


Commentary

Medical food therapy for the long-term management of non-alcoholic fatty liver disease

Chester Yan Jie Ng¹, Keyi Pan², Enkang Wang³, Jianye Yuan^{2,*} and Linda L. D. Zhong ^{1,*}

¹School of Biological Sciences, Nanyang Technological University, Singapore, Singapore

²Clinical Research Unit, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, P. R. China

³Beicai Community Health Service Center of Pudong New Area, Shanghai, P. R. China

*Corresponding authors. Linda L. D. Zhong, School of Biological Sciences, Nanyang Technological University, 60 Nanyang Drive, Singapore 637551, Singapore. Email: linda.zhong@ntu.edu.sg; Jianye Yuan, Clinical Research Unit, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, 725 Wanping Road South, Shanghai 200032, China. Email: yuanjianye@hotmail.com

Dear Editor,

We read with great interest the article published by Wang *et al* [1]. In this article, the authors discussed the use of berberine in alleviating non-alcoholic fatty liver disease (NAFLD). It was found that berberine promoted SIRT1 deacetylation of CPT1A at the Lys675 site, which reduced the ubiquitin-dependent degradation of CPT1A and ameliorated non-alcoholic liver steatosis. NAFLD is one of the most common chronic liver diseases worldwide, and drug and lifestyle interventions are the two major therapeutic tools for NAFLD, but with limited effects [2]. Chinese herbal medicine is currently receiving attention as an alternative treatment modality for NAFLD, and hence, we would like to share our thoughts and further perspectives from a Chinese Medicine point of view to complement the original study.

Berberine (BBR) is a natural benzylisoquinoline alkaloid with anti-inflammatory, antioxidative, antibacterial, hypolipidemic, hypoglycemic, and anti-insulin resistance properties [3]. As the main natural active compound in *Coptis chinensis*, berberine has potential benefits in the treatment of metabolic diseases including diabetes and NAFLD. Although the complex mechanisms involved have been explored by numerous studies in recent years, the specific mechanisms and clinical relevance still warrant further insight.

Based on the findings of this study, an interesting extension of this finding would be to evaluate a possible link between BBR and the modulation of gut microbiota in the management of NAFLD. The gut microbiome is an extremely complex ecosystem consisting of bacteria, fungi and viruses, and archaea, which participate in the regulation of human health [4]. BBR has been shown to enrich beneficial gut bacteria species. Some research groups have also shown that *Coptis chinensis* has lipid-lowering effects and its active component BBR is largely dependent on the modulation of gut microbiota. For instance, Yang *et al* [5] showed that Berberrubine (BRB) a main metabolite of BBR, prevented lipid accumulation by regulating the protein expression of ATGL, GK, PPAR α , CPT-1, ACC1, FAS, and CD36. In addition, 16S rRNA gene sequencing found that BBR and BRB treatment could greatly modify the structure and composition of gut microbiota [5]. It was

observed that BBR and BRB treatment decreased *Lactobacillus* and *Romboutsia*, while BBR increased beneficial bacteria, such as *Akkermansia* and *Bacteroides*, and BRB increased beneficial bacteria, such as *Ileibacterium* and *Mucispirillum* [5]. Collectively, BRB and BBR could alleviate NAFLD *in vivo* and thus, BRB could be beneficial in the management of NAFLD. Some possible mechanisms of action of gut microbiota modulation have also been proposed, which mainly include the intestinal microbiota and bacterial metabolites usually connected with intestinal permeability triggering the release of lipopolysaccharide, cytokines, and gut microbiota DNA into the system circulation and to the liver, accelerating inflammation, production of short-chain fatty acids, and changes in metabolism [6]. Hence, there lies a link between the modulation of gut microbiota and the incidence of NAFLD, and it would be beneficial if BBR or its derivatives could be developed into medicinal products for the management of NAFLD.

