

Polyphenolic gallotannins 1,3,6-Tri-O-galloyl-β-D-glucose and corilagin attenuate IAPP amyloid formation and cytotoxicity by primarily targeting secondary nucleation

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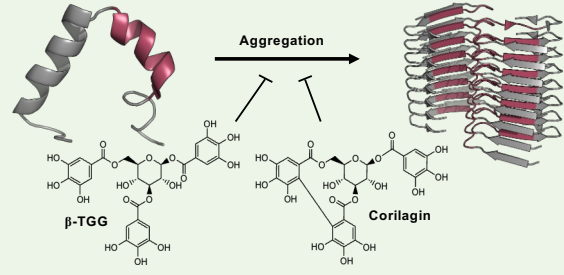
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CONTEXT

- Amyloidosis are a group of diseases characterized by the aberrant and cytotoxic aggregation of proteins and peptides into insoluble fibrils.
- Islet amyloid polypeptide (IAPP) is a hormone that aggregates in the pancreas, playing a role in type 2 diabetes (T2D) pathology.
- Polyphenolic gallotannins, a group of amyloid aggregation modulators, are natural molecules with many phenolic groups that confer antioxidant and anti-inflammatory properties. Despite their anti-aggregative potential, gallotannins effects on amyloid aggregation are still not fully elucidated, e.g., in the context of T2D and Alzheimer's Diseases.
- In this project, we investigated the effects of polyphenolic β-TGG and corilagin on IAPP aggregation and cytotoxicity, as well as the inhibitory mechanism underlying their action.

HYPOTHESIS



RESULTS

1. β-TGG and corilagin inhibit amyloid fibril formation

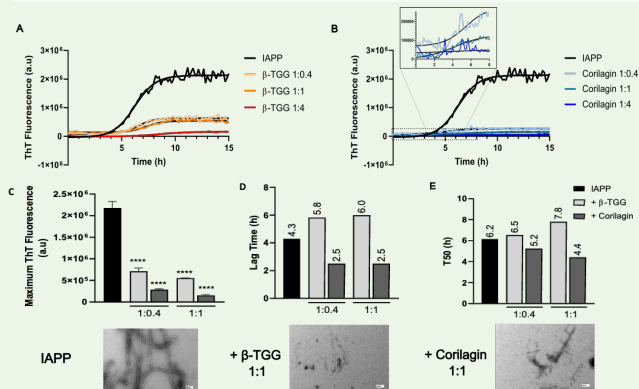


Figure 1. ThT kinetics of IAPP with A) β-TGG and B) corilagin at different IAPP:gallotannin ratios. C) Circular dichroism of IAPP at 0 hours and D) at 72 hours of incubation. E) TEM images of IAPP alone or with β-TGG and corilagin.

2. β-TGG and corilagin interact with IAPP mainly through hydrogen and hydrophobic bonds

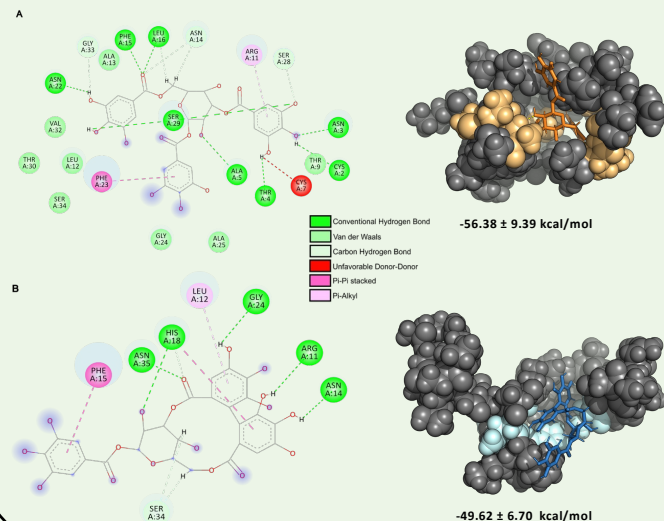


Figure 2. Two-dimensional interaction map after 2000 ns molecular dynamics simulations of IAPP with A) β-TGG and B) corilagin.

3. Corilagin has a cytoprotective effect against IAPP toxicity

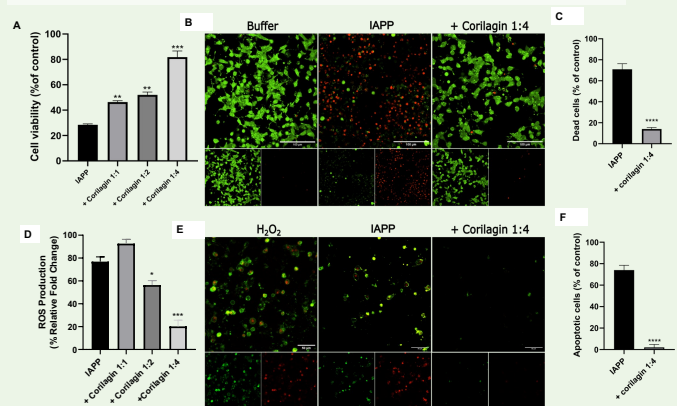


Figure 3. IAPP was pre-incubated at 25 μM alone or with corilagin at different IAPP:corilagin ratios during 3 hours before being applied on cells. A) resazurin assay on INS-1E pancreatic cells, B) DHE ROS assay on CHO-K1 cells, C) Live/Dead assay and D) Annexin V assay on INS-1E cells were done.

4. Corilagin mediates IAPP aggregation by targeting secondary nucleation

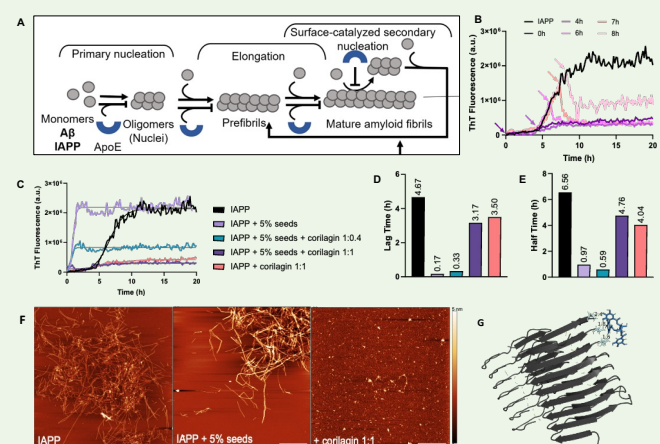


Figure 4. Mechanistic study of corilagin. A) Aggregation mechanism of IAPP to illustrate the targeted steps. ThT fluorescence was used to study the B) time-dependent effect of corilagin on IAPP aggregation and C) seeded kinetics of IAPP alone or in the presence of corilagin. D) Lag times and E) Half times were quantified. F) AFM images taken at the end of the kinetic assay in C).

CONCLUSIONS

- β-TGG and corilagin inhibit IAPP fibril formation, with corilagin showing a significantly better performance.
- Corilagin shows an important cytoprotective effect on INS-1E and CHO-K1 cells.
- Results suggest that corilagin mediates IAPP aggregation by targeting secondary nucleation and promoting off-pathway aggregation.

REFERENCES

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- Gharibyan AL, Wasana Jayaweera S, Lehmann M, Anan I, Olofsson A. Endogenous human proteins interfering with amyloid formation. *Biomolecules*. 2022 Mar 14;12(3):446.