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

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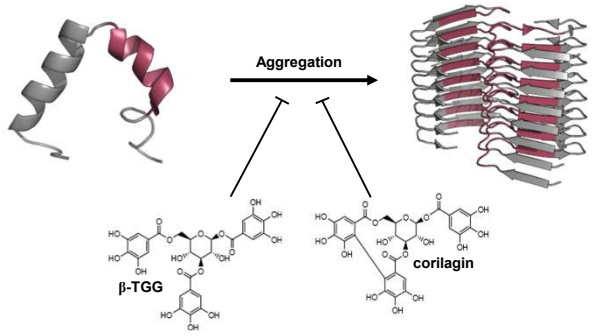
CONTEXT

- Islet amyloid polypeptide (IAPP) is a peptide hormone that forms toxic aggregates in the pancreas, playing a role in type 2 diabetes pathology.
- A group of amyloid aggregation modulators are polyphenols, natural molecules characterized by numerous phenolic groups, giving them important antioxidant and anti-inflammatory properties
- Gallotannins are polyphenols with a characteristic structure of a polyol core esterified with galloyl moieties. Despite their interesting anti-aggregative potential, gallotannins effects on amyloid aggregation are still not fully elucidated.
- In this project, we studied the effects of β-TGG and corilagin on IAPP aggregation and cytotoxicity and investigated the associated action mechanism.

HYPOTHESIS



RESULTS

1. β-TGG and corilagin inhibit amyloid fibril formation

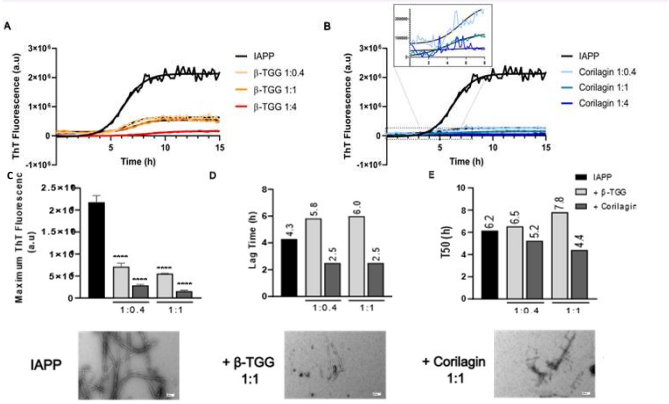


Figure 1. ThT kinetics of IAPP with A) β-TGG and B) corilagin at different IAPP:gallotannin ratios. C) Circular dichroism of IAPP at 0 hours and D) at 72 hours of incubation. E) TEM images of IAPP alone or with β-TGG and corilagin.

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

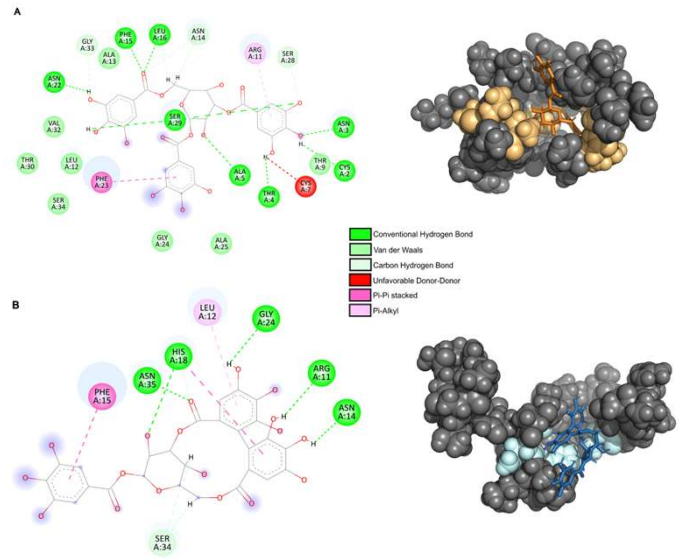


Figure 2. Two-dimensional interaction map after 2000 ns molecular dynamics simulations of IAPP with A) β-TGG and B) corilagin.

3. Corilagin has a cytoprotective effect against IAPP toxicity

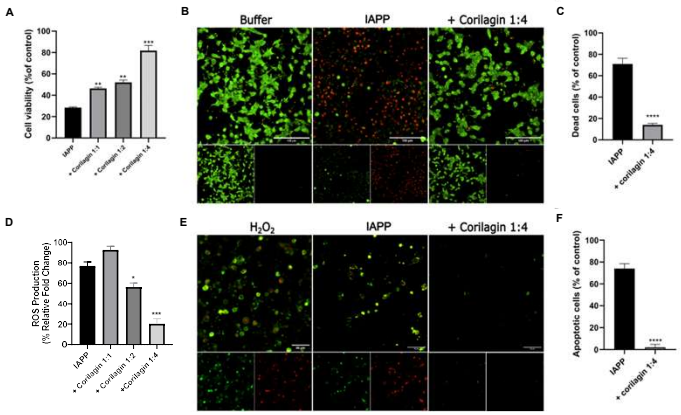


Figure 3. IAPP was pre-incubated at 25 µM alone or with corilagin at different IAPP:corilagin ratios during 3 hours before being applied on cells. A) resazurin assay on INS-1E pancreatic cells, B) DHE ROS assay on CHO-K1 cells, C) Live/Dead assay and D) Annexin V assay on INS-1E cells were done.

4. Corilagin mediates IAPP aggregation by targeting secondary nucleation

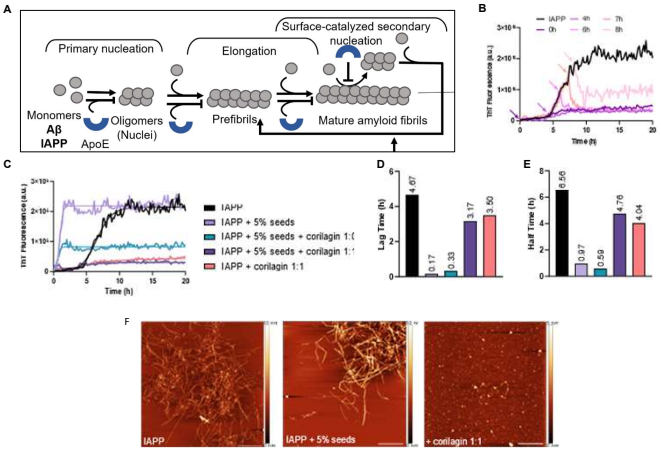


Figure 4. Mechanistic study of corilagin. A) Aggregation mehcanism of IAPP to illustrate the targeted steps. ThT fluorescence was used to study the B) time-dependent effect of corilagin on IAPP aggregation and C) seeded kinetics of IAPP alone or in the presence of corilagin. D) Lag times and E) Half 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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