Lastly, we would like to propose the integration of medicinal food in the management of NAFLD. As NAFLD is a chronic disease, there is a need to source for long-term and sustainable therapies to manage this disease. The theory of medicinal food has been a long-standing one, and Chinese Medicine has advocated the theory of "Medicine and Food Homology," which promotes the use of medicinal food therapy to manage diseases [7]. This theory refers to an overlapping relationship between food and drugs, whereby the use of Chinese herbal medicine as a food product or a drug is largely dependent on its dosage. Such Chinese herbal medicines are usually low in toxicity and can be consumed in larger amounts as a source of food. Hence, they serve both dietary and therapeutic purposes, proving that food and medicine are not mutually exclusive. A dietary intervention as such is also beneficial as medicinal foods can be easily integrated into one's lifestyle and diet. Therefore, we would propose the consumption of berberine containing foods, such as the barberry fruit, and future research could focus on deepening our understanding of these medicinal foods as well [8]. Hopefully, using new and enhanced technology to its maximum potential will allow for the optimization of the stages involved in the research

Received: 25 October 2023. Accepted: 29 January 2024

© The Author(s) 2024. Published by Oxford University Press and Sixth Affiliated Hospital of Sun Yat-sen University

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

and development of medicinal foods. However, a key point to take into consideration is that for those with G6PD deficiency, berberine containing foods need to be consumed with caution as it has been shown that berberine consumption may induce jaundice and hemolysis in susceptible people, and possibly cause kernicterus in infants [9]. Hence, medicinal food therapy must be administered with caution, and under the supervision of a qualified health professional as well.

In closing, BBR is a promising means of treatment for NAFLD. Many functional foods contain BBR, and it could be beneficial to promote the long-term consumption of functional foods as a means of medical food therapy for the long-term management of NAFLD.

Funding

None.

Conflicts of Interest

None declared.

References

1. Wang P, Li R, Li Y et al. Berberine alleviates non-alcoholic hepatic steatosis partially by promoting SIRT1 deacetylation of CPT1A in mice. *Gastroenterol Rep (Oxf)* 2023;**11**:goad032.
2. Xiao H, Jiang J, Xie Y et al. Colon hydrotherapy plus Traditional Chinese Medicine to treat non-alcoholic fatty liver disease: a pilot study. *J Tradit Chin Med* 2017;**37**:393–6.
3. Pirillo A, Catapano AL. Berberine, a plant alkaloid with lipid-and glucose-lowering properties: from in vitro evidence to clinical studies. *Atherosclerosis* 2015;**243**:449–61.
4. Yang Y, Lu W, Zhang X et al. Gut fungi differentially response to the antipyretic (heat-clearing) and diaphoretic (exterior-releasing) traditional Chinese medicines in *Coptis chinensis*-conditioned gut microbiota. *Front Pharmacol* 2022;**13**:1032919.
5. Yang S, Cao S, Li C et al. Berberrubine, a main metabolite of berberine, alleviates non-alcoholic fatty liver disease via modulating glucose and lipid metabolism and restoring gut microbiota. *Front Pharmacol* 2022;**13**:913378.
6. Schwenger KJ, Clermont-Dejean N, Allard JP. The role of the gut microbiome in chronic liver disease: the clinical evidence revised. *JHEP Rep* 2019;**1**:214–26.
7. Hou Y, Jiang J-G. Origin and concept of medicine food homology and its application in modern functional foods. *Food Funct* 2013;**4**:1727–41.
8. Neag MA, Mocan A, Echeverría J et al. Berberine: Botanical occurrence, traditional uses, extraction methods, and relevance in cardiovascular, metabolic, hepatic, and renal disorders. *Front Pharmacol* 2018;**9**:557.
9. Rad SZK, Rameshrad M, Hosseinzadeh H. Toxicology effects of *Berberis vulgaris* (barberry) and its active constituent, berberine: a review. *Iran J Basic Med Sci* 2017;**20**:516–29.