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The effects of Rhein and Thymoquinone on obesity and diabetes in diet-induced obese mice.

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Natural product extracts and chemicals isolated from natural products (e.g., plants, berries, seeds) have been commonly used in various types of traditional medicines. In addition, some drugs on the market today have been derived from natural product sources. The purpose of our study was to evaluate two natural products, Rhein and Thymoquinone, as potential anti-diabetic and anti-obesity agents. According to the Center for Disease Control (CDC), the number of people in the US diagnosed with diabetes has increased from 11.8 million people in the year 2000 to 20.8 million people in the year 2011. Rhein is a natural compound and a major component of Rheum palmatum, or Rhubarb. It has been used in Chinese medicine to treat constipation, gastrointestinal hemorrhage, ulcers as well as metabolic disorders such as diabetes. Recently, Rhein had been shown to improve non-alcoholic fatty liver disease (NAFLD) at doses of 150 mg/kg/day in diet induced obese mice through reducing body fat, improving serum lipid and glucose metabolism, and decreasing liver lipids, and reversing hepatic steatosis (Sheng et al., 2011). Rhein has also been shown to influence the Liver X receptors (LXRs) which play important roles in regulating cholesterol homeostasis, and lipid and energy metabolism. (Sheng et al., 2012). Thymoquinone (TQ) is a compound found in the plant Nigella sativa, or black cumin and has been documented to exhibit anti-diabetic, anti-obesity, hypotensive and hypolipidemic properties in human and animal studies. (Razavi and Hosseinazadeh, 2014). Extracts from Nigella sativa significantly increased hepatic and intestinal apolipoprotein A-1 which is a major protein component of high density lipoprotein (HDL) secretion. The extract also induced peroxisome proliferator-activated receptor alpha (PPARα) expression by 9-fold and retinoid X receptor alpha (RXRα) expression by 2.5-fold. (Haas et al., 2014). The PPARα and RXRα nuclear receptors play and important role in regulating major lipid metabolism proteins. The purpose of our study was to evaluate whether daily administration of Rhein or TQ could improve obesity-induced diabetes in mice. First, male C57BL/6 mice that were 6 weeks of age were fed a low fat diet (10% kcal, LFD) or a high fat diet (60% kcal, HFD) for 12 weeks. Over the twelve-week period, body weight, fasting blood glucose and glucose tolerance were determined to assess whether the high fat diet could induce a diabetic condition. Starting week 12, mice were administered canola oil vehicle (CO, 5 mg/kg), Rhein (20 mg/kg, 5 mg/kg in CO), or TQ (1 mg/kg, 5 mg/kg) daily. After three weeks of dosing the Rhein and TQ doses were increased to Rhein (50 mg/kg, 2.5 mg/kg) and TQ (10 mg/kg, 2.5 mg/kg). There were six groups of mice in this study, with the following groups: i) LFD + CO, ii) LFD + Rhein, iii) LFD + TQ, iv) HFD + CO, v) HFD + Rhein, vi) HFD + TQ. Body weight and food consumption were measured daily. At periodic points throughout the study, fasting blood glucose (FBG) and glucose tolerance (GTT) were measured in the mice.

Materials and Methods

Average blood glucose measurements in (mg/dL) taken at various time points, after giving a oral dose of glucose (1 mg/kg).

Conclusions

- There are differences in body weight, FBG, and GTT between the mice feed a HFD and LFD as expected.
- The body weights, FBG, and GTT of the groups dosed with rhein compared with the groups dosed with the vehicle CO show little differences.
- The body weights and GTT of the groups dosed with TQ compared with the groups dosed with the vehicle CO show little differences.
- There is a slight difference between the FBG of the HDF group dosed with TQ compared with the HFD group dosed with the vehicle CO. Which may be an indication that TQ may lower blood sugar but more studies need to be conducted and this group is also missing from the GTT data due to unforeseen circumstances.

References


CDC - Number of Adults - Diagnosed Diabetes - Data & Trends - Diabetes DTT.
Male C57BL/6 mice that were 6 weeks of age were given a LFD or HFD for 12 weeks.

- Low fat diet (10% kcal, LFD)
- High fat diet (60% kCal, HFD)

During the 12 week period, body weight, FBG and GTT were determined to assess whether the HFD could induce a diabetic condition.

Mice dosed daily by oral gavage:
- Dosed with Canola oil Vehicle (CO, 5 ml/kg),
- Dosed with Rhein (20 mg/kg in 5 ml/kg CO)
- Dosed with TQ (1 mg/kg, in 5 ml/kg CO)

After 3 weeks, doses were increased and continued for 69 days:
- Dosed with CO (2.5 ml/kg),
- Dosed with Rhein (50 mg/kg in 2.5 ml/kg CO)
- Dosed with TQ (10 mg/kg, in 2.5 ml/kg CO)

Preformed necropsy and collected tissue samples:
- Collected: Blood, Liver, Kidneys, Skeletal muscle, Adipose tissue, Small intestine, and colon

Fasting Blood Glucose (FBG) and Glucose Tolerance Testing (GTT):
- Mice were fasted overnight
- The end of the mouse’s tail was pricked and blood was collected and measured with a glucometer twice.
- Mice were given a dose of glucose (1g/kg) by oral gavage.
- Average of the two values were recorded at initial blood glucose and FBG.
- At 15, 30, 60, and 90 minutes after the dose of glucose, mouse tail blood was collected and measured with the glucometer twice and the average of the two values were recorded.