Alternative Therapies for ATTR

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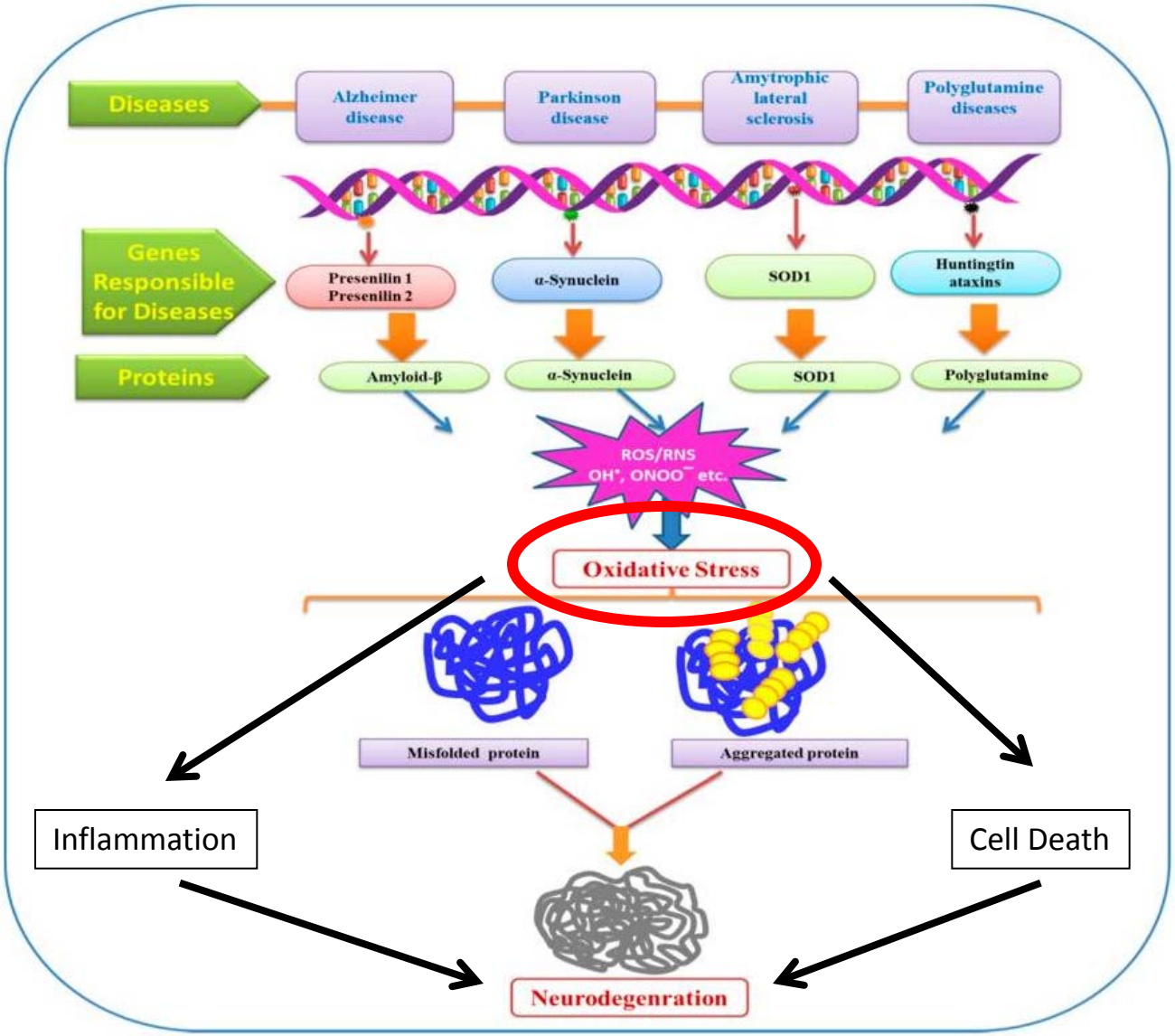
Biannual Amyloid Support Group Meeting
Chicago, IL
26 October 2019

