Pharmacological Effects of Acacetin on Liver Protection, Improvement of Osteoarthritis, Depression, and Myocardial Ischemia-reperfusion Injury

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Abstract This article reviews the latest research progress on acacetin: regarding cardioprotection, it mitigates myocardial ischemia-reperfusion injury and chronic heart failure by modulating the HMGB1/RAGE and GAS6/Axl pathways. In the liver, it alleviates alcoholic liver injury through antioxidant and anti-inflammatory mechanisms. In the nervous system, it improves depression-like behaviors by inhibiting the HIF-1α/NLRP3 pathway. In bones and joints, it ameliorates osteoarthritis by blocking the JAK/STAT pathway. Furthermore, it reduces acute lung injury by inhibiting the NLRP3 inflammasome and improves diabetic vascular endothelial dysfunction via the eNOS/PERK pathway. These findings provide a theoretical basis for the development and utilization of acacetin.

Key words Acacetin, Liver protection, Osteoarthritis, Depression, Myocardial ischemia-reperfusion injury

0 Introduction

Acacetin is a natural flavonoid mainly isolated from *Robinia pseudoacacia*, *Pseudostellaria heterophylla*, and other medicinal plants. within the family Fabaceae, also known as "Ya Zao Shu" or "Niu Jiao Hua"[1]. According to the *Dictionary of Traditional Chinese Medicine*, Acacia possesses efficacy in clearing heat, reducing swelling, astringing bleeding, and exerting antibacterial and anti-inflammatory effects, making it commonly used in traditional Chinese medicine for treating inflammation, injuries, and other ailments. Acacetin (Aca) is a natural flavonoid compound extracted from parts of the Acacia plant such as flowers and leaves[2], with a molecular formula of $C_{16}H_{12}O_5$, a molecular weight of 284.27, and an appearance of yellow needle-like crystals. In recent years, with the deepening research into the pharmacological activities of natural medicines, the pharmacological effects of acacetin, including its anti-inflammatory, antioxidant, cardioprotective, neuroprotective, and chondroprotective properties, have attracted widespread attention from scholars both domestically and internationally. This paper will review the pharmacological effects and molecular mechanisms of acacetin in recent years, providing a theoretical basis for its further development and utilization.

1 Cardioprotective effects and molecular mechanisms

Myocardial injury refers to a pathological state where cardiomyocytes, stimulated by various pathogenic factors, undergo structural damage, functional abnormalities, and even necrosis[3]. As a natural flavonoid compound, acacetin possesses multiple biological activities such as anti-inflammatory, antioxidant, and cardioprotective effects, which can alleviate myocardial injury.

Li Geishi *et al.* [4] employed methods including animal experiments, HE staining, echocardiography, enzyme-linked immunosorbent assay (ELISA), TUNEL staining, and Western blot to investigate the regulatory effect of acacetin on cardiomyocyte pyroptosis and the HMGB1/RAGE signaling pathway in rats with myocardial ischemia-reperfusion injury (MIRI). The results showed that, compared to the sham operation group, rats in the model group exhibited significant cardiomyocyte swelling, disorganization, necrosis, and inflammatory infiltration; the left ventricular ejection fraction (LVEF) was significantly reduced, while the left ventricular end-diastolic dimension (LVIDd) and left ventricular end-systolic dimension (LVIDs) were significantly increased. Serum levels of CK-MB, LDH, IL-1β, and IL-18 were elevated, the cardiomyocyte apoptosis rate increased, and the expression of HMGB1, RAGE, and pyroptosis-related proteins (NLRP3, Caspase-1, GSDMD) was upregulated. Acacetin improved the aforementioned indicators in a dose-dependent manner, with the high dose showing the most significant effect; after the addition of the HMGB1/RAGE activator DEX, its protective effect was partially offset, and Western blot confirmed the rebound in the expression of related proteins. In summary, acacetin suppresses cardiomyocyte pyroptosis and alleviates myocardial injury in MIRI rats in a dose-dependent manner by inhibiting the HMGB1/RAGE signaling pathway, providing experimental evidence and a candidate natural drug for the clinical prevention and treatment of MIRI.

Hao Yuhui *et al.* [5] utilized various methods, including animal experiments, echocardiography, and biochemical assays, to explore the cardioprotective effect of acacetin on rats with chronic heart failure by modulating the GAS6/Axl signaling pathway. The

Received: February 25, 2026 Accepted: June 6, 2026

Supported by Central Support Fund for Local University Reform and Development Talent Project (2020GSP16); Heilongjiang Province College Student Innovation and Entrepreneurship Training Program (202510223075); Heilongjiang Bayi Agricultural University Graduate Innovation Research Project (YJSCX2025-KJQN66).

