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# Danning tablets might improve glucose and lipid metabolism in asymptomatic T2MD patients after cholecystectomy

## A cohort study

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**Abstract**

Considering the role of bile acids in glucose metabolism and the effect of farnesoid X receptor agonists on bile acids, we investigated the possible effect of Danning tablets (DNTs), a type of farnesoid X receptor agonist, on glucose and lipid metabolism in asymptomatic type 2 diabetes mellitus (T2DM) patients.

A series of asymptomatic T2DM patients who underwent cholecystectomy at least 2 years prior and were regularly followed up in our hospital were included in our analysis. According to their choice, they were divided into 2 groups: the DNT group and the control group. Demographic data, body weight, food intake, effects on diabetes control, and biomedical variables were collected.

After propensity score matching, a total of 64 T2DM patients (41 males and 23 females) were included in the analysis. The amount of daily food intake (kcals) and diet composition were little changed 6-months after DNT administration ($P = .612$). However, the average fasting glucose level of the DNT group decreased from $9.5 \pm 1.4$ mmol/L to $8.3 \pm 1.6$ mmol/L ($P < .001$), and the level of hemoglobin A1c decreased from $8.3 \pm 1.1\%$ to $7.6 \pm 1.0\%$ ($P = .001$). The total cholesterol level ($P = .024$) and low-density lipoprotein cholesterol level ($P = .034$) decreased significantly ($P = .018$). Moreover, the average level of total bile acids decreased from $6.05 \pm 2.60$ μmol/L to $5.10 \pm 1.83$ μmol/L in the DNT group ($P = .037$), and the level of glucagon-like peptide-1 significantly increased from $6.93 \pm 4.94$ pmol/L to $11.25 \pm 5.88$ pmol/L ($P < .001$).

The results of our study show that DNT intake improved glucose and lipid metabolism and increased the level of glucagon-like peptide-1.

Trial registration: registered in Chinese Clinical Trial Registry (No. ChiCTR1900027823).

**Abbreviations:** BMI = body mass index, DNTs = danning tablets, FPG = fasting plasma glucose, FXR = farnesoid X receptor, HbA1c = hemoglobin A1c, GLP-1 = glucagon-like peptide-1, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, PS = propensity score, T2DM = type 2 diabetes mellitus, TC = total cholesterol.

**Keywords:** bile acids, glucagon-like peptide-1, glucose, lipids, type 2 diabetes

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*The study was approved and supervised by the ethics committee of our hospital, and registered in Chinese Clinical Trial Registry (No. ChiCTR1900027823). Informed consents of patients were obtained.*

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*The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.*

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## 1. Introduction

Type 2 diabetes mellitus (T2DM) is one of the most serious chronic diseases, and is a set of metabolic disorders of carbohydrates, proteins, and lipids. These metabolic abnormalities include elevated fasting and postprandial glucose, insulin resistance and lipid metabolism disorders.[1] With more applications and investigations of metabolic surgery for T2DM patients, the role of bile acids (BAs) and their receptors has been widely recognized.[2] BAs are not only involved in the digestion of lipids, but are also signal molecules that play an important role in glucose and lipid metabolism.[3] The BA level increases significantly after metabolic surgery, and high levels of BAs might improve glucose metabolism in T2DM patients.[4]

Danning tablets (DNTs) are a composite prescription of traditional Chinese medicine,[5] and they comprise extracts of many medicinal materials, including *Rheum officinale Baill* (46.4 mg/tablet), *Polygonum cuspidatum Siebold & Zucc* (68 mg/tablet), *Citrus reticulata Blanco* (27.2 mg/tablet), *Curcuma kwangsiensis S.G.Lee & C.F.Liang* (40.8 mg/tablet), *Crataegus pinnatifida Bunge* (68 mg/tablet) and *Imperata cylindrica (L.) P. Beauv.* (40.8 mg/tablet) etc.[6] Every 1 g DNT contains approximately 6.68 mg hyperin, 5.50 mg hesperidin, 0.55 mg resveratrol, 6.55 mg nobiletin, 1.10 mg curcumine, 18.03 mg emodin, 1.01

mg chrysophanol, and 4.57 mg physcion.[6] It is commonly prescribed in China as a cholagogic formula, because DNTs can activate farnesoid X receptor (FXR) and promote BA and bilirubin elimination by regulating the expression of hepatic and renal transporters.[7] In addition, FXR is also a metabolic regulator that can affect glucose and energy metabolism.[5] FXR activity can inhibit gluconeogenesis, increase insulin secretion and enhance insulin sensitivity.[8] Therefore, DNTs might affect glucose metabolism.

