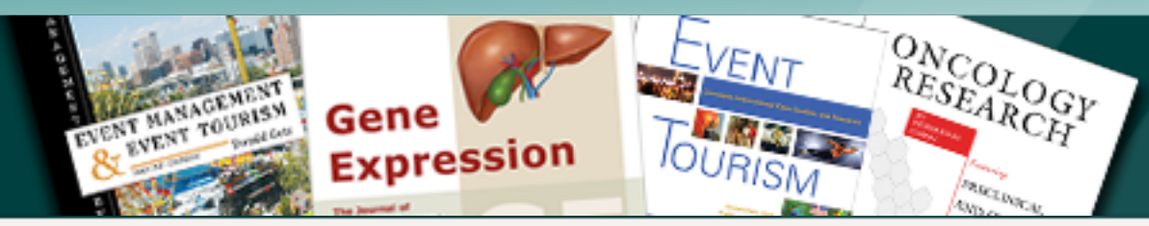




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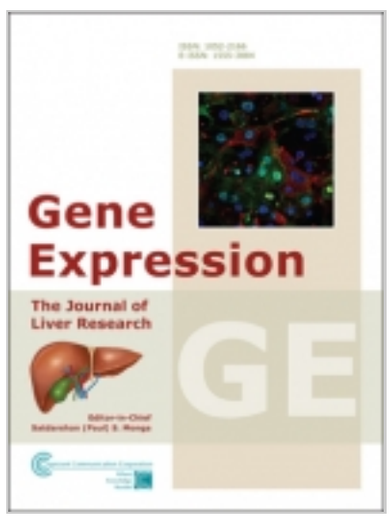


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# Gene Expression - The Journal of Liver Research

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GENE EXPRESSION

*The Journal of Liver Research*

**Drinking coffee may help prevent advanced liver fibrosis**

*Researcher concludes that 2-4 cups of drip coffee daily can help patients with liver fibrosis slow progression to cirrhosis*

*Putnam Valley, NY (December 15, 2017)* – A researcher who reviewed a number of studies investigating coffee consumption and changes in liver enzymes, liver fibrosis and liver cancer in patients with a variety of liver diseases, has concluded that coffee can serve as an antifibrotic agent in the liver. Patients with chronic liver disease could lower their risk of progressing to advanced liver fibrosis by drinking two to four cups of coffee daily. Only drip coffee provided this benefit.

The paper appears in the current issue of *Gene Expression: The Journal of Liver Research* and is currently freely available on-line as an unedited, early epub at: http://www.ingentaconnect.com/content/cog/ge

“Coffee is the world’s most widely used drug and favored stimulant,” said study author Jonathan A. Dranoff, MD, of the University of Arkansas for Medical Sciences. “But only recently have studies in animal models provided evidence that coffee can be an antifibrotic agent in the liver.”

Dranoff, who reviewed a number of retrospective studies, cited a 2001 study published in the *Annals of Epidemiology* (2001;11:458-465) that found a single cup of coffee daily lowered the risk for cirrhosis in patients with chronic liver disease to an odds ratio of 0.47. Four cups of coffee lowered the odds ratio to 0.16.

“The benefit appears to be dose-related,” explained Dranoff. “Interestingly, only coffee made by the drip method offers this benefit. Neither Turkish coffee, made by boiling ground coffee beans, nor espresso, made by pressurize hot water, offer this benefit.”

Other caffeine-containing products have not had the same antifibrotic effect, he noted.

What mechanism allows coffee to play an antifibrotic effect? Many reports suggest that adenosine, a chemical that is present in all human cells, may play an important role because caffeine is a known antagonist for adenosine receptors, especially for the adenosine *A2a* receptor.  Liver myofibroblasts express the *A2a* receptor, said Dranoff, and recent research using animal models of cirrhosis has shown that the direct and indirect markers of liver fibrosis were blocked by caffeine, but not blocked by decaffeinated coffee.

The benefit of coffee in reducing the risk of liver fibrosis appears to be dose-related. In studies, rats were greatly “over dosed” on caffeine to have the effect observed, but the benefit for humans may be realized  by drinking two to four cups of drip-made coffee daily, preferably not loaded down with sweeteners.

"There is insufficient evidence that more than four cups of coffee per day would further the benefit," suggested Dranoff, who also cautions about emerging data that suggests that coffee has been associated with "all-cause mortality."