Neurodegenerative Disease

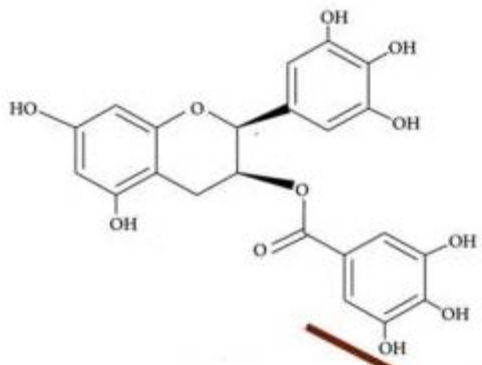


Singh A et al. Molecules. 2019;24(8):1583

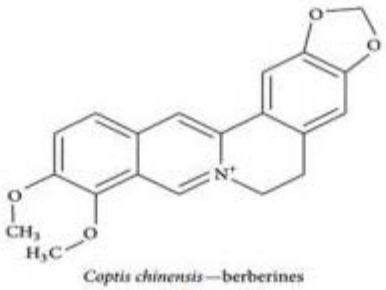
Polyphenolic Nutraseuticals

- Flavonoids
  - Vegetables, fruits, grains, bark , stems, teas, wine
- Effects on AD pathology
  - Limit oxidative injury
  - Inhibit Aβ fibril/aggregation, destabilize formed Aβ
  - Inhibit killer cell activation
  - Increase cell survival signaling
- Curcumin (active spice of Tumeric)
- Resveratrol (grapes/wine)
- Epigallocatechin gallate (EGCG)

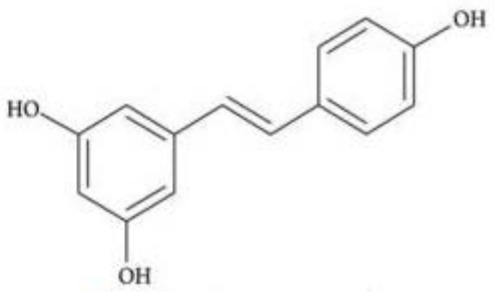
Phytochemical (herbal medicines)



