Alternative Therapies for ATTR

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Neurodegenerative Disease

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

• 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
- Resveratrol
- Curcumin
- Quercetin

Neurogenerative Disease

Compounds: Epigallocatechin-3-galate, Resveratrol, Curcumin, 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 curcumin in drinking water
• Poor bioavailability
• Unachievable levels
• Does not recapitulate human disease

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

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 $A\beta$ toxicity
- **Low dose** inhibits inflammatory pathways
  - IL1$\beta$, TNF, TGF$\beta$
- 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)

EGCG

AL Amyloid Cardiomyopathy

EGCG for ATTR Cardiomyopathy

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

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

Neurologic Stability (%)

Month 12

Month 24

** P = 0.007
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