"I propose that two to four cups of coffee should be prescribed to patients with chronic liver disease," said Dranoff, who suggested patients not drink too much coffee to the point where they feel anxious or "jittery" or lose sleep. "In my practice I ensure that patients stop consuming other caffeine-containing beverages, from coffee-based milkshake-like products, to sodas with caffeine, and "energy drinks" high in caffeine."

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GENE EXPRESSION

*The Journal of Liver Research*

**Mechanisms of acetaminophen toxicity unraveled**

*Hoping to provide a wider window for treatment, researchers add new insight to acute liver failure caused by overdose of commonly used pain reliever, acetaminophen.*

*Putnam Valley, NY (December 12, 2017)* – In the U.S. and around the world, the most common cause of acute liver failure is acetaminophen (APAP) over dose. This commonly used pain reliever is safe and effective when used at recommended doses, but if taken at toxic levels, either by accident or purposefully, acetaminophen overdose lead to liver cell damage, acute liver failure, and death.

A significant public health problem, APAP hepatotoxicity accounts for about half of all acetaminophen-related acute liver failure cases and contributes to around 70,000 hospitalizations in the U.S. every year. APAP overdose is responsible for 46 percent of all cases of acute liver failure in the U.S.

In an effort to better understand the mechanisms of APAP toxicity, and to apply that increased understanding to provide better interventions than currently available, researchers at the University of Kansas Medical Center (UKMC) studied a broad range of cellular toxicity mechanisms that could lead to APAP-induced acute liver failure and liver cell (hepatocyte) death.

The authors note that decades of investigations into the mechanisms of APAP-induced liver injury "have provided significant insight into the role of APAP metabolism" into the cascade of events that can lead to liver injury. However, more insight is needed.

"Although acetaminophen is safe and effective when taken at therapeutic doses, the therapeutic window for treating acetaminophen overdoses is quite narrow and an APAP overdose is highly toxic to the liver." said Dr. Hartmut Jaeschke of the Department of Pharmacology, Toxicology and Therapeutics at UKMC. "Our research is aimed at gaining a better understanding the mechanisms involved in APAP-induced liver injury so that more effective therapeutic interventions can be developed."

According to Dr. Jaeschhke and co-researcher Dr. Anup Ramachandran, also of the UKMC Department of Pharmacology, Toxicology and Therapeutics, when consumed at therapeutic doses, the majority of APAP is excreted through the kidneys. However, after an overdose of APAP the body's metabolic pathways are saturated and a variety of subsequent reactions lead the body form "APAP-protein adducts." Adducts are products of a direct addition of two or more distinct molecules, resulting in a single "reaction product" containing all atoms of the components.

The initial oxidative stress caused by APAP-protein adducts occurs in the cells' mitochondria, the site of cellular energy generation. According to the researchers, mitochondria can also play significant roles in cellular signaling and mitochondrial stress has emerged as a key factor in the cell signaling mechanism involved in APAP-induced liver cell death. This stress, however, has cellular ramifications, including mitochondrial failure.

"A better understanding of APAP-protein adduct formation and their relationship to liver cell death is very important," explained Ramachandran. "Their formation on mitochondrial proteins is most relevant for understanding how APAP toxicity can lead to hepatocyte death."

With APAP toxicity and mitochondrial APAP-protein adduct formation comes oxidative stress and the induction of "mitochondrial permeability transition pore" (MPTP), which ultimately compromises the mitochondrial membrane and shuts down mitochondrial function. Thus, MPTP is central to understanding APAP-induced liver injury, said the authors, who also note that it is now evident that the mitochondrial organelle also plays a significant role in the recovery and regeneration process after toxic injury.

On the positive side, the formation of APAP-protein adducts and their release into the circulatory system might be useful "biomarkers" for diagnosing APAP overdose. Too, they suggested that APAP overdose is a "clinically relevant model" for studying other causes of liver cell death and livery injury and is a model that can be used to study and test potential therapeutic intervention strategies.

What does their work mean for improving clinical interventions to save the lives of those with acute liver failure due to APAP toxicity?

“It is critical to connect these newly-discovered mediators and pathways of APAP metabolism to the already established mechanisms,” concluded the authors. “Although more can be learned about various aspects of these mechanisms, it is important to keep in mind potential effects of intervention strategies on drug metabolism, which can lead to misinterpretations.  The relevance of these studies will, therefore, depend on the solid understanding of the various toxicity mechanisms.”

Their paper appears in the current issue of *Gene Expression: The Journal of Liver Research.* It is freely available on-line as an unedited, early epub at: http://www.ingentaconnect.com/content/cog/ge/

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