

# Inflamed Tissue-Targeting Polyphenol-Condensed Antioxidant Nanoparticles with Therapeutic Potential

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Inflammation is essential for pathogen eradication and tissue repair; However, chronic inflammation can bring on multi-organ dysfunction due to an overproduction of reactive oxygen species (ROS). Among various anti-inflammatory agents, polyphenol-based nanotherapeutics offer potential advantages, including enhanced stability, targeted delivery, multiple therapeutic functions, and personalized therapy tailored to the severity. Despite these advantages, the development of biocompatible nanomedicines capable of selective accumulation in inflamed tissues and efficient inhibition of ROS-induced inflammatory signaling pathways remains a considerable challenge. In this study, a novel anti-inflammatory nanotherapeutic is engineered through the temperature-dependent condensation of polyphenolic catechin facilitated by hydrothermal reactions. The resulting catechin-condensed nanotherapeutic (CCN150), synthesized at a relatively low temperature, retains physicochemical and functional properties akin to its precursor, catechin, but with a marked enhancement in water solubility. CCN150 protects cells from oxidative stress by eliminating intracellular ROS and augmenting antioxidant enzymes. In vivo studies reveal that intravenously administered CCN150 predominantly accumulates in inflamed tissues, with minimal distribution to healthy regions. Furthermore, CCN150 effectively reduces systemic inflammation in mouse models by disrupting the cycles of ROS instigated by a pro-inflammatory oxidative milieu. Exhibiting negligible toxicity, CCN150 holds substantial promise for extensive therapeutic applications in the treatment of various ROS-mediated inflammatory diseases.

## 1. Introduction

Inflammation, a complex immune response to harmful stimuli, is beneficial in clearing pathogens and regenerating tissue. However, sustained production of pro-inflammatory mediators can induce oxidative stress within cells and tissues.<sup>[1,2]</sup> This stress arises from an imbalance in redox cycles, increasing reactive oxygen species (ROS) levels due to a dysfunctional antioxidant defense system.<sup>[3]</sup> Excessive ROS accumulation can cause uncontrolled inflammation by damaging cellular components and releasing pro-inflammatory cytokines.<sup>[4,5]</sup> This interplay between inflammation and oxidative stress can lead to chronic inflammatory conditions linked to diseases such as atherosclerosis, sepsis, rheumatoid arthritis, cancer, type 2 diabetes, and inflammatory bowel diseases.<sup>[6–11]</sup> Antioxidants are being explored as potential therapeutics to neutralize excessive ROS and mitigate pathological inflammation.

Recent strides in nanotechnology have yielded promising nanotherapeutics that modulate disease microenvironments.<sup>[12–15]</sup> A variety of anti-inflammatory nanotherapeutics, including nanoceria,<sup>[16]</sup> metal oxides,<sup>[17]</sup> carbon-based

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