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Editorial

A novel biomarker and hepato-protector for acetaminophen-induced liver injury

As the most common cause of acute liver failure in Western countries, acetaminophen-induced liver injury (AILI) is always a significant public health concern.[1,2] Acetaminophen, also known as paracetamol, is one of the most commonly used medications for its analgesic and antipyretic effects.[1,2] It is available over the counter both as a single formulation and in combination with other medications. While acetaminophen is a safe and effective drug at recommended doses, it has the potential of acute liver injury when overdose. It is not acetaminophen itself that causes liver injury, but rather the reactive metabolites.[1,2] When taken at recommended doses, near 90% of acetaminophen is metabolized by glucuronidation or sulfation and then excreted into the urine. About 2% is excreted into the urine unchanged, and <10% is metabolized by the cytochrome p450 2E1 (CYP2E1) into the reactive metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI). In normal condition, NAPQI is converted to non-toxic metabolites by glutathione (GSH). However, under the circumstance of GSH depletion, such as acetaminophen overdose, chronic alcohol ingestion, or malnutrition, NAPQI persists and leads to hepatotoxicity.[1,2] The NAPQI can form protein adducts with mitochondria, leading to mitochondrial dysfunction and cell death. The mitochondrial dysfunction seen in AILI is due to the disruption of the mitochondrial membrane and cessation of ATP production. Mitochondrial protein adduct formation with NAPQI causes oxidant stress and creation of reactive oxygen species within the mitochondria.[3]

Alteration of innate immunity also plays a significant role in the progression of liver injury after acetaminophen overdose.[1,2] Early cell death due to mitochondrial damage causes the release of multiple damage-associated molecular patterns including DNA fragments, heat shock proteins, and high-mobility group box 1 protein which subsequently activate toll-like receptors on Kupffer cells. Activated Kupffer cells release pro-inflammatory cytokines and chemokines that recruit neutrophils and monocytes and cause liver injury further.[1,2]

Early detection of liver injury may help us in managing AILI and preventing grave hepatic failure. The conventional serum markers for hepatocyte damage are alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which were always found to be elevated in the 2nd or third days after acetaminophen overdose, and cannot be regarded as an early biomarker. In this issue of *Journal of Chinese Medical Association*, Shi CX et al. found that serum glutathione S-transferase A1 (GSTA1) activity is a more sensitive indicator than aminotransferase in the detection of AILI.[4] GSTs are a family of phase 2 drug-metabolizing enzymes, and the main GST in the human liver, GSTA1, plays a pivotal role in protecting against toxic electrophiles and products of oxidative stress.[4] Although serum ALT and AST are the most commonly used indicators for hepatocyte injury, AST is a non-specific marker because it may be elevated in non-hepatic conditions such as heart injury, skeletal muscle disease, renal lesions or hemolysis.[4] The serum ALT level is more specific than AST as a marker of hepatic injury, but with a longer serum half time. It has been reported that GSTA1 has a short half-life of 1 h, and its serum level could be elevated earlier than that of ALT and decreased earlier in the resolution stage of liver injury.[5] Although the diagnostic and prognostic value of GSTA1 in the hepatotoxicity warrants further studies to validate it, the serum GSTA1 seems to have the potential as an early biomarker of liver injury. In addition, the systems biology omics technologies (transcriptomics, proteomics and metabolomics) have been used to discover potential translational biomarkers of liver injury. MicroRNA (miRNA)-122, -192, superoxide dismutase 1, calmodulin, keratin-18 and high-mobility group box-1 (HMGB1) have been suggested to the early biomarkers for AILI.[6,7] However, they have not been validated and are not in clinical use. We hope these novel markers could add substantial value to the current management of AILI in the near future.

Folium syringae (FS) has been used as a medicinal plant for its antibacterial and anti-oxidative property in China for a long time.[4] It is expected that anti-oxidants may have the potential to be therapeutic supplements against hepatotoxicity.[8] In this issue of Journal of Chinese Medical Association, Shi CX et al. have also assessed the protective effects of ethanol extracts of FS on the AILI *in vitro* and *in vivo*.[4] They found that pretreatment with FS could scavenge free radicals and enhance the anti-oxidation activities *in vivo* and *in vitro*.[4] This hepatoprotective effect was found to be related to its modulation on some de-toxification and anti-oxidation enzymes.[4] Although *N*-acetylcysteine is the drug of choice for the treatment of AILI,[1,2] FS has the potential as a nutrient supplement in the amelioration of AILI from this mechanistic investigation.[4]

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Although Shi's study has demonstrated the mechanism and potential hepato-protective role of FS in AILI using the hepatocyte and mice model,[4] it still has a long way to clinical application. Plentiful vegetables and herbs have been shown to have some hepato-protective effects for xenobiotics and alcohol in earlier studies using cellular or animal models.[5,8,9] However, no one vegetable or herb has solid efficacy in the therapy of liver injury. Accordingly, virtually all medicinal herbs cannot be successfully demonstrated to have proven efficacy and safety as an authentic drug. In addition, the pathogenesis of liver injury induced by different chemicals, such as acetaminophen, carbon tetrachloride, lipopolysaccharide, alcohol and other chemicals, are diverse. Whether FS has similar hepato-protective effect in different hepatotoxins is unknown.

The other limitation of this kind of bio-pharmaceutical studies is that the lacking of the identification and purification of the active component of the medicinal herbs. Ethanol extracts from FS was used in Shi's study.[4] The main compositions of FS include organic acids, eugenol, glycosides and volatile oil. The real ingredients from the FS ethanol extracts were not identified and the major constituent for the hepato-protection is unknown. Further studies in the identification and purification of hepato-protective medicinal plants are of value in the therapeutic application.

Hepatotoxicity is always a major concern in the pre-marketing drug development, and post-marketing safety surveillance. Although many efforts have been enforced to ameliorate the hepatic injury by health authorities and pharmaceutical industries, hepatic injury by drugs, food, and other chemicals have still occurred unrelentingly. Under this situation, the hepato-protectants are urgently needed. Therefore, the mechanistic exploration of hepato-protectants, such as the FS study in this issue,[4] is worthy of encouraging. This kind of approach may help us realize the pathogenesis of liver injury, and consolidate our confidence to utilize FS and other hepato-protectants properly.

Conflicts of interest

The author declares that he has no conflicts of interest related to the subject matter or materials discussed in this article.

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