Drug Design, Development and Therapy Dovepress

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LETTER

Aqueous Extract of Rhubarb Promotes Hepatotoxicity via Facilitating PKM2-Mediated Aerobic Glycolysis in a Rat Model of Diethylnitrosamine-Induced Liver Cancer [Letter]

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Dear editor

We are writing to express concerns regarding the recently published study by Zhao et al, titled "Aqueous Extract of Rhubarb Promotes Hepatotoxicity via Facilitating PKM2-Mediated Aerobic Glycolysis in a Rat Model of Diethylnitrosamine-Induced Liver Cancer[1]".

First, we believe that, in addition to the lactic and succinic acids mentioned in the article, we can detect other metabolites related to energy metabolism through metabolomics, such as ATP, NADH / NAD +, and etc. Oxidative stress levels should be more closely monitored because reactive oxygen species (ROS) have been linked to hepatotoxicity and cancer development. Potapova EV et al proposed that measuring NADH and NADPH levels in vivo identifies a shift in glucose metabolism in cancer towards energy production.[2] The experiment did not detect serum alpha-fetoprotein (AFP) liver cancer detection indicators, glypican 3 (GPC3) and total bilirubin, etc. These indicators may reflect liver damage and functional status. Key biomarkers such as alpha fetoprotein (AFP), glypican 3 (GPC3), and des gamma carboxy prothrombin (DCP) have demonstrated promise in improving hepatoma clinical outcomes.[3] Liver fibrosis was another prominent feature of the typical environment in which cancer occurs in a DEN-induced liver cancer model. Therefore, liver fibrosis indicators should be added to metabolomics measurements: such as chitinase 3-like protein 1, hydroxyproline, etc.

Second, PKM2 expression upstream regulators were not included in the study. We wonder how the components of rhubarb lead to the up-regulation of PKM2, which in turn activates glycolysis. The authors could research c-Myc or HIF-1α, which are known to control the glycolysis pathway in cancer. According to one study, the HDAC2/FOXA3 pathway was used by hypoxia-induced LncRNA DACT3-AS1 to upregulate PKM2 and encourage metastasis in hepatocellular carcinoma.[4] Hepatotoxicity tests on other rhubarb active compounds, such as aloe-emodin's function in enhancing PKM2 expression or hepatotoxic effects, were not conducted for this article. According to Liu et al, aloe-emodin inhibits multidrug resistance protein 2 to cause hepatotoxicity.[5]

Third, the level of PKM2 in humans was not confirmed in this study, and it is advised to conduct a prospective clinical cohort study. The effects of specific physiological and pathological conditions on rhubarb's hepatotoxicity or hepatoprotective activity were not covered in the article. We recommend that future research on the hepatotoxicity of rhubarb take into account individual differences, such as gender, age, genetic background, and other factors. Although this study suggested that hepatotoxicity is caused by mitochondrial dysfunction, it did not offer concrete proof that mitochondria play a role in rhubarb-induced hepatotoxicity. It is recommended to measure mitochondrial respiratory chain function, membrane potential, oxygen consumption rate, and other direct indicators of mitochondrial health. Additionally, it is recommended that the statistical analysis in the article include details on the power calculation and effect size. The preparation and quality control of the rhubarb aqueous extract were not comprehensively covered. The research findings will be repeatable if the article includes.

Received: 8 November 2024
Accepted: 15 November 2024
Published: 19 November 2024

Disclosure

The authors declare no competing interests.

References

1. Zhao A, Liu X, Chen X, et al. Aqueous Extract of Rhubarb Promotes Hepatotoxicity via Facilitating PKM2-Mediated Aerobic Glycolysis in a Rat Model of Diethylnitrosamine-Induced Liver Cancer. *Drug Des Devel Ther*. 2024;18:4497–4510. doi:10.2147/DDDT.S476273
2. Potapova EV, Zherebtsov EA, Shupletsov VV, et al. Detection of NADH and NADPH levels in vivo identifies shift of glucose metabolism in cancer to energy production. *FEBS J*. 2024;291(12):2674–2682. doi:10.1111/febs.17067
3. Yu B, Ma W. Biomarker discovery in hepatocellular carcinoma (HCC) for personalized treatment and enhanced prognosis. *Cytokine Growth Factor Rev*. 2024;79:29–38. doi:10.1016/j.cytogfr.2024.08.006
4. Wang L, Li B, Bo X, Yi X, Xiao X, Zheng Q. Hypoxia-induced LncRNA DACT3-AS1 upregulates PKM2 to promote metastasis in hepatocellular carcinoma through the HDAC2/FOXA3 pathway. *Exp Mol Med*. 2022;54(6):848–860. doi:10.1038/s12276-022-00767-3
5. Liu DM, Yang D, Zhou CY, et al. Aloe-emodin induces hepatotoxicity by the inhibition of multidrug resistance protein 2. *Phytomedicine*. 2020;68:153148. doi:10.1016/j.phymed.2019.153148

https://doi.org/10.2147/DDDT.S505426