Nutraceuticals in Heart Failure Prevention

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Disclosures

• none
Complementary and Alternative Medicines

“A group of diverse medical and healthcare systems, practices, and products that are not presently considered to be part of conventional medicine”

– National Institutes of Health (NIH)

• Alternative whole medical systems (ex. homeopathic, Chinese medicine, Ayurveda)
• Mind-body interventions (ex. meditation, art, tai chi)
• Biologically based therapies (vitamins, herbals, dietary supplements)
• Manipulative body-based methods (ex. osteopathic, chiropractic, massage)
• Energy Therapeutics (ex. therapeutic touch, Reiki)
Complementary vs. Alternative Medicine

• Complementary Medicine
  • Used together with conventional medicine

• Alternative Medicine
  • Used in place of conventional medicine
Contributing factors

- Ads and television
- “Alternative medicine and therapies are natural and therefore safe”
- “OTCs are too weak to cause any harm”
- Self-prescribing and easy access
- Cost
- Cultural and ethnic influence
Background

• 1/3 of HF patients use CAM
• 1 in 5 adults use herbal therapy within a year
• Increasing trend
• Used across different populations
  • Age
  • Gender
  • Income level
  • Education

The problem in HF

- Regulation
- Lack of efficacy
- Priority over conventional therapies
- Interactions
  - Drug-Drug
  - Drug-Nutrient
- Adverse effects
- Informing healthcare providers

First Do No Harm

• Consider whether alternative therapy is
  • Effective and safe with evidence of efficacy and safety
  • Effective but evidence of potential danger or side effects
  • Inadequately studied but safe
  • Both ineffective and dangerous
Oversight and Regulation of CAM

**Dietary Supplements**

• **1994 Dietary Supplement Health and Education Act (DSHEA)**
  • Maintain health in some manner
  • Regulated like foods
    • Requires identity, quantity, nutrition, ingredients, name/place of manufacturer
  • Exempted premarket safety and efficacy testing

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Which could be toxic?
Standards and Transparency

US Pharmacopeia
• Standards for drugs and supplements
• Ensures compliance with standards
  • Quality, quantity, purity, strength, packaging, labeling
• Many dietary supplements are not endorsed!
• [Website Link](www.usp.org/verification-services/dietary-supplements-verification-program)
• Nature made and Kirkland
2. Many nutritional supplements and hormonal therapies have been proposed for the treatment of HF. Ultimately, most studies are limited by small sample sizes, surrogate endpoints, or nonrandomized design. In addition, adverse effects and drug-nutraceutical interactions remain unresolved. There is a lack of evidence of benefit from vitamin D, thiamine, carnitine, and taurine, and potential harm from vitamin E. The largest RCT of coenzyme Q10—Q-SYMBIO (Coenzyme Q10 as adjunctive treatment of chronic heart failure with focus on symptoms, biomarker status, and long-term outcome [hospitalisations/mortality])—showed no changes in NYHA functional classification at 16 weeks, although the incidence of major adverse cardiovascular events at 2 years was significantly reduced (hazard ratio, 0.50; 95% CI, 0.32-0.80; P=0.003). Despite these findings, concerns about slow recruitment in this trial have tempered enthusiasm for coenzyme Q10 supplementation in clinical practice.
Tai Chi

Tai Chi is safe and well tolerated adjunctive therapies for HF. Improves mood and QOL

CoQ10    Q-SYMBIO trial

• 420 pts, randomized, double blind, placebo controlled trial.
• CoQ10 – 100mg three times daily x 2 years
• Major endpoint – composite of worsening HF, CV death, mechanical assist implant, urgent transplant.
• 88% Class III, 90% ACE, 72% BB, 46% Dig, 34%AA.
• EF = 31%
HR CoQ₁₀ vs placebo: 0.50 (95% CI: 0.32–0.80)  
P-value=0.003
### 7.3.6. Other Drug Treatment

Referenced studies that support the recommendations are summarized in the Online Data Supplements.

