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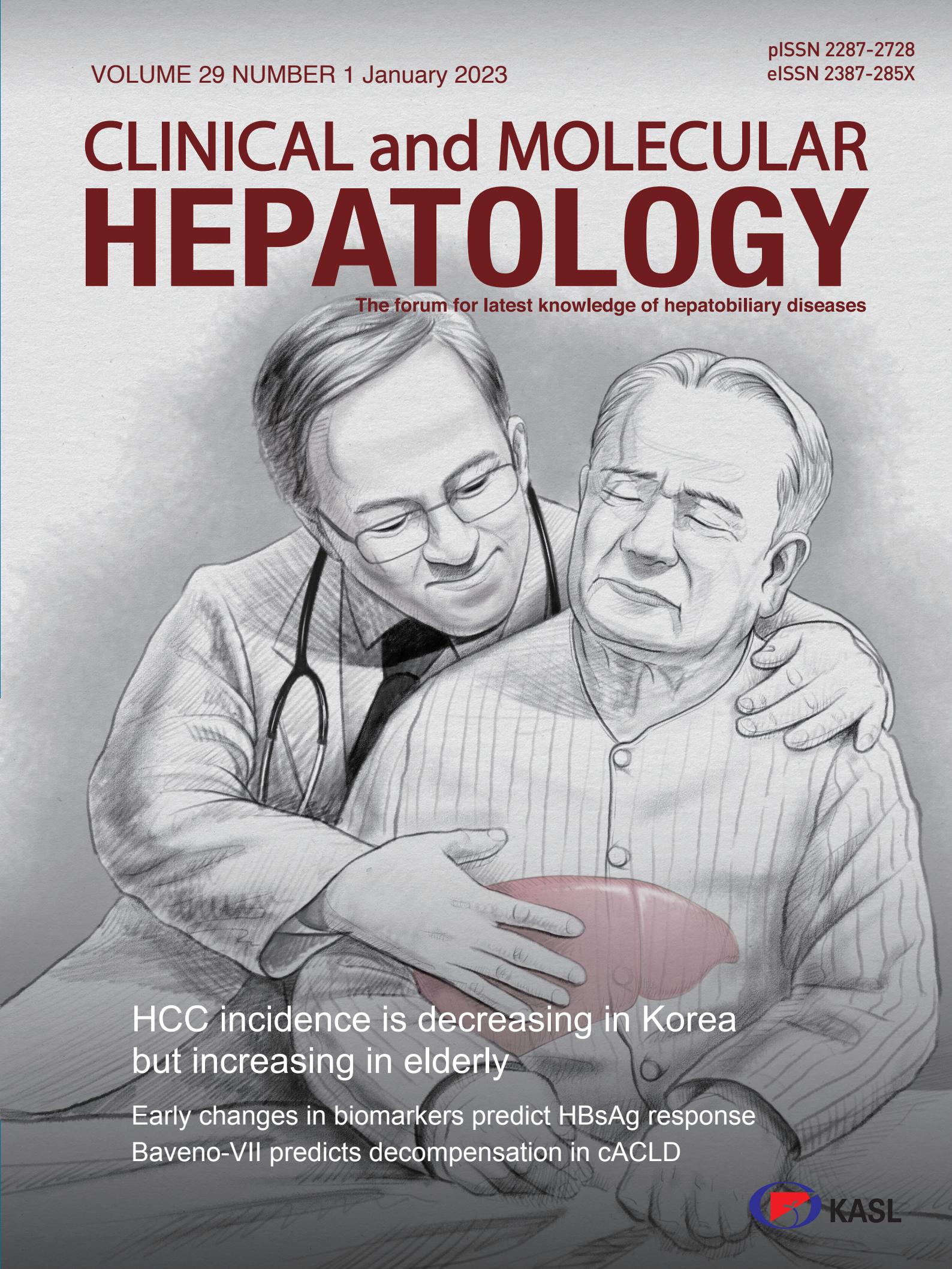

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Letter to the Editor

Letter regarding "Auranofin attenuates hepatic steatosis and fibrosis in nonalcoholic fatty liver disease via NRF2 and NF-κB signaling pathways"

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Keywords: Non-alcoholic fatty liver disease; Auranofin

