

## Potential efficacy of ginger as a natural supplement for nonalcoholic fatty liver disease

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### Abstract

Nonalcoholic fatty liver disease (NAFLD) is one of the most common liver diseases and its prevalence is likely to reach epidemic proportions. According to the "two-stage hypothesis" proposed for the pathophysiology of NAFLD, insulin resistance, oxidative stress and pro-inflammatory cytokines are among the key promoters of the disease. Here, ginger has been hypothesized to prevent NAFLD or blunt its progression *via* several mechanisms, such as sensitizing insulin effects, activating peroxisome proliferator-activated receptor  $\gamma$  which induces adiponectin and down-regulates pro-inflammatory cytokines, changing the balance between adiponectin and tumor necrosis factor- $\alpha$  in favor of adiponectin, promoting considerable antioxidant effects and antidiabetic properties, and reducing hepatic triglyceride content which can prevent steatosis. The aforementioned mechanisms imply that ginger possesses interesting potentials for serving as a natural supplement for the prevention and treatment of NAFLD. Therefore, conducting trials to explore its benefits in clinical practice is greatly recommended.

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**Key words:** Nonalcoholic fatty liver disease; Ginger; Insulin resistance; Oxidative stress; Inflammation

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### TO THE EDITOR

Nonalcoholic fatty liver disease (NAFLD), one of the most common liver diseases, is growing fast into an epidemic problem in Western countries. NAFLD, covering a wide spectrum of hepatic conditions from simple steatosis to nonalcoholic steatohepatitis (NASH), may lead to more severe disorders such as cirrhosis and hepatocellular carcinoma. The pathophysiology of NAFLD has been conceptualized to be a two-stage process, consisting of fat accumulation in hepatocytes and consequent hepatic steatosis in the first stage, and hepatic injury or NASH in the second stage. Insulin resistance plays a central role in both stages of NAFLD pathogenesis while oxidative stress and pro-inflammatory cytokines [in particular tumor necrosis factor (TNF)- $\alpha$ ] are among the important promoters of the second stage.

Ginger (underground rhizomes of *Zingiber officinale*) is a famous spice which has been used for centuries as a medicinal plant in different traditional medicine systems. The therapeutic effects of ginger have also been validated by modern research, rendering it as a potential medication for a variety of disorders. Gingerols and shogaols represent the predominant pungent constituents of ginger responsible for many of its medicinal properties. Herewith, it is hypoth-

esized that ginger might be applied as a potential natural medicine that could counteract the biochemical abnormalities involving the pathogenesis of NAFLD as follows.

Insulin resistance is a common feature in patients with NAFLD and NASH. Regarding the key role of insulin resistance and resulting hyperinsulinemia in hepatic triglyceride accumulation, insulin sensitizing is an important therapeutic mechanism against NAFLD. A previous preliminary study reported that the insulin sensitivity to adipocytes could be improved using ginger, with gingerol as its active component for this effect<sup>[1]</sup>.

It is considered that peroxisome proliferator-activated receptors  $\alpha$  (PPAR $\alpha$ ) and  $\gamma$  (PPAR $\gamma$ ) can influence hepatic triglyceride accumulation and thereby pathogenesis of NAFLD. It was reported that PPAR $\gamma$  can improve insulin sensitivity and decrease the flux of fatty acids into liver<sup>[2]</sup>. Moreover, PPAR $\gamma$  activation is associated with other beneficial effects such as induction of adiponectin expression and secretion, and down-regulation of the expression of pro-inflammatory cytokines including TNF- $\alpha$ . Hence, PPAR $\gamma$  agonists have been hypothesized to be of therapeutic importance in NAFLD<sup>[2]</sup>. Noteworthy, ginger's 6-shogaol has been reported to be a significant agonist of PPAR $\gamma$  in adipocytes<sup>[3]</sup>.

Previous studies showed that both TNF- $\alpha$  and adiponectin play an important role in the development of hepatic steatosis and in its progression to NASH<sup>[4,5]</sup>. These cytokines have conflicting activities and antagonize each other's production and effects. While adiponectin has several protective effects against NAFLD such as improvement of insulin resistance and reduction of fat accumulation in hepatocytes. TNF- $\alpha$  antagonizes these effects and promotes hepatic steatosis. Therefore, down-regulation of TNF- $\alpha$  may be a potential approach to the treatment of NAFLD and amelioration of liver damage. Ginger is deemed to be effective for this purpose as several previous studies have shown that ginger extract and its bioactive constituents can decrease the TNF- $\alpha$  expression<sup>[6,7]</sup>. Moreover, it has been found that both 6-gingerol and 6-shogaol can significantly inhibit TNF- $\alpha$  mediated down-regulation of adiponectin expression<sup>[5]</sup>.

Along with cytokines, oxidative stress also plays an important role in the second stage of NAFLD, mediating the progression of hepatic steatosis to NASH. Therefore, antioxidants such as vitamin E have gained therapeutic application in the treatment of NAFLD. In addition to the other benefits mentioned, ginger possesses considerable antioxidant properties including radical scavenging activity and inhibitory effect on lipid peroxidation, which can be ascribed to the presence of polyphenols such as gingerol and curcumin in this plant<sup>[8]</sup>. Besides, ginger protects the liver against hepatotoxic agents by enhancing the hepatic antioxidant activity<sup>[9,10]</sup>.

Triglyceride accumulation in hepatocytes is the hallmark of NAFLD. There is evidence that ginger can reduce hepatic triglyceride content, induce LDL receptor and down-regulate HMG-COA expression in the liver<sup>[11]</sup>.

Moreover, ginger extract has been reported to exert its anti-hyperlipidemic effects by decreasing serum levels of total cholesterol, LDL-C and triglycerides and increasing HDL-C<sup>[12]</sup>. Thus, supplementation with ginger might be effective in the prevention of steatosis and control of dyslipidemia which is a risk factor for NAFLD<sup>[10]</sup>.

In spite of the aforementioned interesting potentials of ginger, the efficacy of this wonderful spice has not been sufficiently investigated in relation to NAFLD. Given the long reputation of ginger as a medicinal herb and dietary spice with a good safety, tolerability and low price, future clinical trials are warranted to identify its efficacy as a multifunctional adjunctive therapy for NAFLD.

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