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
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<tbody>
<tr>
<td>2b</td>
<td>B-R</td>
<td>1. In patients with HF class II to IV symptoms, omega-3 polyunsaturated fatty acid (PUFA) supplementation may be reasonable to use as adjunctive therapy to reduce mortality and cardiovascular hospitalizations.(^1)(^4)</td>
</tr>
</tbody>
</table>

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Heidenreich PA, et al. 2022 AHA/ACC/HFSA Guidelines for the Management of HF. Circulation 2022 May 3;145(18):e895-e1032
Fish oil on HF

- n-3 PUFAs 1-2 g/day
- Cardiac Fibrosis
- Cardiac Remodeling
- Systolic and Diastolic ventricular function
- HF Hospitalization
- HF Death

Oppedisano F et al. PUFA Supplementation and Heart Failure: Effects on Fibrosis and Cardiac Remodeling. Nutrients. 2021 Aug 26;13(9):2965
GISSI-HF Trial

• Randomized double-blind, placebo-controlled trial
• N=6,975   NYHA Class II-IV, HFrEF
• PUFA 3 fa  <1 g daily vs. placebo
• Mean 3.9 yr f/u
• Primary endpoint: time to death, and time to death or CV hospitalization

GISSI-HF: Time to all-cause death or CV hospitalization

8% relative risk reduction
Divergence at 2 yrs

GISSI-HF: Time to all-cause death or CV hospitalization

8% relative risk reduction
Divergence at 2 yrs

More than 2g/d of Fish oil may increase risk of Afib.

Circulation

AHA SCIENTIFIC STATEMENT

Complementary and Alternative Medicines in the Management of Heart Failure: A Scientific Statement From the American Heart Association

Sheryl L. Chow, PharmD, FAHA, Chair; Biykem Bozkurt, MD, PhD, FAHA, Vice Chair; William L. Baker, PharmD, FAHA; Barry E. Bleske, PharmD; Khadijah Breathett, MD, MS, FAHA; Gregg C. Fonarow, MD, FAHA; Barry Greenberg, MD, FAHA; Prateeti Khazanie, MD, MPH; Jacinthe Leclerc, RN, PhD, FAHA; Alanna A. Morris, MD, MSc; Nosheen Reza, MD; Clyde W. Yancy, MD, FAHA; on behalf of the American Heart Association Clinical Pharmacology Committee and Heart Failure and Transplantation Committee of the Council on Clinical Cardiology; Council on Epidemiology and Prevention; and Council on Cardiovascular and Stroke Nursing
## Safety of CAM in HF

### Agent

- **Hawthorn**
- **Oleander**
- **Vitamin E**
  - ≥ 400 IU/day
- **Caffeine** 500 mg within 5 hrs
  - 3-5 cups coffee

### ADRs/ Interactions

- ↑ HF progression, digoxin?
- Cardiac glycoside
- ↑ risk of new onset HF
- Increases BP, ↑diuresis

Natural Medicines Database, 2021
<table>
<thead>
<tr>
<th>Potentially harmful</th>
<th>Interactions</th>
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<tbody>
<tr>
<td>Bitter Orange</td>
<td>√</td>
</tr>
<tr>
<td>Blue Cohash</td>
<td></td>
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<tr>
<td>Devil's claw</td>
<td>√</td>
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<tr>
<td>Ginko</td>
<td>√</td>
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<tr>
<td>Gossypol</td>
<td></td>
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<tr>
<td>Grapefruit Juice (dose dependent)</td>
<td>√</td>
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<tr>
<td>Khella</td>
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<tr>
<td>Licorice</td>
<td></td>
</tr>
<tr>
<td>Lily of the Valley</td>
<td>√</td>
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<tr>
<td>Oleander</td>
<td>√</td>
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<tr>
<td>Strophanthus</td>
<td>√</td>
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<tr>
<td>Vitamin E</td>
<td></td>
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<tr>
<td>Potentially beneficial</td>
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<td>------------------------</td>
<td></td>
</tr>
<tr>
<td>Co-Q10</td>
<td></td>
</tr>
<tr>
<td>D-Ribose</td>
<td></td>
</tr>
<tr>
<td>L-arginine</td>
<td></td>
</tr>
<tr>
<td>L-carnitine</td>
<td></td>
</tr>
<tr>
<td>Omega-3 fatty acids</td>
<td></td>
</tr>
<tr>
<td>Thiamine (with deficiency)</td>
<td></td>
</tr>
<tr>
<td>Vitamin C (with deficiency)</td>
<td></td>
</tr>
<tr>
<td>Vitamin D (with deficiency)</td>
<td></td>
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<tr>
<td>Yoga with GDMT</td>
<td></td>
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<tr>
<td>Tai-Chi with GDMT</td>
<td></td>
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<tr>
<td>Bidirectional</td>
<td>Interactions</td>
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<tr>
<td>---------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
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<tr>
<td>Aloe Vera</td>
<td></td>
</tr>
<tr>
<td>Caffeine</td>
<td></td>
</tr>
<tr>
<td>Guar gum</td>
<td></td>
</tr>
<tr>
<td>Hawthorn</td>
<td>✓ PD, theoretical</td>
</tr>
<tr>
<td>L-arginine</td>
<td></td>
</tr>
<tr>
<td>Policosanol</td>
<td></td>
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</tbody>
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Chow SL, et al. Circulation. 2023;147:e4-e30

15th Annual Orange County Symposium for Cardiovascular Disease Prevention
Turmeric in CVD?

