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CORRESPONDENCE

Letter to the Editor: Xietu Hemu prescription: A novel therapeutic strategy for obesity and metabolic dysfunction-associated steatotic liver disease?

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Abstract

In the recent issue of the *World Journal of Hepatology*, Cheng *et al* investigated the mechanisms by which the traditional Chinese medicine Xietu Hemu prescription (XHP) exerts therapeutic effects on metabolic dysfunction-associated steatotic liver disease (MASLD). XHP has been shown to reduce hepatic lipid accumulation and improve metabolic parameters. In this study, serum containing XHP decreased lipid deposition in HepG2 cells and inhibited adipogenic differentiation of 3T3-L1 cells in a dose-dependent manner, reducing triglycerides, cholesterol, and adipogenic markers. UPLC-QTOF/MS/MS identified 233 XHP metabolites, mainly flavonoids, while network pharmacology revealed targets associated with lipid metabolism and obesity-related pathways, particularly AMPK signaling. Integrated analyses identified PPARG as a central hub gene. Functional experiments demonstrated that XHP enhances leptin secretion, activates AMPK phosphorylation, and suppresses lipogenic regulators, effects that were abolished by LEPR silencing. These findings suggest that XHP exerts anti-lipogenic effects through leptin-mediated AMPK activation, supporting its potential as a multi-target therapeutic for MASLD and related metabolic disorders.

Key Words: Traditional Chinese medicine; Xietu Hemu prescription; Therapies; Metabolism; Liver; Metabolic dysfunction-associated steatohepatitis; Metabolic dysfunction-associated steatotic liver disease

Core Tip: The study by Cheng *et al* provides new insights into how Xietu Hemu prescription (XHP) may exert beneficial effects on obesity and metabolic dysfunction-associated steatotic liver disease through AMPK activation and leptin-mediated modulation of lipid metabolism. While promising, these findings should be interpreted with caution, as the specific metabolites responsible for the observed effects remain unclear, and the use of rat serum to treat human and murine cells introduces relevant translational limitations. Notably, XHP-derived metabolites may also influence inflammatory and survival pathways, including IL-17 and PI3K/AKT signaling, potentially broadening the therapeutic implications of XHP. Further studies are needed to validate these mechanisms in human systems, explore the anti-inflammatory potential of XHP, and identify its key active metabolites to enhance translational relevance.

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TO THE EDITOR

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a pathological condition whose incidence is closely linked to the global obesity pandemic[1]. Obese individuals often exhibit insulin resistance, which drives lipolysis and leads to an overflow of free fatty acids (FFAs) to the liver, where they are esterified into triglycerides and progressively accumulated. As a result, the liver of obese patients frequently shows steatosis[2]. MASLD is generally reversible: Indeed, when body weight decreases by 5%-10%, hepatic fat content can significantly improve[3]. This often leads to the perception of MASLD as a benign condition; however, it can progress to metabolic dysfunction-associated steatohepatitis (MASH), a more severe stage characterized by hepatocellular damage, oxidative stress, and lobular/portal inflammation with or without fibrosis. In turn, MASH may evolve into cirrhosis and, ultimately, hepatocellular carcinoma (HCC)[4].

Multiple factors drive the transition from MASLD to MASH-HCC, but chronic inflammation is widely recognized as the key determinant, promoting oxidative stress, tissue injury, DNA mutations, and immune cell exhaustion[5]. Briefly, the overflow of FFAs induces mitochondrial dysfunction and oxidative stress, leading to cell damage and activation of inflammatory responses aimed at restoring tissue homeostasis. However, the persistent influx of FFAs triggers a vicious cycle, attracting additional immune cells such as monocyte-derived macrophages and T lymphocytes[5]. In this context, the crosstalk between innate and adaptive immunity, mediated also by costimulatory molecules, emerges as a crucial player in perpetuating inflammatory responses[6].

To convey the magnitude of the problem, current estimates indicate that approximately 38% of the global population is affected by MASLD. As a consequence, MASLD is expected to become the leading cause of HCC worldwide[7]. Unfortunately, therapeutic options for MASLD remain limited and rely primarily on lifestyle modifications aimed at achieving weight loss[8]. Only one drug, resmetirom, a selective agonist of thyroid hormone β receptor has been approved by the United States Food and Drug Administration, and no pharmacological options are available for advanced stages[9]. There is therefore an urgent need to develop new therapeutic strategies to halt MASLD/MASH progression and, ideally, counteract the evolution to HCC.

