**Infliximab-loaded Chunga Nanoparticles show enhanced efficacy in a 3D model of Inflammatory Bowel Disease**

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**Background:** Inflammatory Bowel Disease (IBD) is a chronic inflammatory condition affecting the gastrointestinal tract (GIT) of patients. Parenteral administration of anti-TNF-α mAbs has been described as the gold standard treatment for IBD; it is however limited by various side effects resulting from its route of administration. Recently, plant-derived exosome-like nanoparticles (PENs),have been explored for their potential as targeted drug delivery systems, in addition to their intrinsic biological activities. In this work, PENs were isolated for the first time from Chunga (*Caralluma edulis*), a succulent indigenous to Pakistan. The aim of this study was to formulate Chunga nanoparticles (ChNPs) with infliximab (I-ChNPs) characterize them and determine their anti-inflammatory effect on an inflamed 3D model of IBD.

**Methods:** Physicochemical properties of ChNPs and I-ChNPs were determined using Dynamic Light Scattering (DLS) and Scanning Electron Microscopy (SEM). Molecular characterization of ChNPs were also determined by miRNA library construction and lipidomics analysis. Confocal Laser Microscopy and Flow cytometry were used to determine the interaction between ChNPs and Caco-2 and THP-1 cells. A 3D model of IBD was constructed, with an inflamed Caco-2 monolayer in the apical compartment and inflamed THP-1 macrophages in the basolateral compartment. Transepithelial Electrical Resistance (TEER) monitoring and cytokine quantification were used to determine the anti-inflammatory effects of ChNPs and I-ChNPs.

**Results:** ChNPs of different average particle sizes (226.3 and 348.18 nm) were isolated. A significant increase in ChNPs particle size was observed after Infliximab loading. miRNA analysis predicted ChNP sequences that could be responsible for their anti-inflammatory properties. Inflamed 3D models treated with I-ChNPs had a higher increase in TEER (~73%) than those treated with infliximab only. The I-ChNP treated 3D system also showed a significant reduction in the secretion of pro-inflammatory cytokines by THP-1 macrophages in the basal compartment, indicating the transport and delivery of infliximab by ChNPs through the Caco-2 monolayer in the apical compartment.

**Conclusions:** Overall, this study showed that ChNPs can act as a nano-vector, while also contributing synergistically with loaded infliximab to enhance the efficacy of infliximab in the inflamed 3D cell model of IBD.

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