Epigallocatechin-3-galate

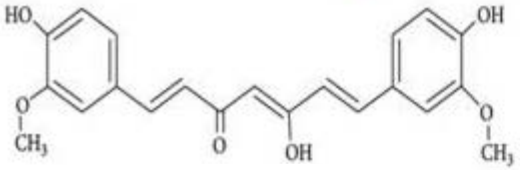


Coptis chinensis—berberines

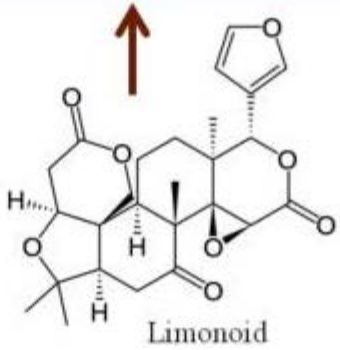


Resveratrol

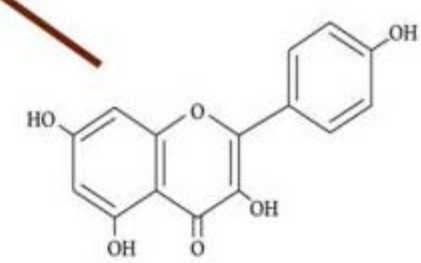
Neurogenerative Disease



Curcumin

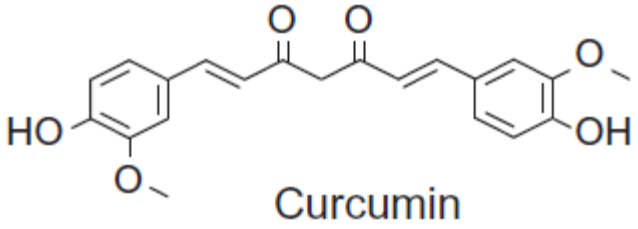


Limonoid



Quercetin

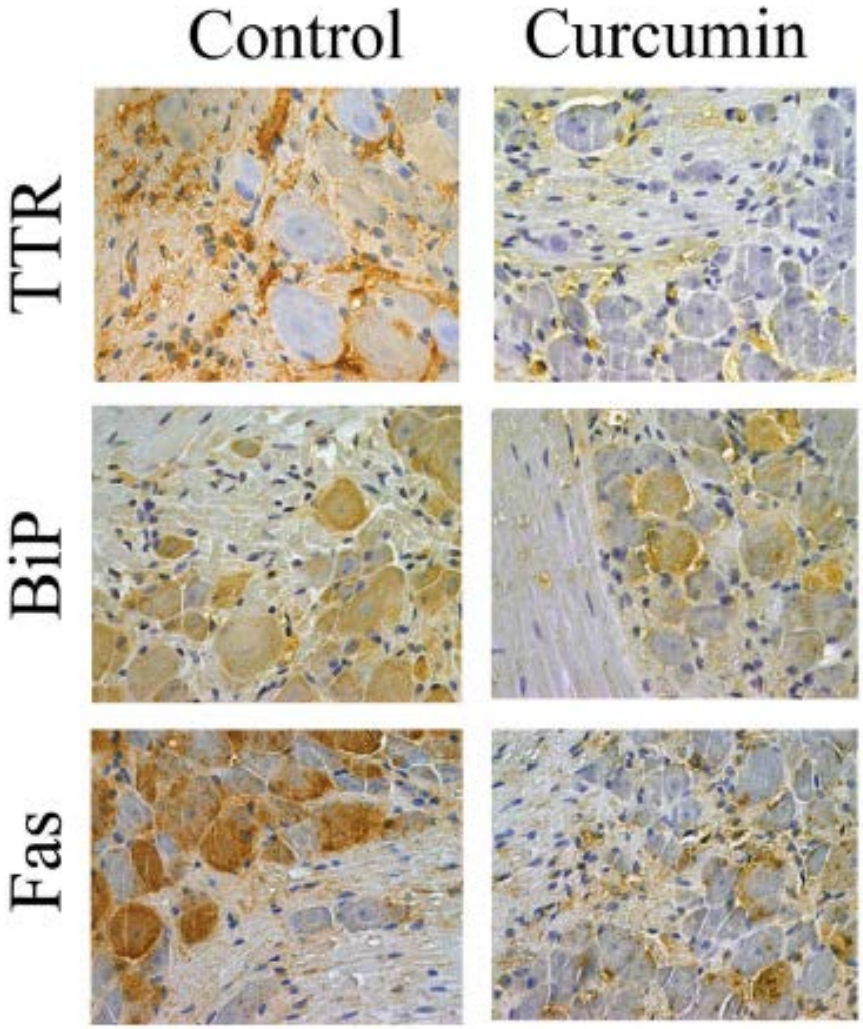
Curcumin



- Natural polyphenol (diarylheptanoid)
- Inhibits Aβ aggregation/breaks up Aβ fibrils
- Blocks toxicity of Aβ fragments on brain cells
- Competes T4 binding to TTR
- Promotes clearance of TTR aggregates
- Inhibits steps of ATTR fibril formation
- Penetrates blood brain barrier – extent unclear
- Poor bioavailability limits use

Ferreira N et al. 2013; 1832(1):39

Curcumin decreases ATTR and injury signals in mouse nerves

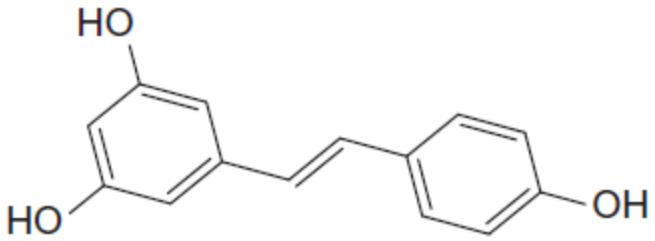


COMMENTS

- Prefibrillar aggregates
- 6 weeks curcurmin in drinking water
- Poor bioavailability
- Unachievable levels
- Does not recapitulate human disease