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results indicated that, compared to the model group, all dosage groups of acacetin improved myocardial pathological injury in a dose-dependent manner, increasing the fractional shortening (FS) and LVEF while decreasing LVDs and LVDd. It also reduced levels of myocardial injury markers (cTnT, cTnI, CK-MB) and heart failure marker NT-proBNP, inhibited cardiomyocyte apoptosis, and upregulated GAS6 protein expression and the p-Axl/Axl ratio, with the 20 mg/kg dose showing effects comparable to the positive control captopril. Upon the addition of the GAS6/Axl inhibitor R428, the protective effect of acacetin was completely neutralized. In conclusion, acacetin improves cardiac function in rats with chronic heart failure by activating the GAS6/Axl signaling pathway, offering experimental evidence and a novel therapeutic target for its prevention and treatment.

2 Hepatoprotective effects and molecular mechanisms

Alcohol-associated Liver Disease (ALD) is a highly prevalent chronic liver disease globally, whose long-term progression can lead to liver fibrosis, cirrhosis, and even hepatocellular carcinoma, posing a severe threat to human physical and mental health[6]. Studies have shown that acacetin can alleviate metabolism-associated liver injuries, such as non-alcoholic fatty liver disease.

Liu Jiabao *et al.*[7] employed methods including animal experiments, HE staining, kit-based assays, and qRT-PCR to investigate the protective effect and preliminary mechanism of acacetin against alcohol-induced liver injury in mice. The results demonstrated that the acacetin intervention groups improved various abnormal indicators in mice in a dose-dependent manner: in the low-dose group, serum ALT activity and liver organ index decreased by 15.29% and 16.54%, respectively; hepatocyte morphology tended towards integrity with reduced lipid droplet vacuoles, and mRNA expression of IL-6 and IL-10 decreased by 69.11% and 80.10%, respectively, while mRNA expression of antioxidant genes such as SOD and Nrf2 increased significantly. The improvement was more pronounced in the high-dose group, where serum ALT activity and liver organ index decreased by 67.52% and 17.92%, respectively; hepatocyte morphology approached normal, mRNA levels of IL-6, IL-10, and TNF-α decreased by 67.85%, 82.14%, and 51.37%, respectively, and antioxidant gene expression was substantially upregulated. In summary, by upregulating the expression of antioxidant genes such as SOD and Nrf2 and inhibiting the expression of inflammation-related genes, acacetin alleviates liver pathological injury and improves liver function. This study confirms for the first time its protective role against alcohol-induced liver injury, providing reliable experimental evidence for the prevention and treatment of alcoholic liver disease and the development of natural hepatoprotective drugs.

3 Antidepressant effects and molecular mechanisms

Depression is a highly prevalent heterogeneous mental disorder characterized primarily by persistent low mood and impaired cognitive function; in severe cases, it may lead to behaviors such as self-harm and suicide, posing a serious threat to the patient's physical and mental health[8]. Research indicates that acacetin can improve depression-like behaviors in rats via the HIF-1α/NLRP3 signaling pathway.

Li Zhuo *et al.*[9] utilized methods including animal experiments, behavioral tests, ELISA, HE staining, Nissl staining, and Western blot to investigate the therapeutic effect of acacetin on depressed rats and its regulatory mechanism on the HIF-1α/NLRP3 signaling pathway. The results showed that, compared to the model group, both low and high doses of acacetin significantly improved various abnormal indicators in rats in a dose-dependent manner: hippocampal tissue structure tended toward normality with intact and neatly arranged pyramidal cells, and an increase in Nissl bodies and neuron count; depression-like behaviors were alleviated, with increased sucrose preference rates and spontaneous activity scores, and shortened immobility time in the forced swim test, where indicators in the high-dose group approached those of the control group. CAT levels increased significantly (6.19 ± 0.47 U/mg in the high-dose group, close to the control), while ROS and MDA levels decreased; the expression of pathway-related proteins including IL-6, IL-1β, TNF-α, HIF-1α, and NLRP3 was significantly downregulated. Mechanism verification revealed that after adding the HIF-1α/NLRP3 pathway activator BMS-986299, the therapeutic effect of acacetin was completely neutralized, with all indicators significantly reversed. In conclusion, acacetin improves depression-like behaviors in depressed rats, alleviates hippocampal damage, and inhibits neuroinflammation and oxidative stress imbalance. It exerts antidepressant effects by suppressing the HIF-1α/NLRP3 signaling pathway, providing reliable experimental evidence and a new therapeutic target for its clinical application and the prevention and treatment of depression.

