

# 学生代表性成果

## 1. 学生代表性论文



**In vitro/vivo antitumor study of modified-chitosan/carboxymethyl chitosan "boosted" charge-reversal nanoformulation**

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**Keywords:** Self-assembly; Charge-reversal; Polyelectrolyte-based nanoformulation; Chitosan; Antitumor nanomedicine

**ABSTRACT**

Major obstacle in the development of nanomedicine as efficient drug delivery systems are the rapid clearance from blood circulation and lysosomal entrapment. To overcome these problems, a polyelectrolyte-based core-shell type charge-reversible nanoformulation (CS-LA-DMAEMA-CMCK/PAMAM/DGDO) is constructed to improve antitumor efficacy of DOX. By applying carboxymethyl chitosan (CMCK) as bridge polymer and negatively charged chitosan-derivative as outer shell, the stability and pH-sensitivity of this nanoformulation is presumably enhanced. Furthermore, the positively charged PAMAM/DGDO could escape from lysosomes via "proton sponge effect" and "catanion-assisted interaction with lysosomal membrane". Adjustable cellular uptake and high apoptosis levels are demonstrated in this study. *In vivo* assay demonstrates that CS-LA-DMAEMA-CMCK/PAMAM/DGDO was internalized into H1292 cells preferentially via the catanion-mediated endocytosis pathway. Interestingly, *in vivo* studies showed that high accumulation of CS-LA-DMAEMA-CMCK/PAMAM/DGDO in tumor tissue led to enhanced tumor inhibition. Compared with free DOX, the tumor inhibition rate of nanoformulation was improved up to 220%.

**1. Introduction**

The ideal antitumor nanomedicine for nanoscale drug delivery of therapeutic agents should be stable in systemic circulation, as well as their therapeutic effect could be completely exerted to kill the tumor cells and inhibit the tumor growth. However, one important challenge facing nano-drug delivery systems is their paradoxical behavior from initial administration to uptake by tumor cells. For example, cationic nanoparticles display high cellular uptake due to the enhanced interaction with tumor cells (Luo et al., 2013). At the same time, they also have strong nonspecific binding with plasma proteins, thus can be easily cleared by reticuloendothelial system (RES) (Chen et al., 2017; Han & Juliano, 2012; Mahesh et al., 2018). In order to optimize the properties of nanomedicine to anti-tumor drug delivery and improve the antitumor therapeutic efficacy, charge-reversal strategies are introduced. The

purpose of charge-reversal strategy is to prolong the circulation time and reduce the nonspecific toxicity of antitumor nanomedicine by shielding the positive charge of nanomedicine during systemic circulation, but reverse the surface charge to positive to facilitate cell internalization in response to specific stimulus, including pH, redox, and enzymes, etc. (Liu et al., 2012; Liu et al., 2017; Sun et al., 2019; Li et al., 2017). Among all the biological stimuli, pH is mostly utilized to regulate the charge-reversal behavior of nanomedicine based on the difference in pH between the external and internal tumor environment. Particularly, the tumor extracellular microenvironment is more acidic (pH 6.5–7.2) than physiological blood environment (pH 7.4), and pH value of endo-lysosomes is even lower (pH 4.5–5.0). To achieve rapid pH-triggered charge conversion, available linkers are extensively used, such as hydrazone bonds, imine bonds, amide bonds, oxime bonds, ester

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**ARTICLE INFO**

**Keywords:** Anti-inflammatory activity; Inflammation; Retinopathy

**ABSTRACT**

Acute lung injury (ALI) presents a significant clinical challenge due to its high mortality rates and the lack of effective treatment strategies. The most effective approaches to treating ALI include disrupting inflammatory cascades and associated inflammatory damage within the lung. Hederagonic acid (HA) is a novel alkaline design and synthesis of 3 hederagonic acid derivatives. Among these derivatives, compound 29 demonstrated potent anti-inflammatory activity without inducing cytotoxicity. Inhibiting nitric oxide (NO) release by 76–86 % (inverted dose-response relationship studies) and the reverse of nitric oxide (NO) release revealed that compound 29 exhibits a high affinity for the iNOS protein. Mechanistic studies revealed that compound 29 suppresses ionophore activation, inhibits the nuclear translocation of NF- $\kappa$ B and p65, and disrupts the TNF- $\alpha$ /NF- $\kappa$ B signaling pathway, thereby attenuating the inflammatory response. *In vivo* administration of compound 29 was sufficient to protect against lipopolysaccharide (LPS)-induced ALI by suppressing the production of inflammatory mediators, including IL-6, TNF- $\alpha$ , and IPNV, thereby preserving lung tissue integrity. These results substantiate the anti-inflammatory efficacy of compound 29, both *in vitro* and *in vivo*, indicating its potential as a promising lead compound in ALI treatment strategies.

