KDT501, a Novel Substituted 1,3-Cyclopentadione, Normalizes Glucose Metabolism in Diet-Induced Obesity Mouse and ZDF Rat Models of Diabetes

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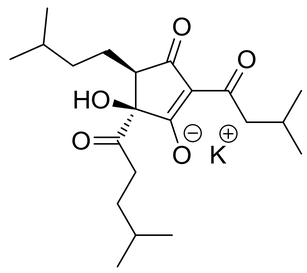
Abstract

Extracts from hops (*Humulus lupulus*) have been widely used as flavoring agents in brewing. Previously, it was reported that mixtures of hop extracts showed anti-inflammatory and anti-diabetic effects. We developed KDT501, a novel, stereo-chemically pure substituted 1,3-cyclopentadione chemically derived from hop extracts, and evaluated it in various *in vitro* and *in vivo* models of diabetes and insulin sensitivity. In a mouse model of diet-induced obesity, oral administration of KDT501 (100 and 200 mg/kg twice/day) for 4 weeks reduced fed blood glucose, and glucose/insulin AUC calculated following an oral glucose bolus. Mice receiving KDT501 at 200 mg/kg exhibited significantly reduced body fat. In ZDF rats, oral administration of KDT501 twice daily for 4 weeks (100, 150 and 200 mg/kg), significantly reduced fed glucose, fasting plasma glucose and glucose AUC after an oral glucose bolus. Similar to metformin (200mg/kg) and pioglitazone (30mg/kg), a significant, dose-dependent reduction of plasma hemoglobin A1c was observed in animals receiving KDT501, when compared to the vehicle control (100mg: -20%, 150mg: -54.6%, 200mg: -54.6%). KDT501 dose-dependently reduced weight gain in ZDF rats, while rats treated with metformin or pioglitazone gained weight compared to vehicle-treated controls. These results suggest that the anti-diabetic mechanism of KDT501 may differ from that of both metformin and pioglitazone and this molecule may be a novel therapeutic for the treatment of Type 2 diabetes in humans. Efforts to elucidate the mechanisms of cellular pathways are underway. KinDex has initiated a Phase 1 clinical study to determine safety, pharmacokinetics, and preliminary efficacy of KDT501.

KDT501 Structure



Methods

High Fat Diet Induced Obesity in Mice: C57Bl6/J male mice were 14 weeks old at the start of the experiment. High fat diet (40% Cal) TD95217 (Teklad Custom Research Diet) was used in this study. The test compounds were administered orally in 0.5% methylcellulose and 0.2% Tween 80 (w/v). Mice (16/group) were given 25, 50, 100, or 200 mg/kg body weight of KDT501 bid (50, 100, 200, 400 mg daily dose) for 30 days. A negative control group was given the vehicle bid (0.5% methylcellulose and 0.2% Tween 80 [MCT]). Control animals were given 200 mg/kg metformin BID (400 mg/kg/day) or 30 mg/kg pioglitazone bid (60 mg/kg/day). Body weight and food consumption were determined weekly. Body composition was measured by QNMR. Insulin and HbA1c glucose levels were determined on days 1, 15 and 29.

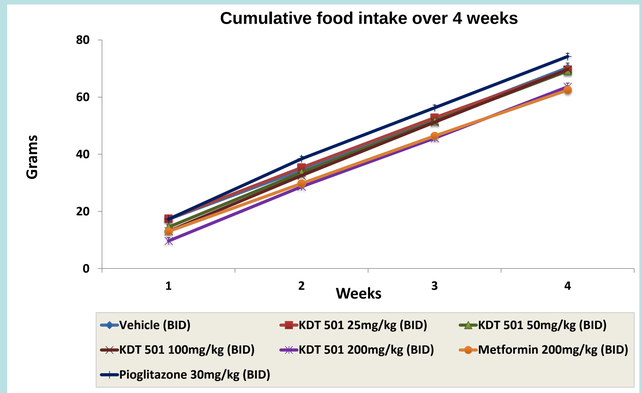
After 30 days of test compound supplementation, 5 mice were selected from each group for glucose tolerance testing (OGTT). An additional 5 animals were used for the insulin tolerance test. The mice were fasted overnight. At 8:00 AM on the experimental day, baseline blood glucose was measured using a glucose analyzer. One hour later, mice were given an oral gavage of glucose solution in water (4ml/kg, 2g/kg). Additional blood samples were taken via tail bleeding at 15, 30, 60, and 120 min for determination of plasma glucose and insulin levels.

Zucker Diabetic Fatty (ZDF) Rats: The efficacy of KDT501 as an anti-diabetic drug was evaluated in 8 week old male ZDF rats. Rats were maintained *ad lib* on Purina #5008, delivering approximately 17% of calories from fat. After acclimatization, animals with fasting glucose between 150- 350 mg/dL were randomized to treatment regimen based on glucose and body weight. The test compounds in MCT were administered by oral gavage. The body weights and food intake were determined weekly. ZDF rats (10/group) were given 100, 150, or 200 mg/kg bid (200, 300 or 400 mg/kg/day) KDT501 for up to 32 days. The negative control animals were administered the vehicle (MCT in reverse osmosis [RO] water). The positive controls were given 200 mg/kg metformin (400 mg/kg/day) or 30 mg/kg pioglitazone both bid (60 mg/kg/day).