4 Anti-osteoarthritis effects and molecular mechanisms

Osteoarthritis (OA) is a highly prevalent degenerative joint disease, with primary pathological features being damage, defects, and degradation of articular cartilage; in severe cases, it can lead to disability, seriously affecting the patient's quality of life[10]. Acacetin has been confirmed to inhibit OA-related pathological processes.

Qin Kan *et al.*[11] employed methods including cell experiments, CCK-8 assay, flow cytometry, Alcian blue staining, ELISA, and Western blot to investigate the effect and mechanism of acacetin on chondrocyte differentiation in OA rats. The results showed that, compared to the OA group, low (6 μmol/L) and high (12 μmol/L) doses of acacetin improved various indicators in a dose-dependent manner: cell proliferation rates increased significantly (62.73 ± 5.81)% for low dose, (83.56 ± 6.47)% for high dose), and apoptosis rates decreased significantly (17.82 ± 2.35)% for low dose, (10.62 ± 1.51)% for high dose. The intensity and area of Alcian blue staining increased (mean optical density value of $34\,849 \pm 1\,231$ for high dose), indicating enhanced chondrocyte differentiation capability. Levels of inflammatory and matrix degradation markers such as TNF-α and IL-6 were

downregulated, while IL-10 levels were upregulated. Expression of cartilage differentiation-related proteins like SOX9 was upregulated, whereas expression of phosphorylated proteins in the MMP-3, MMP-13, and JAK/STAT pathways was downregulated. Mechanism verification showed that after adding the JAK/STAT pathway activator Colivelin, the improving effect of acacetin was completely neutralized, with all indicators significantly reversed (proliferation rate dropped to (54.28 ± 4.92)%, and apoptosis rate rose to (26.58 ± 3.29)%. In summary, by inhibiting the JAK/STAT signaling pathway, acacetin promotes chondrocyte proliferation and differentiation in OA rats in a dose-dependent manner, while suppressing apoptosis, inflammation, and matrix degradation, providing reliable experimental evidence and a new therapeutic target for its application in OA treatment.

5 Improvement of lung injury and molecular mechanisms

Acute lung injury is a common and severe pulmonary inflammatory disease, primarily manifested by diffuse damage to lung tissue and declining lung function, posing a serious threat to patient life and health[12]. Studies suggest that acacetin can alleviate lung injury and inflammatory responses in mice with acute lung injury by inhibiting NLRP3 inflammasome activation.

Chu Yingjie *et al.*[13] conducted experiments including animal studies, HE staining, qRT-PCR, Western blot, and ELISA to explore the therapeutic effect of acacetin on LPS-induced acute lung injury (ALI) and its regulatory mechanism on the NLRP3 inflammasome and cell pyroptosis. *In vivo* experiments showed that 45 hours after modeling with LPS at 20 mg/kg, all mice in the model group died, whereas the survival rate in the acacetin (40 mg/kg) group reached 60%. After LPS (10 mg/kg) stimulation, acacetin significantly alleviated lung tissue injury, reduced injury scores, decreased TNF, IL6, and IL1B mRNA levels, lowered IL-1β levels in peritoneal lavage fluid, and downregulated NLRP3 and GSDMD-NT protein expression in lung tissue. In *in vitro* experiments, acacetin (5, 10, 20 μmol/L) showed no obvious cytotoxicity and could dose-dependently reduce the expression of NLRP3, Caspase-1, and GSDMD-NT proteins in PMs cells induced by LPS combined with various stimuli, significantly lowering the rate of cell pyroptosis. In conclusion, acacetin alleviates lung injury and inflammatory responses in ALI mice by inhibiting NLRP3 inflammasome activation and cell pyroptosis, providing reliable experimental evidence for its potential as a clinical candidate therapeutic drug for ALI.

6 Improvement of endothelial dysfunction and molecular mechanisms

Endothelial dysfunction is a core link in the occurrence and development of diabetic vascular complications; excessive endoplasmic reticulum stress can induce endothelial cell apoptosis, calcium homeostasis imbalance, and impaired vascular function, thereby promoting the progression of atherosclerosis[14]. As a natural flavonoid active ingredient, acacetin holds potential application value in metabolic vascular diseases.