Ferreira N et al. (2016) Sci Rep 6:26623

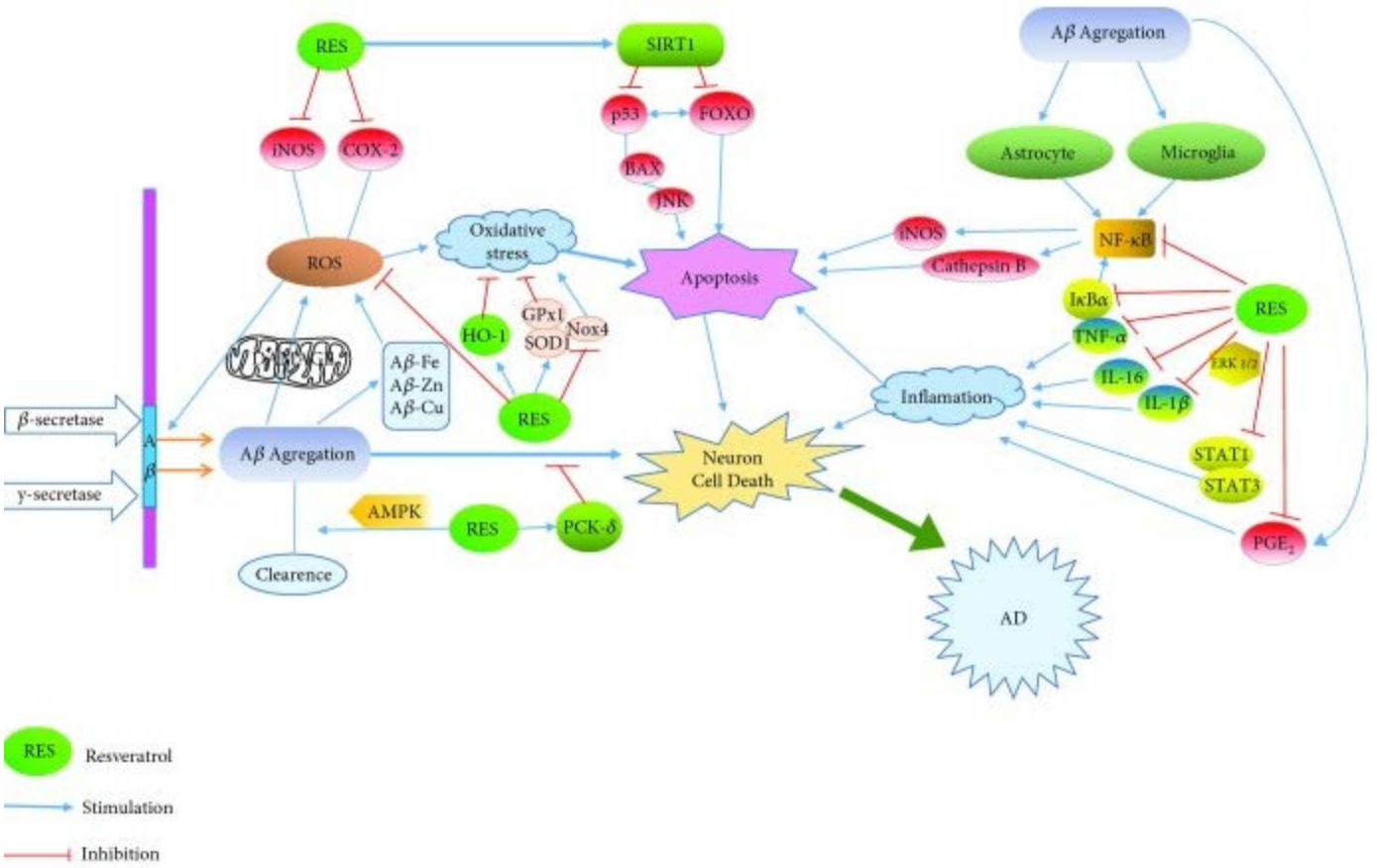
Resveratrol



- Damaged grapevines, pines, peanuts
- Stabilizes TTR tetramer conformation (T4 pocket)
- Promotes aggregation of potentially toxic TTR monomers
- In mouse models, inhibits Aβ aggregation, disrupts plaques
- Attenuates oxidative damage of Aβ aggregates in neuronal cell culture and brains (hippocampus) of AD patients
- Poor bioavailability
- Effective dose undefined
- CNS penetration appears limited
- Inconclusive data from human clinical trials

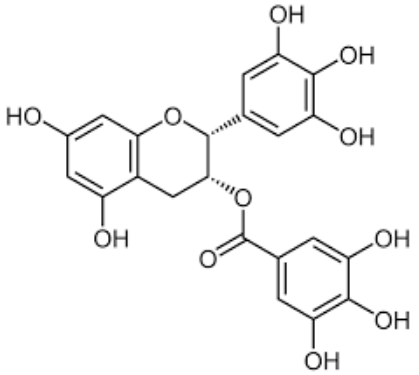
Bourgault S et al. Biochem Biophys Res Comm. 2011; 410(4):707
Gomes B et al. Oxid Med Cell Longev. 2018

Role of Resveratrol in AD



Gomes B et al. Oxid Med Cell Longev. 2018

EGCG



- Inhibits neurodegeneration in ALS/AD
- Protects rat brain neurons from Aβ toxicity
- Low dose inhibits inflammatory pathways
    - IL1β, TNF, TGFβ
- Activates cell survival (PI3K/Akt) pathway
- Stabilizes TTR tetramers
    - Different mechanism than **diflunisal**
- Inhibits ATTR amyloid fibril formation
- Promotes breakdown of amyloid deposits
    - Non-toxic aggregates

EGCG

ATTR

- 14 ATTR cardiomyopathy patients
- EGCG 500-700 mg/day x 12 months
- Findings
    - Echo: no change in LV wall thickness
    - Cardiac MRI: 12.5% decrease LV mass