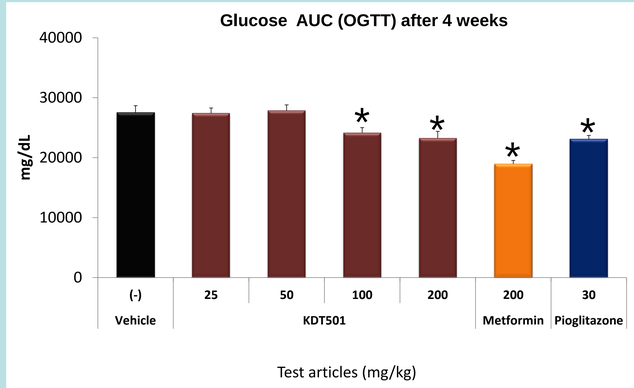
Blood was collected via tail bleed on days -3 (used for randomization) and 1 and on day 8, 15 and 29 whole blood glucose was evaluated. Blood was collected in 5 animals on Days 15 and 29 for determination of glucose, insulin, lipids, hematocrit, and HbA1c. Animals were fasted overnight on day 30 and 31st and OGGT was conducted on Days 31 and 32 for determination of glucose and insulin levels. A second ZDF rat study was conducted and the resulting data on total cholesterol are presented. *P=<0.05 versus corresponding vehicle group.

Diet Induced Obesity Mice

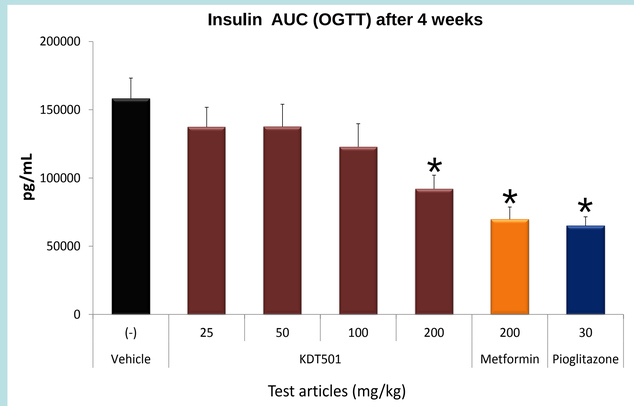
KDT501 does not change food intake in DIO mice