In this regard, traditional Chinese medicine, with its thousand-year history, may offer new perspectives for this relatively recently recognized disease, first described only in the 1980s[10]. By leveraging the thousands of active compounds naturally present in botanical species, phytotherapy may provide valuable tools to alleviate the burden of MASLD, potentially acting not only on the metabolic imbalances underlying steatosis but also on the inflammatory processes driving disease progression.

We read with great interest the recent paper by Cheng *et al*[11], published in the recent issue of the *World Journal of Hepatology*, which describes the beneficial effects of the traditional Chinese medicine formulation Xietu Hemu prescription (XHP). Notably, XHP treatment has been associated with reductions in hepatic steatosis and improvements in metabolic parameters in prior observational studies involving MASLD patients[12]. In the present study, Cheng *et al* [11] extended this knowledge by exploring the mechanisms through which XHP may affect obesity and MASLD. To this end, they administered XHP to rats and used XHP-containing sera to treat cells, demonstrating its ability to decrease lipid accumulation in HepG2 cells and inhibit adipogenic differentiation of 3T3-L1 cells. Moreover, they identified 19 XHP-derived metabolites that appear to target pathways related to obesity and lipid regulation, with a prominent involvement of the AMPK signaling pathway. Functional *in vitro* experiments further showed that XHP-derived metabolites were associated with increased leptin secretion, enhanced AMPK phosphorylation, and reduced expression of PPARγ, mTOR, and SREBP1/2, consistent with inhibition of lipogenesis and adipocyte maturation. Together, these findings suggest that XHP may exert anti-lipogenic and anti-obesity effects through leptin-dependent activation of AMPK, supporting the mechanistic plausibility of XHP as a multitarget therapeutic strategy for MASLD and related metabolic disorders.

Although this study is certainly noteworthy, several limitations should be considered, and the results should therefore be interpreted with caution. First, it remains unclear which specific metabolites, and at what concentrations, are responsible for the observed effects. Moreover, the authors used rat serum to treat human (HepG2) and murine (3T3-L1) cells, an experimental approach that may introduce translational limitations, as hepatic metabolism in humans and rodents overlaps only partially. Accordingly, future studies should prioritize the analysis of serum samples from XHP-treated patients, coupled with metabolomic profiling and validation in human-relevant cellular systems, to determine

whether similar metabolites are present at biologically active concentrations and mediate comparable effects. For now, we can only speculate that the clinical effects observed in humans depend on the mechanisms described by Cheng *et al*[11].

Furthermore, the manuscript does not emphasize that some XHP-derived metabolites may also affect pathways related to inflammatory responses, such as IL-17 signaling and Th17 cell differentiation, as well as survival pathways like PI3K/AKT signaling. While this additional layer of complexity complicates mechanistic interpretation, it also broadens the potential therapeutic scope of XHP. Notably, these pathways have been implicated in hepatic carcinogenesis, raising the possibility that XHP may exert anti-tumorigenic effects by modulating cell proliferation or the tumor microenvironment. However, this hypothesis requires dedicated experimental validation[13,14].

Overall, we believe that additional experiments are required to confirm the mechanisms by which XHP exerts its beneficial effects on obesity and MASLD, possibly exploring the still-unaddressed pathways related to inflammation. It cannot be excluded that XHP, beyond its metabolic benefits, may also display anti-inflammatory properties, an aspect that would significantly increase interest in this formulation. Further studies using hepatic cell models are warranted to gain deeper mechanistic insights. We also suggest isolating individual metabolites to identify those responsible for the anti-lipogenic and anti-steatotic effects, as such an approach may pave the way for the development of refined drug formulations.

In conclusion, these findings open promising avenues for the treatment of obesity and MASLD, a condition with limited therapeutic options and no approved therapies for advanced stages. Traditional Chinese medicine and phytotherapy may help complement existing weight-loss and liver-health-improving strategies, such as physical activity, GLP-1 receptor agonists, and specialized dietary regimens, including ketogenic diets[15,16]. Future clinical translation will also require careful evaluation of safety profiles, batch-to-batch standardization, and potential herb-drug interactions, particularly in patients receiving concomitant metabolic therapies.

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FOOTNOTES

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