclerosis, making it a valuable tool for brain preservation.[44,45] The etiology of ALI is intimately associated with apoptosis, oxidative stress, inflammation, and fibrosis. Numerous studies, both in basic experimental researches and clinical settings, have investigated the use of edaravone in mitigating these mechanisms in the context of ALI. These studies have demonstrated that edaravone, whether used alone or in combination with other medications, can effectively suppress oxidative stress, apoptosis, inflammation, and fibrosis associated with ALI (Figure 2). As a result, edaravone not only reduces the risk of ALI but also lessens the disability and mortality rates associated with lung injury.

On the other hand, edaravone has the potential to serve as a preventative treatment. Studies conducted on septic lung injury and acute drug-induced lung injury models have shown that early administration of edaravone can significantly reduce the severity of lung injury, exerting a preventive effect.[69,76,79] Prophylactic drugs for ALI are currently lacking in the medical community. As a result, this research emphasizes edaravone's potential as a preventive measure for ALI, providing novel perspectives for the development of lung injury prevention plans.

However, the current state of research on the use of edaravone to treat ALI is restricted to basic experimental cellular and animal investigations, with very few retrospective clinical studies. Furthermore, the use of edaravone is not supported by more pertinent clinical studies or application evidence. Hence, to fully implement edaravone in clinical practice for treating ALI, it is necessary to conduct multi-phase clinical trials to validate its clinical effectiveness and potential drug risks. Meanwhile, This article has many limitations and deficiencies when assessing the therapeutic effects of edaravone on ALI. This report exclusively focuses on the pertinent research about the beneficial impacts of edaravone in the management of ALI. The approach fails to collect the relevant publications and reports regarding the detrimental effects of edaravone on ALI. In clinical application and related studies, edaravone was found to have specific side effects and adverse reactions, such as chest pain, cough, nausea, vomiting, rash, cardiac arrhythmia, neurological reactions, and other discomforts in some patients,[93] and also hepatic and renal failure, thrombocytopenia, granulocytopenia, rhabdomyolysis, shock, disseminated intravascular coagulation syndrome and severe allergic reactions.[93,94] The adverse reactions were associated with age and co-medication, with a significantly higher incidence of adverse reactions in elderly patients (>80 years) and those with >3 co-medications.[94,95] Hence, it is advisable to exercise caution or avoid using it altogether in high-risk patients who are elderly, have impaired hepatic or renal function, abnormal blood clotting, heart disease, or are allergic to edaravone. Furthermore, it is crucial to avoid any irrational combination of drugs and to monitor for any adverse reactions in future studies closely.

As a result, this review concludes that edaravone may be helpful in the treatment of ALI and offers fresh perspectives and recommended treatment avenues.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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