Polyphenolic gallotannins inhibit amyloid aggregation and associated cytotoxicity primarily by interfering with secondary nucleation

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Amyloidoses result from protein misfolding and aggregation into insoluble amyloid deposits, impairing organ function. These deposits are linked to diseases like Alzheimer's, Parkinson's, and type 2 diabetes (T2DM). T2DM involves the pancreatic deposition of islet amyloid polypeptide (IAPP), a peptide hormone critical for glucose regulation. However, IAPP can misfold, forming cytotoxic aggregates in pancreatic islets and leading to β-cell dysfunction. Targeting IAPP aggregation is a promising treatment strategy for T2DM. Naturally occuring gallotannins are potential amyloid-aggregation inhibitors, although their effects are not fully understood. This study examines two gallotannins, corilagin and 1,3,6-tri-O-Galloyl-β-D-glucose (β-TGG), and their inhibitory effects on IAPP aggregation. Thioflavin T fluorescence, atomic force microscopy and circular dichroism showed that gallotannins delay IAPP self-assembly and reduce the length and quantity of amyloid fibrils. By monitoring cell metabolism, release of cytosolic enzymes and the production reactive oxygen species, we showed that corilagin protects INS-1E pancreatic cells against IAPP toxicity and plasma membrane damage. Peptide-gallotannin interactions were further investigated using all-atom explicit solvent molecular dynamic simulations, revealing hydrogen bonds and π-π stacking interactions. Overall, these experimental and computational findings highlight the potent anti-aggregative and cytoprotective properties of gallotannins, thus, potential candidates to prevent or modulate the progression of amyloidoses.