Development of cross-linked tannic acid-based nanoparticle for lung cancer treatment

Rahul Tiwari
The University of Texas Rio Grande Valley, rahul.tiwari@utrgv.edu

Vivek K. Kashyap
The University of Texas Rio Grande Valley

Eswara Naga Hanuma Kumar Ghali
The University of Texas Rio Grande Valley

Subhash C. Chauhan
The University of Texas Rio Grande Valley

Murali M. Yallapu
The University of Texas Rio Grande Valley

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Tiwari R[1,2], Kashyap VK[1,2], GENH Kumar[1,2] Chauhan SC[1,2], Yallapu MM[1,2*]

[1]Department of Immunology and Microbiology, School of Medicine, University of Texas Rio Grande Valley, McAllen, TX, 78504, USA
[2]South Texas Center of Excellence in Cancer Research, School of Medicine, University of Texas Rio Grande Valley, McAllen, TX 78504, USA

Background: Lung cancer is a predominant cause of cancer-related morbidity and mortality across the world including in the United States. Treatment modalities for lung cancer include surgery, chemotherapy, radiotherapy, and/or targeted therapies depending on the cancer stage. Despite the survival benefits of chemotherapy, its value is offset by severe systemic side effects such as renal and/or hepatic toxicity or insufficient amounts of drug reaching to the target site. Such pitfalls can be handled by inhalable therapy which avoids first-pass metabolism and increases patients' compliance. In this study, we have investigated the inhalable therapy of cross-linked tannic acid-based nanoparticles (CTA NPs) into cancer cells and determined the synergistic effect of gambogic acid (GA) and gemcitabine (Gem)**.**

Methods: The CTA NPs formulations were characterized for particle size, chemical composition, and drug loading efficiency using various physicochemical methods (FT-IR, DSC, SEM, and TGA). Cellular uptake of CTA NPs was evaluated in lung cancer cell lines (A549 and NCI-H1299) using fluorescence microscopy and flow cytometry analysis. Further, the therapeutic efficacy of GA-Gem encapsulated CTA NPs (G-G CTA NPs) formulation was determined by various *in vitro* assays (CCK-8, mucoadhesion Boyden chamber, and apoptosis assays). The molecular effects of G-G CTA NPs formulation were also observed in lung cancer cell lines.

Results: Our novel CTA NPs formulation provided an average size of 110 nm in dynamic light scattering with a sustained release of the drug(s). CTA NPs formulation showed a remarkable mucoadhesion and mucopenetration penetration potential in-vitro model(s). Cellular uptake studies show that CTA NPs formulation allows for effective endosomal release into the cytosol. Additionally, the G-G CTA NPs formulation showed superior *in vitro* anti-cancer activity in lung cancer cells (A549 and NCI-H1299) compared to free drugs.

Conclusions: Taken together, our results demonstrate that G-G CTA NPs formulation exhibits superior anti-cancer potential than free drug against lung cancer and could be a novel therapeutic modality for the management of lung cancer.