- Curcumin: polyphenol compound from turmeric
- Anti-inflammatory
- Anti-oxidant effects
- Normally poor absorption
- Reduced activation of LVH and BNP (hypertensive rats)

Sunagawa Y et al. Nutrients. 13;2021:1-13
Curcumin for the prevention of hypertensive heart disease

- Randomized double-blind, placebo-controlled trial
- $N=142$ LVEF $60\%$ [https://en.wikipedia.org/wiki/Curcumin]
- Curcumin 90 mg twice daily vs. placebo (n=73 vs. 69)
- 24 weeks
- Primary endpoint: E/E’ from baseline to 6 months
- Secondary endpoint: % change in BNP

Funamoto M et al. EHJ. 2022;2:1-9
Curcumin: Change in BNP based on age

<table>
<thead>
<tr>
<th>End points</th>
<th>Placebo, n=25</th>
<th>Curcumin, n=24</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ SBP (%)</td>
<td>3.8</td>
<td>-5.3</td>
<td>0.022</td>
</tr>
<tr>
<td>Δ DBP (%)</td>
<td>1.2</td>
<td>-4.2</td>
<td>0.112</td>
</tr>
<tr>
<td>Δ E/A (%)</td>
<td>-7.1</td>
<td>-5.9</td>
<td>0.826</td>
</tr>
<tr>
<td>Δ E/E’ (%)</td>
<td>1.4</td>
<td>-3.9</td>
<td>0.386</td>
</tr>
</tbody>
</table>

Percent change
Baseline age <65 years

Funamoto M et al. EHJ. 2022;2:1-9
Turmeric (Curcumin) conclusions

• High-absorption curcumin did not affect E/E’ ratio
• Attenuated an increase in BNP with early hypertensive heart disease/LV diastolic dysfunction
• Unknown if prevents progression to HFpEF
Low Antihypertensive Med Adherence
CoSMO Humana population

N=2180 Black and White adults ≥ 65 years of age on antihypertensive medications

<table>
<thead>
<tr>
<th></th>
<th>Prevalence %</th>
<th>P</th>
<th>Prevalence Ratio</th>
<th>P</th>
<th>Multivariable adjusted Ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blacks</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No CAM</td>
<td>26%</td>
<td>&lt;0.001</td>
<td>1.71</td>
<td>0.001</td>
<td>1.56</td>
<td>0.006</td>
</tr>
<tr>
<td>CAM</td>
<td>15%</td>
<td></td>
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</tbody>
</table>

| Whites         |              |     |                  |     |                              |     |
| No CAM         | 12.3%        | 0.956 | 0.97          | 0.872 | 0.95                        | 0.728 |
| CAM            | 12.2%        |       |                |     |                              |     |

Adherence based on Morisky Medication Adherence Scale (MMAS-8)

How Does CAM Influence Adherence?

- Higher educational status associated with CAM use
- Blacks were less likely than whites to discuss health food supplements
- Hispanics and Asians are also less likely to disclose CAM use to their physician or pharmacist
- White participants with more comorbidities were more likely to use CAM
- Lack of federal oversight can lead to misuse and misunderstanding

Closing gaps to improve counseling

- 72% of patients do not report use of alternative therapy to healthcare providers
- Healthcare professionals do not routinely ask, document, or monitor dietary supplements
  - Physicians lack resources to answer patient inquiries
  - Community retail pharmacists less likely to inquire about supplements than inpatient pharmacists.
- Utilize multidisciplinary team care
  - Consult pharmacy to counsel patient and assess for nutrient-drug interactions.
  - Include CAM during Medication Reconciliation (nurses and pharmacists). Ask patients directly about diet, supplements and herbs.

Counseling patients

Do NOT
• Avoid asking patients about CAM use
• Criticize or judge patients
• Make demands, paternalistic approach

Do
• Reserve judgement
• Be ethnically sensitive
• Provide objective lack of evidence and potential safety concerns.
Summary

• Studies show that healthcare professionals need further knowledge, confidence, and training in CAM therapy.

• CAM agents are frequently used in conjunction with traditional therapies and careful consideration of efficacy and safety are important.

• Modest improvements on CV outcomes have been observed with select CAM agents but larger, more robust randomized trials are needed.

• Discussions between clinician and patient should occur routinely to improve safety and adherence.