सी.एस.आई.आर. - हिमालय जैवसंपदा प्रौद्योगिकी संस्थान

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**Brief summary of the Research Work**

In our studies, we explored the interaction mechanism, complexation chemistry and characterization of inclusion complexes involving two bioactive flavonoids, genistein (GEN) and phloretin (PHL), with various β-cyclodextrin (β-CD) derivatives to enhance their solubility and therapeutic potential.

First, we successfully prepared inclusion complexes of GEN with hydroxypropyl-β-cyclodextrin (HP-β-CD) and methyl-β-cyclodextrin (M-β-CD) using the spray-drying technique. Phase solubility studies revealed a positive correlation between GEN solubility with β-CD derivatives, with a 1:1 stoichiometric ratio. The structural characterization through FT-IR, XRD, and SEM confirmed the encapsulation of GEN within the β-CD cavities, with SEM images showing no uncomplexed GEN, highlighting the efficiency of the spray-drying method. NMR spectroscopy provided insights into the molecular inclusion mechanism, showing that the hydroxyphenyl ring and chromone ring of GEN were respectively encapsulated within the M-β-CD and HP-β-CD cavities. Computational analysis, including molecular modelling and MD simulations, (first time for upto 1000 nanoseconds) further supported the experimental data, revealing stronger interactions and a more compact structure for the GEN/M-β-CD complex compared to the GEN/HP-β-CD complex.

In parallel, we addressed the solubility challenge of phloretin (PHL), a dihydrochalcone flavonoid, by forming an inclusion complex with sulfobutylether-β-cyclodextrin (SBE-β-CD, Captisol®). Phase solubility studies showed that SBE-β-CD had the highest apparent stability constant (Ks: 15,856 $M^{-1}$), indicating strong host-guest interactions. Solid-state characterizations (SEM, FT-IR, PXRD, DSC, TGA) provided direct evidence of complex formation. Detailed molecular interactions, examined via 1H NMR and 2D-NOESY, revealed that the aromatic phenyl ring of PHL was closely associated with the inner cavity of SBE-β-CD. The anticancer potential of the PHL/SBE-β-CD complex was evaluated in vitro using lung carcinoma (A549) and pancreatic cancer (MiaPaCa–2) cell lines, demonstrating significantly enhanced cytotoxicity compared to free PHL. The complex induced apoptosis through caspase 3/7 activation, reactive oxygen species generation, and mitochondrial membrane potential disruption. These results suggest that the SBE-β-CD complex is a promising vehicle for PHL delivery and could be extended to other hydrophobic bioactive molecules, broadening their application in the food and pharmaceutical industries.

Together, these studies underscore the potential of cyclodextrin-based inclusion complexes to enhance the solubility, stability, and bioactivity of flavonoids, paving the way for their broader application in functional foods, supplements, and therapeutic interventions.

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