

Modulation of Linoleic Acid Metabolism by *Camellia Japonica Radix* Alleviates Oxidative Stress in Metabolic Dysfunction-Associated Steatotic Liver Disease

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Abstract

Background: The incidence of metabolic dysfunction-associated steatotic liver disease (MASLD) has been escalating annually, establishing itself as a principal etiology of liver disease. Despite recent advances in intervention strategies, no pharmacological treatment has been universally accepted as a standard therapy, with lifestyle modifications remain the cornerstone of MASLD management. *Camellia japonica radix* (CJR), the root of *Camellia japonica L.*, has emerged as a promising herbal tea substitute for MASLD management, owing to its systemic benefits, absence of side effects, convenient administration, and long-term applicability. However, the mechanisms underlying its therapeutic efficacy in MASLD remain unclear. Thus, our study aims to elucidate its therapeutic mechanisms in MASLD remain unclear to provide evidence supporting its clinical application. **Methods:** The therapeutic effects of CJR were evaluated using a water-supplementation model in MASLD mice. Integrated microbiome, transcriptome, proteome, and metabolome analyses were employed to comprehensively explore the mechanisms involved. Fecal microbiota transplantation in antibiotic-treated ABX mice was conducted to confirm the critical role of gut microbiota and its metabolites. Drug-target pull-down assay was performed to identify specific protein targets of small molecule metabolites in vitro. Furthermore, customized medicated feed supplemented with linoleic acid was used to evaluate its dietary intervention potential. **Results:** CJR extract alleviated hepatic inflammation and steatosis in MASLD model mice, with its pharmacological mechanism associated with gut microbiota, linoleic acid metabolism, and GPX4-mediated ferroptosis. 9(S)-HpODE, emerged as a key metabolite, which could target both KEAP1 and SLC7A11, bidirectionally regulating GPX4-mediated ferroptosis, while acting as a signaling molecule at low doses to induce redox adaptation via oxidative preconditioning, thus ameliorating oxidative stress in MASLD. **Conclusion:** Our findings indicate that both CJR and linoleic acid demonstrate significant potential as dietary interventions for MASLD management, offering promising avenues for future research and clinical application.

Keywords

Camellia Japonica Radix, Metabolic Dysfunction-associated Steatotic Liver Disease, Linoleic Acid, Tea Substitute, Dietary Management