The importance of target population selection of auranofin in nonalcoholic fatty liver disease

Running title: target population of auranofin

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List of Abbreviations

NAFLD, non-alcoholic fatty liver disease; GSH, glutathione; GPX, glutathione peroxidase; TXNRD, thioredoxin reductase; NLRP3, NOD-like receptor family pyrin domain containing 3.
We appreciate your interest in our study. As pointed out by Liu et al., non-alcoholic fatty liver disease (NAFLD) has a broad heterogeneous spectrum and a diverse pathophysiology 1-7. The relationship between auranofin-induced ferroptosis and NAFLD is somewhat complex 8. It depends on the cell type and disease condition. Ferroptosis is associated with the pathogenesis of NAFLD, and inhibiting ferroptosis can inhibit necrotic cell death, inflammatory cell infiltration, and inflammatory cytokine expression in early-stage NAFLD 8. However, in late-stage NAFLD and hepatocellular carcinoma, inhibition of ferroptosis is associated with disease progression 9,10. In previous studies, the expression of glutathione peroxidase 4, which protects cells against membrane lipid peroxidation, has been shown to vary according to the severity of NAFLD. In addition, the association between ferroptosis and NAFLD has been observed to vary depending on the animal model of NAFLD. This indicates that ferroptosis may play varying roles at different stages of NAFLD. System Xc^- and NAFLD also share a complex relationship. A large body of evidence suggests that auranofin induces ferroptosis via the cystine-glutamate antiporter system Xc^- Auranofin has been shown to induce ferroptosis via the GSH/GPX axis. Additionally, our previous study indicated that auranofin inhibits system Xc^- in macrophages and the NLRP3 inflammasome in inflammatory cells 11. However, ferroptosis can simultaneously induce iron-dependent lipid peroxidation. Yang et al. demonstrated that auranofin at high doses (25 mg/kg) induces ferroptosis but causes lipid peroxidation by inhibiting thioredoxin reductase (TXNRD) activity 12. In conclusion, it is evident that auranofin acts as an inhibitor of system Xc^- However, ferroptosis induced by system Xc^- inhibitors appears to play a different role in disease progression depending on the liver cell type and severity of NAFLD. Therefore, for the clinical application of auranofin, it is important to select a target population that is anticipated to have a positive therapeutic effect.
References


12. Yang, L. *et al.* Auranofin mitigates systemic iron overload and induces ferroptosis via distinct