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Phytochemicals in fenugreek seed prevent high fat diet induced metabolic inflammation and NAFLD via the mediation of *Akkermansia muciniphila*

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Abstract

Introduction: Fenugreek (Trigonella foenum-graecum) is an annual legume that has been used as a spice throughout the world to enhance the sensory quality of foods. A number of health-beneficial bioactive compounds (i.e. trigonelline and diosgenin) have been identified in the seed of fenugreek. These compounds exert multiple health beneficial effects, including anti-obesity and anti-type 2 diabetes. The objective of our study is to determine the underlying mechanism of whole grain of fenugreek seed and purified bioactive compounds, trigonelline and diosgenin, in ameliorating high fat diet (HFD) induced metabolic inflammation and non-alcoholic fatty liver disease (NAFLD).

Materials and Methods: Two groups of C57B6 mice were fed a HFD containing either a vehicle control or 2% of fenugreek seed for 7 weeks. Caloric intake and body weight were monitored weekly during the feeding trial. Glucose tolerance test was conducted to determine the insulin sensitivity. Q-RT-PCR, immunoblotting analysis and histological analysis were used to determine the expression of genes involved in metabolic inflammation and lipid metabolism.

Results and Discussion: While caloric intake and body weight were comparable between control and fenugreek treated groups during the feeding trial, fenugreek seed containing diet significantly reduced circulation level of inflammatory cytokine TNFa. In the liver, fenugreek suppressed the gene expression of inflammatory cytokines, such as IL-1b and IL-6, and ameliorated hepatic ER stress. The improvement of metabolic inflammation was associated with less activation of genes involved in hepatic de novo lipid synthesis (i.e. FASN and ACC) and enhanced fatty b-oxidation which resulted in significant amelioration of HFD-induced hepatic steatosis, hyperlipidemia and insulin resistance. Analysis the populations of gut microbiota further revealed that the population of *Akkermansia muciniphila*, a gut bacterial strain that is involved in body weight regulation and insulin sensitivity, was significantly increased by fenugreek seed containing diet. *In vitro*, treating McA-RH7777, a rat hepatoma cell line, with purified phytochemicals of fenugreek seeds, trigonelline and diosgenin, inhibited hepatic de novo lipogenesis, attenuated ER stress induced by a saturated fatty acid, palmitic acid. These actions improved insulin sensitivity in McA-RH7777 cells by enhancing the functional activity of insulin signaling molecules, such as insulin receptor and AKT.

Conclusion: Our study unveils a novel mechanism of the bioactive compounds, trigonelline and diosgenin, in fenugreek seed that ameliorate metabolic inflammation and hepatic steatosis via the mediation of gut bacteria. This finding may lend support for developing phytochemicals in fenugreek seed as prebiotic supplement for the prevention and treatment of hyperlipidemia and insulin resistance.

Conflict of Interest

There is no conflict of interest