**1. Introduction**

Acute lung injury (ALI) is a severe respiratory condition characterized by rapid onset, diffuse alveolar damage, and persistent hypoxemia, often progressing to acute respiratory distress syndrome (ARDS) and potentially resulting in fatal respiratory failure. Due to its lack of effective treatment strategies, ALI continues to be a leading cause of mortality in critically ill patients [1]. Epidemiologic studies estimate that 1 million individuals throughout the globe are diagnosed with ALI annually, accounting for 10 % of all patients receiving intensive care unit (ICU) care, with mortality rates that range from 30 to 50 % [2]. Although direct lung injury or systemic damage can trigger ALI, the disease progression is chiefly driven by an excessive and uncontrolled inflammatory response. ALI is

characterized by the pulmonary infiltration of large numbers of immune cells, which secrete pro-inflammatory cytokines and thereby induce an inflammatory cascade response, ultimately compromising the integrity of the alveolar-capillary barrier integrity, increasing the permeability of the lung tissue and causing increasingly severe pulmonary edema. The administration of anti-inflammatory agents early during the process thus represents a promising approach to mitigating ALI-associated pulmonary damage.

Stimulation of endoplasmic stress (ER) is a stimulatory molecular signaling on the endoplasmic reticulum (ER) that can trigger the activation of an innate immune response when activated by cyclic guanosine monophosphate (cGMP)-adenosine triphosphate (cAMP), which is a pattern recognition receptor that primarily functions by detecting abnormal

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**ARTICLE INFO**

**Keywords:** Retinal ischemia-reperfusion injury; Keap1/Nrf2/ARE signaling pathway; Oxidative stress; Inflammation

**ABSTRACT**

Retinal ischemia-reperfusion (RIR) injury is a condition in which further retinal damage occurs in areas of reperfusion after ischemia, which can lead to retinal ganglion cell (RGC) death, severe retinal degeneration, and potential vision loss.<sup>1–3</sup> RIR injury is a common pathophysiological process associated with various ophthalmic diseases, such as retinal arteriovenous occlusion, diabetic retinopathy, and glaucoma; it is a leading cause of visual impairment and blindness worldwide.<sup>4–6</sup> RIR injury increases the levels of reactive oxygen species (ROS), which can directly damage cells and trigger inflammatory processes.<sup>7–9</sup> There is increasing evidence that ROS-induced oxidative stress and inflammation are key causes of retinal damage.<sup>10–12</sup> Therefore, an in-depth understanding of intrinsic mechanisms for regulation of oxidative stress in retinal tissues is urgently needed to develop safe and effective treatments for RIR injury.

Activation of the Keap1/Nrf2/ARE signaling pathway, a major endogenous intracellular antioxidant pathway,<sup>13</sup> promotes the expression of downstream antioxidant stress enzymes and attenuates oxidative stress damage.<sup>14,15</sup> Nuclear factor erythroid 2-related factor 2 (Nrf2) is a key regulator of multiple cytoprotective responses.<sup>11</sup> Under physiological conditions, Nrf2 is located in the cytoplasm and bound to its specific inhibitory receptor, Kelch-like ECH-associated protein 1 (Keap1); this binding interaction promotes Nrf2 ubiquitination and subsequent degradation by the 26S proteasome.<sup>16,17</sup> In

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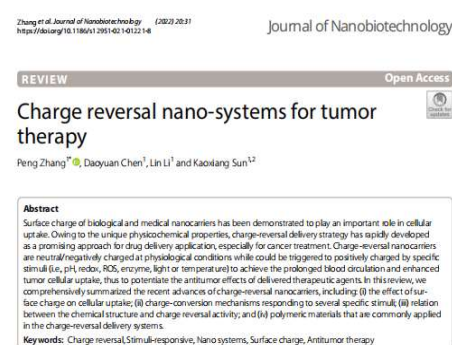
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**Charge reversal nano-systems for tumor therapy**

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**Abstract**

Surface charge of biological and medical nanocarriers has been demonstrated to play an important role in cellular uptake. Owing to the unique physicochemical properties, charge-reversal delivery strategy has rapidly developed as a promising approach for drug delivery application, especially for cancer treatment. Charge-reversal nanocarriers are neutral/negatively charged at physiological conditions while could be triggered to positively charged by specific stimuli (i.e., pH redox, ROS, enzyme, light or temperature) to achieve the prolonged blood circulation and enhanced tumor cellular uptake, thus to potentiate the antitumor effects of delivered therapeutic agents. In this review, we comprehensively summarized the recent advances of charge-reversal nanocarriers, including (i) the effect of surface charge on cellular uptake; (ii) charge-conversion mechanisms responding to several specific stimuli; (iii) relation between the chemical structure and charge reversal activity; and (iv) polymeric materials that are commonly applied in the charge-reversal delivery systems.