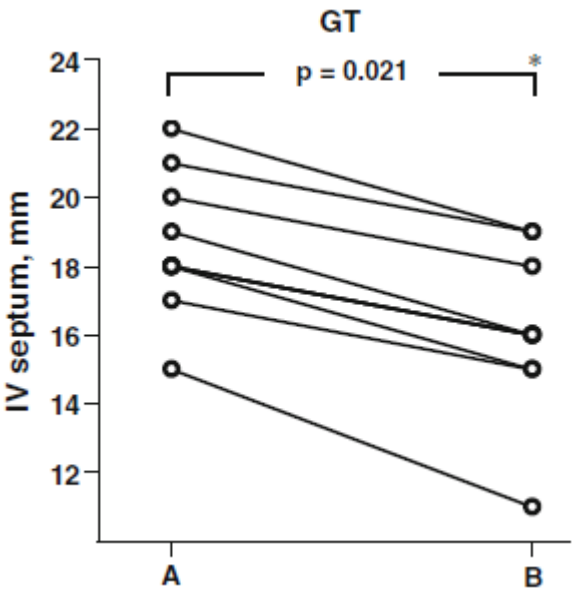
AL

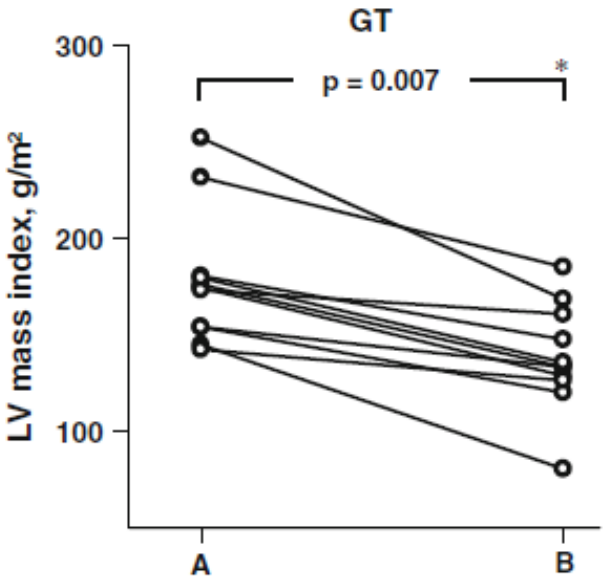
- 59 patients with AL amyloid cardiomyopathy
- ECGC 600-800 mg/day + **AL amyloid treatments**
- Findings
    - 11 patients -- > 2 mm septal wall decrease
    - 6 months (range, 3-10)

Kristen AV et al. Clin Res Cardiol 2012; 101(10):805
Mereles D et al. Clin Res Cardiol 2010; 99:483

EGCG

AL Amyloid Cardiomyopathy





Mereles D et al. Clin Res Cardiol 2010; 99:483

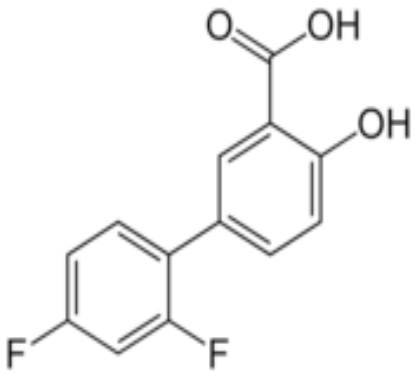
EGCG for ATTR Cardiomyopathy

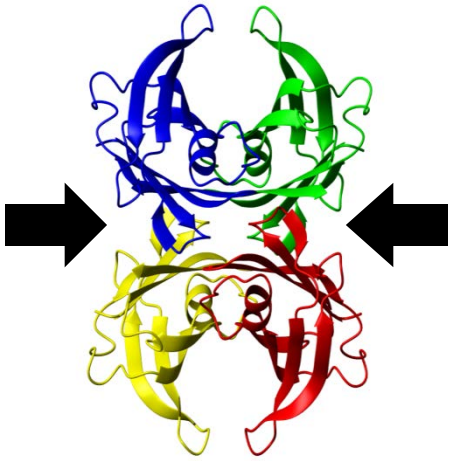
- Retrospective study of ATTR CM patients
- Tuscan Regional Amyloid Center, Florence Italy
- 30 pts (+) EGCG 675 mg/day $\geq$ 9 months;
- 35 pts (-) EGCG
- Median follow up 691 days
- 5 deaths (+) EGCG; 8 deaths (-) EGCG
- Survival estimates 60$\pm$15% v. 61$\pm$12%, p=0.276