Dear Editor,

We read with great interest the recently published article by Lee and colleagues,[1] which demonstrated that auranofin, a gold compound, can inhibit the progression of nonalcoholic steatohepatitis (NASH) in both *in vivo* and *in vitro* models. This study revealed that auranofin reduced fibrosis and the expression of nuclear factor kappa B (NF-κB) and inhibitor of NF-κB alpha in LX-2 cells; while in HepG2 cells, auranofin increased nuclear erythroid 2-related factor 2 expression and significantly reduced inflammation and adipogenesis.[1] Furthermore, auranofin has also been shown to impede disease progression in fibrosis and NASH models.[1] This study is of great importance as there is currently no effective pharmacological treatment for nonalcoholic fatty liver disease (NAFLD), and auranofin may have potential for repurposing in NAFLD as an agent historically used in rheumatoid arthritis. However, as a reintroduced compound that may have beneficial effects in NAFLD, we would like to provide additional insights regarding the role of auranofin in NAFLD.

Hepatic inflammatory infiltration is a significant feature in NAFLD. Hwangbo et al.[2] suggested that auranofin could reduce the expression of inflammatory markers, including the NOD-like receptor family pyrin domain containing 3, in NAFLD and inhibit hepatic steatosis in both *in vivo* and *in vitro* models. These results confirmed that auranofin also has anti-inflammatory properties in NAFLD. A recent study combining *in silico* screen, *in vivo* and *in vitro* models demonstrated the antidiabetic effects of auranofin at the 1 mg/kg dose in obese mice fed with high-fat diet.[3] Auranofin was proved to accumulate in the white adipose tissue of obese mice, improve insulin sensitivity, exert anti-inflammatory effects, and abolish fatty liver disease.[3] Notably, auranofin reduced serum leptin levels, and intact leptin signaling was required for auranofin to exhibit insulin sensitizing effects.[3] The presence of hyperleptinemia and leptin resistance in obese patients suggest that partial reduction of leptin by auranofin may be used as a strategy against obesity and NAFLD. The interferon regulatory factor 3 (IRF3) signaling pathway promotes hepatocyte inflammation and apoptosis in NAFLD.[4] Auranofin inhibited fatty acid-induced hepatocyte apoptosis in an *in vitro* model by inducing cellular autophagy and thereby degrading IRF3.[5]

Auranofin is also known as a pan-inhibitor of thioredoxin

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reductase (TrxR).[6] By inhibiting TrxR, auranofin induced apoptosis in hepatocellular carcinoma (HCC) cells and inhibited tumor growth, together with improved resistance to sorafenib.[7] Ferroptosis is a recently proposed iron-dependent form of cell death characterized by lipid peroxidation and accumulation of reactive oxygen species.[8] High-dose auranofin has been shown to induce ferroptosis by inhibiting TrxR.[6] The role of ferroptosis in NAFLD has been recently studied, and the effects are varied at different stages. Ferroptosis promotes the progression of hepatic steatosis, NASH, and associated fibrosis, while inhibiting the development of cirrhosis and HCC.[9] Auranofin and buthionine sulfoxime co-treatment induced ferroptosis in HCC cell lines.[10] These findings indicate that auranofin could inhibit cell proliferation by regulating cell death in HCC. However, there has been no relevant study suggesting the effects of TrxR inhibition by auranofin in hepatic steatosis and NASH progression. Furthermore, given that ferroptosis may have opposite effects on different stages of NAFLD, future studies are needed to explore the effect of auranofin on ferroptosis in NASH. Whether there is an optimal time point for modulating ferroptosis still requires further exploration, as NASH will eventually progress to HCC.

Overall, the present study demonstrated that auranofin can inhibit NASH progression under experimental conditions, suggesting that it could be a promising repurposed anti-NAFLD agent. Further research is warranted to reveal the mechanisms of auranofin in NAFLD and develop the potential for clinical translation.

Authors' contribution

Liu YB and Chen MK proposed the idea for the article; Liu YB carried out the literature search, wrote the manuscript, and prepared the language refinement; Chen MK revised the manuscript as the corresponding author and provided comments; and all authors have read and approved the final manuscript.

Conflicts of Interest

The authors have no conflicts to disclose.

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Abbreviations:

HCC, hepatocellular carcinoma; IRF3, interferon regulatory factor 3; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NF-κB, nuclear factor kappa B; TrxR, thioredoxin reductase

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