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Furfural Produces Dose-Dependent Attenuating Effects on Ethanol-Induced Toxicity in the Liver

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Background: Alcohol-associated liver disease (ALD) increases the health burden worldwide, but effective drugs to prevent ALD are lacking. Furfural is a small molecule that can limit alcohol production in microorganisms and may have the capacity to attenuate ethanol-induced toxicity.

Methods: Human HepG2 cells were incubated with ethanol and furfural, and cell viability, NAD^+/NADH ratio, and mitochondrial function assays were performed. RNA sequencing (RNA-seq) data were used to annotate enriched pathways, and these findings were confirmed by reverse transcription-quantitative PCR (RT–qPCR) and Western blotting. C57BL/6J mice were fed a Lieber-DeCarli liquid diet. After 4 weeks, biochemical analysis of mouse serum and histological analysis of mouse livers were performed.

Results: Different concentrations of furfural exerted different effects on mitochondria: low-dose furfural reduced reactive oxygen species (ROS) production, maintained mitochondrial transmembrane potential, and inhibited apoptosis pathway activation, while high-dose furfural led to the opposite effects. In mice, furfural mitigated transaminase increases and attenuated the lipid metabolism disorder that had been induced by ethanol.

Conclusion: Low-dose furfural reduced ethanol-induced toxicity in the liver. Consuming food or beverages containing the appropriate level of furfural when drinking alcohol may be a convenient and useful way to prevent ALD.

Keywords: furfural, NAD^+, mitochondrial function, PI3K-Akt pathway, alcohol-associated liver disease

Abbreviations: ALD, alcohol-associated liver disease; NAD, nicotinamide adenine dinucleotide; DEGs, differentially expressed genes; GO, gene ontology; KEGG, kyoto encyclopedia of genes and genomes; BP, biological process; CC, cellular component; MF, molecular function; IGFBP3, insulin-like growth factor binding protein 3; IGF-1 (R), insulin-like growth factor 1 (receptor); IL-11, interleukin-11; TGF-β1, transforming growth factor-beta 1; PI3K, phosphoinositide 3-kinase; mTOR, mammalian target of rapamycin; Apaf-1, apoptotic peptidase activating factor 1; CytC, cytochrome c; SOD2, superoxide dismutase 2; CAT, catalase; GSH-Px1, glutathione peroxidase 1; 5-HMF, 5-hydroxymethyl-2-furfural.