The hepatoprotective effect of ginger

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Ginger (*Zingiber officinale*) is a pungent, aromatic spice, which has been commonly used in food and medicine recipes around the world for thousands years.[1] Ginger has been found to contain more than 400 compounds, but is mainly composed of carbohydrates, lipids, and volatile oils. The fragrance and flavor of ginger result from volatile oils that consist of zingerone, shogaols, and gingerols with [6]-gingerol as the major pungent compound.[1] Fresh ginger contains an enzyme zingibain, which is a cysteine protease. Ginger is commonly used as a dietary supplement to alleviate nausea and vomiting. There is tentative preliminary evidence that ginger may reduce pain in the setting of dysmenorrhea and osteoarthritis, which is thought to be related possible anti-inflammatory effects of gingerol and related compounds.[1] Evidences based on the studies of rat and mice have suggested that ginger may play a role in the protection of liver from various liver diseases as follows.[2–17]

1. DRUG-INDUCED LIVER INJURY AND TOXIC HEPATITIS

The hepatoprotective effect of the extract from ginger on many chemical and drug-induced liver injuries (DILI) has been shown in rat studies by serum biochemical and histopathological evidences in recent two decades.[2–9] The hepatotoxic agents studied consists of acetaminophen, carbon tetrachloride, bromobenzene, paraben, malathion, phosphamidon, lead acetate, cadmium, dimethylnitrosamine, carbendazim, and aflatoxin B1.[2–9] The hepatoprotective effect of ginger is hypothesized from its antioxidant and anti-inflammatory properties. Furthermore, this effect may be explained partially by downregulating the transforming growth factor-β1/Smad3 and nuclear factor-kappa B (NF-κB)/IκB signaling pathways.[6]

In the current issue of the *Journal of Chinese Medical Association*, Badawi underlines the important role of ginger on the protection of piroxicam-induced liver toxicity.[9] Piroxicam is a nonsteroidal anti-inflammatory drug widely used in rheumatic diseases. Piroxicam-induced liver injury has been reported as one of its principal side effects. This study has demonstrated that administration of ginger can decrease elevated serum aminotransferase, alkaline phosphatase, and immune-expression of the proapoptotic protein (Bax), induced by piroxicam in mice. Ginger also ameliorated the morphological changes induced by piroxicam. It is concluded that ginger has protective effects against piroxicam-induced liver injury by reducing serum marker enzymes, liver fibrosis, and apoptosis.[9] It is noticeable that quantitative morphometric measurement of the diameter of blood sinusoids and central veins in control and treated groups was performed in this study. Diameters of blood sinusoids and central veins were significantly increased in piroxicam-treated mice. Combined piroxicam and ginger group has showed significantly decreased the diameter of blood sinusoids and central veins compared to piroxicam-treated group.[9] This pathological finding has proposed a novel evidence to support the hepatoprotective role of ginger in DILI.

To date, only one relevant study of DILI was implemented in human.[10] A randomized controlled trial in patients under antituberculosis treatment has shown that ginger could alleviate nausea related to antituberculosis drugs.[10] Patients in the ginger group experienced less, but not statistically significant, antituberculosis DILI than the placebo group (16.7% vs 36.7%, respectively, $p = 0.07$).[10] The limited cases number of this study (30 patients in each group) and marginal statistical results could not verify the role of ginger in the hepatoprotection to DILI in human.

2. ALCOHOLIC LIVER DISEASE

A few rat studies have shown that ginger possesses the protective role against alcohol-related liver disease and fatty liver, based on the biochemical data and histopathological examination.[11,12] Metabolomic data indicated the amounts of metabolites such as glycerol-3-phosphate, pyruvic acid, lithocholic acid, and prostaglandin E1 were increased after alcohol administration, but the levels were recovered in the ginger-treatment mice group.[11] There is still no human study in this setting.

3. NONALCOHOLIC FATTY LIVER DISEASE

Nonalcoholic fatty liver disease (NAFLD) is the most prevalent liver disease globally now, which may develop into liver fibrosis, cirrhosis, and hepatocellular carcinoma in severe cases. The pharmaceutical industry and healthcare providers have endeavored in the prevention and treatment of NAFLD recently. The pathogenesis of NAFLD is closely associated with obesity and insulin resistance. Ginger may have hypolipidemic and antioxidant effects, and act as an insulin sensitizer. A few animal studies have shown the potential of hepatoprotective effect of ginger on the NAFLD.[13,14] In a randomized, double-blind, placebo-controlled clinical trial, 44 patients with NAFLD were assigned to take either a ginger supplement of 2 g/day or the identical placebo for 12 weeks.[15] Ginger supplementation

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resulted in a significant reduction in alanine aminotransferase, γ-glutamyl transferase, inflammatory cytokines, as well as the insulin resistance index and hepatic steatosis grade in comparison to the placebo.[15] Further studies are recommended to assess the long-term supplementation effects with a large sample size.

4. HEPATOCELLULAR CARCINOMA

A few rat studies have disclosed that ginger supplement can suppress liver carcinogenesis by scavenging the free radical formation and by reducing lipid peroxidation.[16,17] Ginger may act as an anticancer and anti-inflammatory agent by inactivating NF-κB through the suppression of the proinflammatory tumor necrosis factor-α.[17] However, no human study in this setting was published to date.

5. LIMITATIONS OF THE GINGER STUDIES AND PERSPECTIVES

Although many studies have demonstrated the mechanism and potential hepatoprotective role of ginger in liver diseases using the hepatocyte and animal model,[2–17] the real therapeutic effect to human is still debatable. Hundreds of vegetables and herbs have been shown to have some hepatoprotective effects in earlier studies of cytomolecular levels and animal models. However, none of them has robust evidence to demonstrate the efficacy in human. There is still a wide gap between the circumstances of a bench study and clinical application in the biopharmaceutical science community and industry. Furthermore, different extract methods to ginger with different components and amount were implemented in the relevant studies.[2–17] The major active ingredient and its dosing to be the therapeutic effect of human liver disease warrants further investigation and standardization. In addition, the above-mentioned human control studies had so limited number of cases with low power in statistics.[10,15] We hope there will be large-scale well-designed randomized controlled trials to validate the real value of ginger in the hepatoprotection in the near future.

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