Zhang Zhen *et al.*[15] employed an integrated approach combining network pharmacology, cellular molecular biology, and *in vivo* animal experiments to investigate the mechanisms by which acacetin ameliorates endothelial dysfunction in diabetic vascular complications. Network pharmacology screening and molecular docking results indicated that acacetin targets eNOS and is closely associated with pathways related to endoplasmic reticulum (ER) stress. *In vitro* experiments demonstrated that acacetin significantly enhanced the viability of human umbilical vein endothelial cells induced by methylglyoxal, inhibited apoptosis, downregulated the expression of pro-apoptotic proteins Bax and Bad, and upregulated Bcl-2 levels; furthermore, it suppressed the PERK/eIF2α/ATF4/CHOP ER stress pathway, alleviated calcium overload, and downregulated the expression of calcium channel proteins such as STIM1, TRPC1, and ORAI1; additionally, it upregulated the expression of phosphorylated eNOS (Ser 1177), thereby increasing nitric oxide (NO) production. In diabetic $ApoE^{-/-}$ mice, acacetin effectively improved disorders of glucose and lipid metabolism and insulin resistance, reduced lipid deposition in the abdominal aorta and the formation of atherosclerotic plaques, and upregulated the expression of the endothelial marker CD31; it exerted vascular protective effects by inhibiting ER stress, reducing endothelial cell apoptosis, and enhancing eNOS expression. These findings confirm that acacetin alleviates endothelial dysfunction in diabetic vascular complications by inhibiting ER stress and calcium overload via the eNOS/PERK signaling pathway, reducing endothelial cell apoptosis, and restoring NO generation, thus providing experimental evidence and a novel candidate strategy for the prevention and treatment of diabetic macrovascular disease.

7 Conclusion and outlook

As a flavonoid active component widely present in various medicinal plants and natural food sources, acacetin exhibits significant research value and application potential in the prevention and treatment of chronic diseases, owing to its multiple pharmacological activities including antioxidant, anti-inflammatory, neuroprotective, hepatoprotective, antitumor, and metabolic regulatory effects. However, most studies remain confined to cellular and animal models, and further elucidation is required regarding its *in vivo* pharmacokinetic characteristics, targeted delivery efficiency, long-term safety, and precise molecular targets. Future research should systematically focus on deepening the understanding of mechanism of action, optimizing dosage forms, enhancing bioavailability, and conducting high-quality clinical trials, thereby promoting the translation of acacetin from basic research to clinical application and new drug development, and providing a more robust theoretical and experimental foundation for the medical application of natural active products.

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dar, satellites, denser automatic stations, GNSS/MET, *etc.*, and improve the accuracy of short-term forecasting. Fourthly, research on terrain and precipitation should be strengthened, and research on the mechanism of terrain amplification for areas with high incidence of rainstorms such as Taining and Jiangle should be conducted.

6.2 Optimization of early warning services Firstly, the issuance of early warnings should be more decisive. Priority is given to rainfall approaching the warning threshold, and high-level warnings are boldly issued to increase the lead time. Secondly, the monitoring scope should be more comprehensive. The movement, development, and merging trends of echoes are tracked, and the affected areas are judged in advance, without being limited to rainfall at a single point. Thirdly, the call response mechanism should form a closed loop, and the full process of "release – tracking – feedback – evaluation" should be improved to ensure that the warnings reach each responsible person directly and the risk warnings reach each household. Fourthly, service products should be more refined. Integrated products including hourly rainfall, risk level, and defense suggestions are produced to enhance the decision-making support capability.

7 Conclusions

The extreme rainstorm in Sanming City on June 13 was the most extreme warm-sector rainstorm event during the continuous heavy precipitation from June 8 to 18 in 2024. It was caused by the interaction of shear lines, southwest jet stream, a deep moist layer, train effect, and topographic amplification. It was characterized by strong rainfall intensity, concentrated rainfall, local extremity, and high disaster-causing potential.

The overall forecast service for this process was effective, and the warnings were timely. Relying on radar, satellites, and regional rapid assimilation products, short-term warnings precisely supported personnel evacuation and emergency response, minimizing disaster losses to the greatest extent. However, there are still deficiencies in short-term forecast deviation, lead time of early warnings, monitoring scope, and model correction.

In the future, it is necessary to deepen research on the mechanism of warm-sector rainstorms, strengthen the integration and application of multiple sources of data, optimize warning services, improve the departmental linkage mechanism, comprehensively enhance the ability to forecast extreme heavy precipitation and provide meteorological support services, and offer more solid support for disaster prevention and mitigation in Sanming City.

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