From network pharmacology to preclinical trials: Embracing modern translational validation of traditional Chinese medicine

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From network pharmacology to preclinical trials: Embracing modern translational validation of traditional Chinese medicine

Da Farmacologia em Rede a Ensaios Pré-Clínicos: Adotando a Validação Translacional Moderna da Medicina Tradicional Chinesa

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Heart failure remains a major challenge in modern healthcare despite remarkable advances in pharmacological treatment, especially for patients with reduced ventricular ejection fraction. Morbidity, mortality and hospitalization rates remain high, sustained by aging populations in high-income countries. In this setting, there is ongoing interest in complementary strategies that could modulate ventricular remodeling and myocardial injury; while maintaining a favorable long-term safety profile. Xing et al. investigate the effects of astragaloside IV, a compound derived from products commonly used in traditional Chinese medicine for their purported cardiovascular health benefits, in a study published in this issue of the *Portuguese Journal of Cardiology*.

The integration of traditional Chinese medicine into mainstream scientific discourse has been controversial, largely because many clinical and preclinical studies are of poor quality, the experimental protocols and settings used vary widely, and there is a lack of convincing mechanistic evidence[2]. In response, a concerted effort has been made to modernize research in traditional Chinese medicine and align it more closely with conventional pharmacology and therapeutics. This process typically involves identifying active molecules, systematically predicting their binding targets and signaling pathways, validating these findings in animal models and, only then, progressing to controlled clinical trials[3,4]. There is still a long way to go, particularly in cardiovascular medicine, where several reviews have highlighted the need to shift from empirical formulas and historical narratives to stable biologically plausible mechanisms [2,5].

Indeed, most cardiovascular traditional Chinese medicine studies stall at these first two steps of so-called network pharmacology, generating complex “herb–target–pathway” nodes with little accompanying experimental confirmation [2,3]. However, the study published in this issue leverages network pharmacology with i*n vivo* functional and preliminary pathway-level validation[1]. The authors provide a clear example of how research in traditional Chinese medicine can begin to achieve solid scientific rigor and credibility. For the mainstream scientific community, lingering skepticism towards traditional Chinese medicine is driven less by cultural bias than by the reality of heterogeneous products and compositions, underpowered, biased or poorly controlled trials and a near-total absence of integration into international clinical guidelines. A small number of traditional Chinese medicine-based formulations have begun to generate randomized data in acute coronary syndromes and heart failure. These are, however, exceptions rather than the rule and are often difficult to evaluate because their active components are not fully characterized[5]. Studies like this one represent a more feasible and potentially translatable line of research.

Astragaloside IV is a saponin isolated from *Astragalus membranaceus* (Huangqi), traditionally used in Chinese medicine formulas aimed at “tonifying qi” and protecting the cardiovascular

system[6]. Preclinical studies have documented cardioprotective effects in ischemia–reperfusion, drug-induced cardiomyopathy and hypertrophy, often associated with attenuation of apoptosis, oxidative stress and fibrosis [6,7]. Using chemical and genomic databases, the authors sought to validate a link between this molecule and the PI3K/Akt pathway in an *in vivo* rodent model of heart failure. Here treatment with astragaloside IV was associated with improved ventricular function and remodeling as well as activation of the predicted PI3K–Akt axis, accompanied by reduced cardiomyocyte apoptosis[1].

While the isoproterenol-induced mouse heart failure model chosen by the authors does not fully recapitulate a clinical heart failure phenotype, given the most common etiologies present in humans, recognizing these limitations is essential if we are to apply the same scientific standards that we demand of any other experimental therapy to traditional Chinese medicine-derived compounds. Questions regarding pharmacokinetics, long-term safety or interactions with guideline-directed medical therapy are also still to be explored in future studies. Still, rather than dismissing these data because of their roots in traditional Chinese medicine, we challenge clinicians to embrace them as part of a demanding translational pathway.

If we consistently apply the same critical filters—specifically, model relevance, mechanistic strength, reproducibility, and clinical trial quality—to traditional Chinese medicine–derived monomers and to synthetic drugs alike, studies such as this one can be seen not as outliers but as early, necessary steps in a shared translational ladder. For a cardiology community that is rightly skeptical yet open to innovation, this is the way forward and involves engagement with the evolving evidence associated with compounds like astragaloside IV.

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