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EDITORIAL COMMENT

Challenges and Opportunities in the Evaluation of Nutraceuticals in Cardiovascular Diseases*

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Food supplements that provide putative physiologic benefits, broadly termed "nutraceuticals," have long intertwined with the history of medicine. Many of the most used cardiovascular drugs today, including aspirin, digoxin, and statins, were identified from dietary food sources that were historically used as natural treatments for a broad number of aliments. The market for nutritional supplements and nutraceuticals is huge, with over $120 billion USD in global sales in 2019. Although the health benefits of nutraceuticals are widely touted by enthusiasts, hard data from rigorously conducted trials supporting improvement in clinically relevant outcomes are scarce.

Pectins are abundant and complex components of the primary plant cell wall and are well known as dietary fiber. Modified citrus pectin (MCP) is a complex water-soluble polysaccharide derived from citrus fruits, specifically the pulp and peel. Emerging evidence suggests that MCP has antineoplastic potential and is now being investigated for therapeutic benefit in a variety of cancers (1). Although MCP likely has pleotropic mechanisms of actions, its key physiologic impact appears to be in targeting and inhibiting the galectin-3 (Gal-3) binding pathway (1). Gal-3 is a member of the β-galactoside binding lectin family, which is expressed in cardiac (and other) cells and has emerged as a potential regulator of physiological and pathological processes including inflammation and fibrosis. Gal-3 has demonstrated prognostic value in predicting incident heart failure (HF) and recurrent HF (2). Therefore, MCP-mediated inhibition of Gal-3 represents a possible strategy for both HF prevention and for treatment of established HF.

In this issue of *JACC: Basic to Translational Science*, Lau et al. (3) explored the question of whether MCP-mediated Gal-3 inhibition among relatively healthy patients with established hypertension could reduce markers of collagen metabolism. Because hypertension is a significant driver of HF development, possibly through enhanced myocardial fibrosis, leveraging MCP to inhibit the Gal-3 pathway, and thereby possibly reduce fibrosis, represents a novel strategy for HF prevention. Additional outcomes included Doppler measurements of vascular stiffness and echocardiographic measurements of diastolic dysfunction. The participants selected to be randomized were required to have elevated Gal-3, as defined by a reference cohort from prior analyses in the Framingham study. A total of 275 participants were screened for eligibility, of whom 68 had elevated Gal-3. Those individuals with elevated Gal-3, reflecting a population of participants with hypertension who had a potentially more pro-fibrotic phenotype, were randomized to receive 3 doses of MCP per day (n = 34) versus matching subjects who received placebo (n = 34) for 6 months. Overall, 52 participants were available for follow-up bloodwork at the end of the study. The MCP appeared to be poorly tolerated, for example, 6 participants (17%) in the active treatment arm dropped out due to

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TABLE 1 Challenges and Opportunities for Future Studies of Nutraceuticals in Cardiovascular Disease

Challenges	Opportunities
Mostly limited and confounded observational studies	Conducting mechanistic randomized evidence to gain insights into possible mechanisms of action
Single-dose studies provide limited insights into mechanisms of action	Consider multiple doses or crossover designs to test different dosage options
Single-biomarker studies	Consider proteomic studies exploring multiple mechanistic pathways at once
Limited magnitude of benefit in broad populations	Targeting populations with disease states that most align with an accepted mechanism of supplemental action
Limited funding to obtain evidence of benefit or harm	Collaboration with nutraceutical industry to conduct robust randomized trials

gastrointestinal side effects (compared to 1 participant in the placebo arm). Furthermore, 5 other participants in the active treatment arm withdrew due to personal preference (compared to 2 participants in the placebo arm). Final results demonstrated no convincing differences between randomization arms in changes of collagen biomarkers, vascular function, or echocardiographic markers.