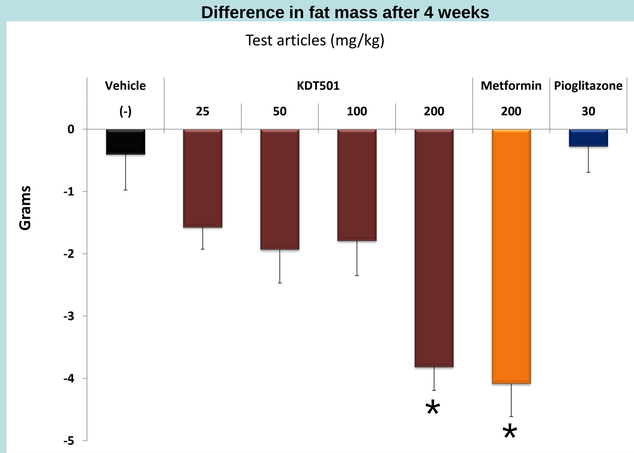
KDT501 reduces glucose AUC in DIO mice



KDT501 reduces insulin AUC in DIO mice

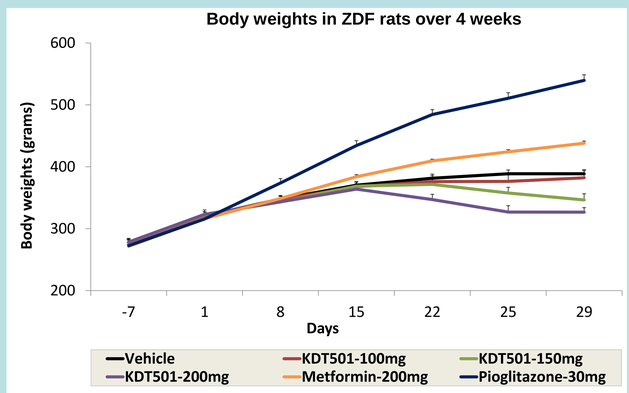


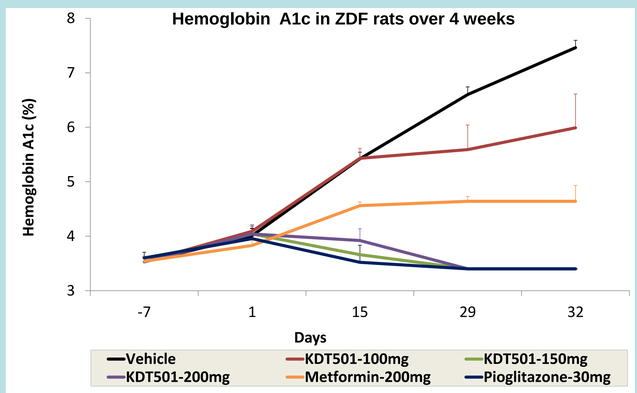
KDT501 reduces body fat in DIO mice



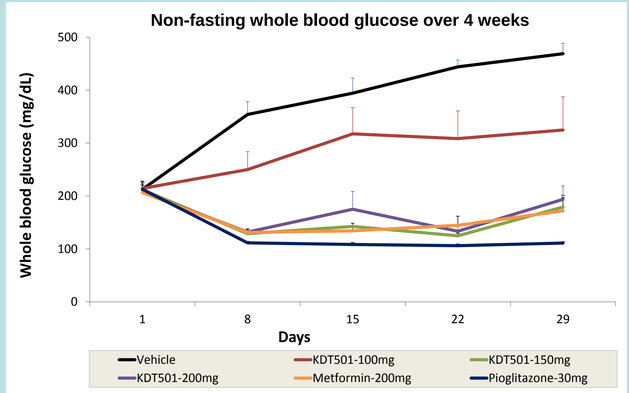
Zucker Diabetic Fatty (ZDF) Rats

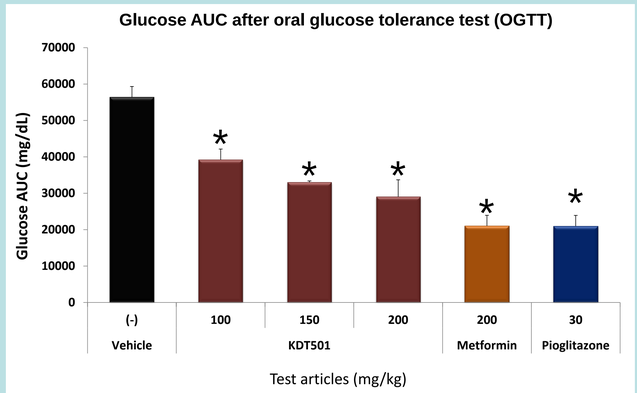
KDT501 prevents weight gain and reduces hemoglobin A1c in ZDF rats



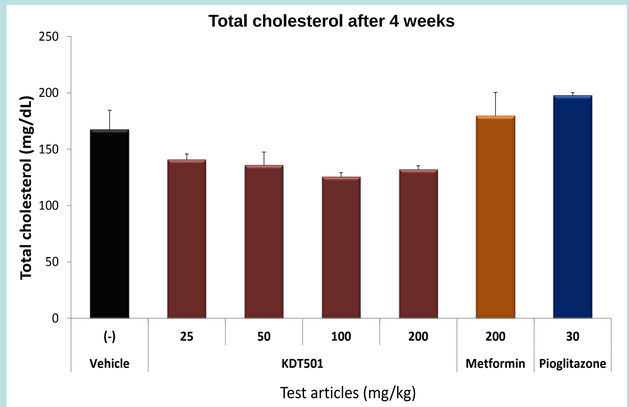


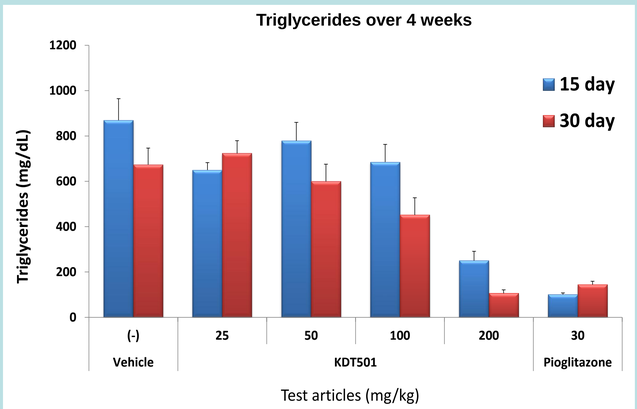
KDT501 improves glucose metabolism in ZDF rats





KDT501 reduces total cholesterol and triglycerides in ZDF rats





Summary & Conclusions

- Oral administration of KDT501 for 4 weeks reduced fat mass and had no effect on food intake in DIO mice.
- KDT501 dose-dependently reduced fed blood glucose, and glucose/insulin AUC calculated following an oral glucose bolus in DIO mice.
- In ZDF rats, oral administration of KDT501 for 4 weeks, significantly reduced fed glucose and fasting plasma glucose and glucose AUC after an oral glucose bolus in a dose-dependent manner.
- Reduced plasma hemoglobin A1c was observed in ZDF rats receiving KDT501, when compared to the vehicle control.
- KDT501 dose-dependently reduced weight gain, total cholesterol and triglycerides in ZDF rats, while rats treated with metformin or pioglitazone gained weight compared to vehicle-treated controls.
- These results suggest that the anti-diabetic mechanism of KDT501 may differ from that of both metformin and pioglitazone and may be a novel therapeutic for the treatment of Type 2 diabetes in humans.
- In a Phase 1a single ascending dose study, KDT501 has been demonstrated to be safe and well tolerated at exposures relevant to our preclinical experience. A Phase 1b multiple ascending dose study will be initiated later this year.