Cappelli F et al. Int and Emerg Med 2018;13(6):873

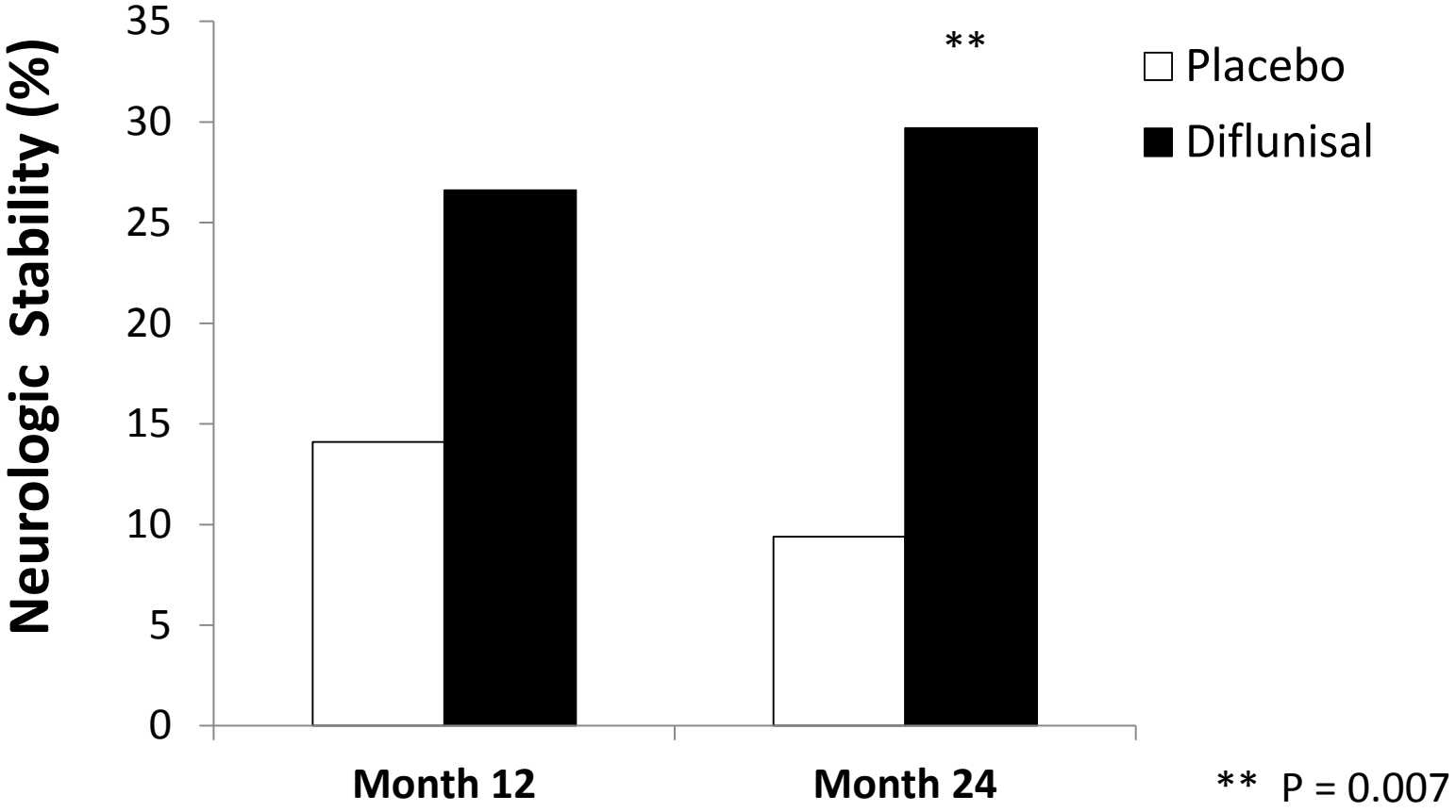
Diflunisal IND 68092

- 2’,4’-difluorophenyl salicylate derivative
- Non-Steroid Anti-Inflammatory Drug (NSAID)
- High serum concentrations and low toxicity





No Decline in 30% taking Diflunisal for 2 YRS



Conclusions

- Diflunisal inhibits neurologic progression and preserves quality of life in patients with ATTR-FAP
- Effective across gender, mutations, and severity of disease at entry
- Cost effective – if no kidney, heart, GI issues