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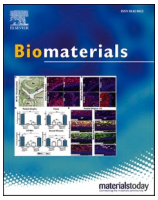

$CaCO_3$ nanoparticles incorporated with KAE to enable amplified calcium overload cancer therapy

Yonglu Li [a,b,c,d], Su Zhou [a,b,c,d], Haizhao Song [e], Ting Yu [a,b,c,d], Xiaodong Zheng [a,b,c,d,**], Qiang Chu [a,b,c,d,*]

[a] Department of Food Science and Nutrition, Zhejiang University, Hangzhou, 310058, People's Republic of China
[b] Zhejiang Key Laboratory for Agro-food Processing, Zhejiang University, Hangzhou, 310058, People's Republic of China
[c] Fuli Institute of Food Science, Zhejiang University, Hangzhou, 310058, People's Republic of China
[d] National Engineering Laboratory of Intelligent Food Technology and Equipment, Zhejiang University, Hangzhou, 310058, People's Republic of China
[e] College of Food Science and Engineering, Nanjing University of Finance and Economics, Nanjing, 210046, People's Republic of China

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ABSTRACT

Calcium overload therapy has attracted widespread attention in oncological field, whereas its efficacy has been limited due to insufficient calcium ions in tumor site and poor efficiency of calcium entering tumor, resulting in dissatisfied therapeutic effect. Kaempferol-3-O-rutinoside (KAE), a biosafe flavone with excellent anti-cancer ability, can effectively disrupt calcium homeostasis regulation and facilitate calcium influx, while calcium carbonate ($CaCO_3$) serves as an ideal calcium ions supplier. Inspired by these concepts, KAE loaded into $CaCO_3$ nanoparticles and incorporated with the cancer cell membrane (M) for synergistic tumor therapy. In this therapeutic platform (M@$CaCO_3$@KAE), membrane coating ensures targeted delivery of $CaCO_3$@KAE. Upon reaching tumor, $CaCO_3$@KAE specifically responds to tumor microenvironment, consequently releases KAE and calcium ions. KAE effectively breaks the calcium balance, while calcium ions remarkably aggravate and magnify KAE-mediated calcium overload. Accordingly, mitochondrial structure and functions are destructed, causing cytoskeleton collapse and oxidative stress, leading to cancerous cellular apoptosis. With the combined and cascaded efficacy, considerable *in vitro* and *in vivo* tumor inhibition was achieved by M@$CaCO_3$@KAE. This study provides an alternative nano-system, acting as a biomimetic calcium bomb, to ensure targeted, synergistic, efficient and biosafe calcium overload tumor therapy.

1. Introduction

Natural products have been long studied and confirmed with versatile bioactivities and low-toxicity [1–4]. Currently, natural phenols have been gradually applied into cancer therapy due to their outstanding anti-tumor property and potent biosafety. However, natural phenols face multiple problems during *in vivo* delivery, such as low solubility, poor oral bioactivity, weak availability and easy degradation, which severely limit their application during cancer prevention and medication [5–7]. Nevertheless, nanotechnology has provided possibilities to solve these obstacles. Song et al. loaded curcumin into methoxy poly (ethylene glycol)-b-poly (ε-caprolactone-co-p-dioxanone) copolymer micelles by solid dispersion method to form nanogels (30 nm), which significantly promoted the solubility of curcumin to 300 mg/mL [8]. Chung et al. used chitosan and γ-polyglutamic acid (γ-PGA) to prepare resveratrol-loaded NPs, which improved their solubility to > 153 μg/mL and UV stability >12% [9]. Therefore, reasonable design of nano-systems for phenols' entrapment and delivery can help overcome the challenges s of solubility, bioavailability and degradation *in vivo*.

Recent studies have uncovered that kaempferol-3-O-rutinoside (KAE) exerts excellent anti-cancer ability, as it is able to regulate calcium signaling pathway, disrupt calcium homeostasis and promote calcium influx to fulfill calcium overload-mediated apoptosis [10]. However, similar to most phenols, KAE also faces various deficiency during *in vivo* delivery, and it also remains challenging to achieve sufficient calcium ions supply and accumulation at tumor sites *in vivo*. Based on these circumstances, it is urgent to explore innovate strategy to prepare KAE-based nano-system for successful delivery and cancer

* Corresponding author. Department of Food Science and Nutrition, Zhejiang University, Hangzhou, 310058, People's Republic of China.
** Corresponding author. Department of Food Science and Nutrition, Zhejiang University, Hangzhou, 310032, People's Republic of China.
E-mail addresses: foodbiotech@zju.edu.cn (X. Zheng), 0619363@zju.edu.cn (Q. Chu).

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