There are several factors that warrant further exploration. It remains unclear whether a hypertensive participant group was the ideal population to evaluate in this proof-of-concept study; the participating population was generally healthy, and the degree of fibrosis might have been relatively mild. As a result, significantly longer treatment with MCP might have been required to demonstrate reduction in collagen markers. The dosages of MCP appear to have been driven by the availability of the commercial product, and potentially different doses might have been required to adequately inhibit the Gal-3 pathway. The tolerability of the MCP also represents a possible challenge in ascertaining benefit; combined with a dosage of 3 times daily, the ability to comply with and adhere to such a treatment schedule remains challenging. This might have been represented in the higher drop-out rate in the active treatment arm and might have confounded the final analysis. As a sample size, the population might have been underpowered to detect significant changes in collagen biomarkers. Furthermore, prevention or reversal of any structural echocardiographic changes in this relatively healthy population might have required years or decades of intervention.

Among primary prevention populations, stratifying for higher levels of baseline Gal-3 or other elevated markers of fibrosis might have identified a cohort that could have derived greater benefit from MCP. Disease states with established pro-fibrotic processes including HF and preserved or reduced ejection fraction may represent additional populations to evaluate in future studies of MCP-based Gal-3 inhibition. Additional studies of appropriate endpoint selection will also be needed. Potentially, rather than single- or multiple biomarker approaches, proteomic approaches to evaluating the impact of MCP can give greater insight into possible mechanistic benefits. Ultimately, MCP may not be the panacea for the prevention or treatment of cardiovascular diseases such as HF. Despite these limitations, Lau et al. (3) deserve recognition for conducting a challenging study within the nutraceutical space. Regulated under the Dietary Supplement Health and Education Act (DSHEA) of 1994, nutraceuticals are not subject to the stringent requirements of other pharmaceutical therapies, resulting in the emergence of an industry that often makes questionable health claims with little or no robust clinical evidence. Such nutraceuticals are often marketed as alternatives to therapies with established cardiovascular and mortality benefit through aggressive and often misleading advertising. Furthermore, the current medical literature relating to food-related products is significantly confounded due to a predominance of association studies and limited mechanistic or clinical endpoint-related randomized trials (4). With some exceptions (5), the multibillion dollar nutraceutical industry has little incentive to conduct large-scale outcome studies. Furthermore, such nutraceutical supplements often either lack, ignore, or downplay any adverse harm risks from such supplemental products. In clinical practice, it is not uncommon to see patients spend significant amount of money on such unproven supplements, often at the expense of therapies with proven cardiovascular benefit and established risk-benefit profile.

In the context of a proof-of-concept study, Lau et al. (3) highlighted the potential challenges but also opportunities relating to randomized trials evaluating nutraceuticals (**Table 1**). There is certainly greater need for such mechanistic and clinical randomized controlled trials to overcome the significant bias in currently available observational studies. Future studies should consider multiple dosage strategies, given the general absence of data for how such nutraceuticals impact outcomes. Early phase studies could consider proteomics-based outcomes to explore multiple mechanisms of action. Specific selection of targeted populations may identify cohorts that can maximally respond to such nutraceuticals. Finally, collaboration with the nutraceutical industry to

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demonstrate efficacy of their supplements should be explored. This study by Lau et al. (3) represents an important step not only in the evaluation of MCP-based therapies in cardiovascular disease but to emphasize the need for more robust randomized mechanistic and clinical studies of nutraceuticals in the future.

AUTHOR DISCLOSURES

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REFERENCES

1. Glinsky VV, Raz A. Modified citrus pectin anti-metastatic properties: one bullet, multiple targets. Carbohydr Res 2009;344:1788–91.

2. Felker GM, Fiuzat M, Shaw LK, et al. Galectin-3 in ambulatory patients with heart failure results from the HF-ACTION study. Circ Hear Fail 2012;5:72–8.

3. Lau SE, Liu E, Paniagua SM, et al. Galectin-3 inhibition with modified citrus pectin in hypertension. J Am Coll Cardiol Basic Trans Science 2021;7:12–21.

4. Ferreira JP, Sharma A, Zannad F. The future of meat: health impact assessment with randomized evidence. Am J Med 2020 Dec 11 [E-pub ahead of print].

5. Sharma A, Fonarow GC, Butler J, Ezekowitz JA, Felker GM. Coenzyme Q10 and heart failure: a State-of-the-Art Review. Circ Heart Fail 2016;9:e002639.

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