**Keywords:** Charge reversal; Stimuli-responsive; Nano systems; Surface charge; Antitumor therapy

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**Ocotillo Derivatives Mitigate Retinal Ischemia-Reperfusion Injury by Regulating the Keap1/Nrf2/ARE Signaling Pathway**

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**Abstract:** Retinal ischemia-reperfusion (RIR) injury can lead to various retinal diseases. Oxidative stress is considered an important pathological event in RIR injury. Here, we designed and synthesized 34 ocotillo derivatives, then examined their antioxidant and anti-inflammatory capacities; we found that compounds 7 (C34-R) and 8 (C24-S) were most active. To enhance their water solubility, sustained release, and biocompatibility, compounds 7 and 8 were encapsulated into liposomes for *in vivo* activity and mechanistic studies. *In vivo* studies indicated that compounds 7 and 8 protected normal retinal structure and physiological function after RIR injury, reversed damage to retinal ganglion cells, and the C configuration exhibited significantly stronger activity compared with the R configuration. Mechanistic studies showed that compound 8 exerted a therapeutic effect on RIR injury by activating the Keap1/Nrf2/ARE signaling pathway; compound 7 did not influence this pathway. We also demonstrated that differential isomerization at the C-24 position influenced protection against RIR injury.

**1. INTRODUCTION**

Retinal ischemia-reperfusion (RIR) injury is a condition in which further retinal damage occurs in areas of reperfusion after ischemia, which can lead to retinal ganglion cell (RGC) death, severe retinal degeneration, and potential vision loss.<sup>1–3</sup> RIR injury is a common pathophysiological process associated with various ophthalmic diseases, such as retinal arteriovenous occlusion, diabetic retinopathy, and glaucoma; it is a leading cause of visual impairment and blindness worldwide.<sup>4–6</sup> RIR injury increases the levels of reactive oxygen species (ROS), which can directly damage cells and trigger inflammatory processes.<sup>7–9</sup> There is increasing evidence that ROS-induced oxidative stress and inflammation are key causes of retinal damage.<sup>10–12</sup> Therefore, an in-depth understanding of intrinsic mechanisms for regulation of oxidative stress in retinal tissues is urgently needed to develop safe and effective treatments for RIR injury.

Activation of the Keap1/Nrf2/ARE signaling pathway, a major endogenous intracellular antioxidant pathway,<sup>13</sup> promotes the expression of downstream antioxidant stress enzymes and attenuates oxidative stress damage.<sup>14,15</sup> Nuclear factor erythroid 2-related factor 2 (Nrf2) is a key regulator of multiple cytoprotective responses.<sup>11</sup> Under physiological conditions, Nrf2 is located in the cytoplasm and bound to its specific inhibitory receptor, Kelch-like ECH-associated protein 1 (Keap1); this binding interaction promotes Nrf2 ubiquitination and subsequent degradation by the 26S proteasome.<sup>16,17</sup> In

response to oxidative stress, Nrf2 dissociates from Keap1 and translocates to the nucleus, where it binds to the antioxidant response element (ARE) and activates downstream antioxidant genes, such as heme oxygenase (HO-1), NAD(P)H dehydrogenase (quinone) 1 (NQO1), and glutathione S-transferase (GST) (epoxide) 1 (GSTA1), and glutathione S-transferase (GST) (omega) 1 (GSTO1). Nrf2 exhibits ubiquitous expression in various retinal cell types and protects those cells from oxidative stress.<sup>18</sup> Therefore, Nrf2 activation has become a promising target for treatments for RIR injury.

Natural products have a long history of serving as major sources of new drugs,<sup>19–21</sup> because of their wide ranges of pharmacological activities and good safety profiles. Natural products have attracted attention as candidates for therapies targeting Nrf2 activation.<sup>22–24</sup> For example, the interphenyl barbiturate methyl (CDDO-Me) (Figure 1) and its analogs, which inhibit Nrf2 ubiquitination by reacting with the a sulphydryl group in Keap1 to activate Nrf2 and induce the expression of cytoprotective factors,<sup>25</sup> have been extensively explored in clinical trials as treatments for kidney diseases.<sup>26–28</sup>

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2. 学生代表性发明专利