However, there have been few reports about modifications to glucose metabolism caused by DNTs. Considering that DNTs are widely applied widely in clinic, we aimed to investigate the effects of DNTs in asymptomatic T2DM patients after cholecystectomy. The exquisite regulation of glucose and lipids is disrupted in T2DM, so treatment with DNTs could expose its positive or negative effects on glucose and lipid metabolism. Bile is concentrated in the gallbladder, which absorbs 23% of cholesterol, 32% of phosphatidylcholine, and 9% of bile salts over a period of 5 hours.[9] To remove the possible effects of the gallbladder, this study focused on the possible effects of DNTs on glucose and lipid metabolism in asymptomatic T2DM patients after cholecystectomy.

## 2. Patients and methods

### 2.1. Patients

A series of asymptomatic T2DM patients who underwent cholecystectomy at least 2 years prior and were regularly followed up in our hospital were included in our study. Asymptomatic T2DM was diagnosed according to guidelines from the American Diabetes Association.[10] The exclusion criteria were as follows:

1. patients with coexisting pregnancy, malignant diseases, debilitating disease or operation complications such as fistula, bile duct injury, and infection, that might affect metabolism;
2. patients with unresolved psychiatric illness and substance abuse that might affect follow-up work;
3. patients taking diabetic agents, lipid-lowering agents or changing dietary habits during the study; and
4. patients with incomplete data. Many T2DM patients refused diabetic treatment advice, probably because no symptoms were present and the cultural shame surrounding a diabetes diagnosis.[11]

### 2.2. Methods

The included patients were divided into 2 groups according to their decisions: the DNT group and the control group. Patients in the DNT group took 5 DNTs 3 times per day for at least 6 months. The control group patients took placebos that could not be distinguished by appearance and taste. Data on sex, age, body mass index (BMI), food intake and comorbidities were collected. Patients were regularly followed up by telephone and outpatient visits every 3 months. The change in food intake amount was assessed using the 2005 Block Food Frequency Questionnaire, which has been used in numerous previous intervention trials, including the Diabetes Prevention Program.[12] Biomedical parameters included fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), total cholesterol (TC), triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total bile acids, and glucagon-like peptide-1 (GLP-1). The procedural protocols were approved and supervised by the ethics committee of our hospital and registered in the Chinese Clinical Trial Registry (No. ChiCTR1900027823). Informed consent was obtained after a detailed explanation of the study.

Glucose metabolism changes were assessed by the HbA1c level, FPG level and previously published definitions.[4,10] T2DM patients who were not taking any antidiabetic medication, had an HbA1c level of less than 6.5%, and had an FPG level of less than 7.0 mmol/L were considered "in remission." Patients with no increase in HbA1c level and decreased FPG level were considered "improved." Patients with an increased HbA1c level and decreased FBG level were considered "unimproved." Patients with an increased HbA1c level and increased FBG level were considered "deteriorated."

### 2.3. Statistical analysis

We conducted the statistical analysis using SPSS Statistics software (version 24.0, IBM, USA) and EmpowerStats (X&Y Solutions, Inc., Boston). The propensity score (PS)-matched comparison was used to reduce confounding bias. We matched the DNT group patients with control group patients (1:1) within a caliper width equal to 0.2 of the standard deviation of the PS. Variables in the PS model included the fasting blood glucose level and hemoglobin A1c level. Quantitative data are shown as the mean ± standard deviation, the differences in continuous variables before and after DNT administration were determined by paired *t*-tests, and the differences between the DNT group and the control group were determined by *t*-tests. All statistics were 2 tailed and *P* values less than .05 were considered statistically significant.

## 3. Results

### 3.1. Patients

From January 2019 to January 2020, a total of 112 asymptomatic T2DM patients were included in our study, and 35 patients joined the DNT group. After PS matching, 64 patients (41 males and 23 females) were included in the analysis. The mean age was 66.8 ± 6.6 years, and the mean BMI was 25.8 ± 2.8. They had asymptomatic hyperglycemia, were not receiving a treatment for diabetes. The mean duration of diabetes was 0.7 ± 1.0 years. The mean FPG level was 9.4 ± 1.5 mmol/L, and the mean HbA1c was 8.3 ± 1.0%.

The DNT group included 32 patients with 21 males and 11 females. The mean age was 66.1 ± 6.8 years, and the mean BMI was 25.5 ± 2.7. The mean FPG level was 9.5 ± 1.4 mmol/L, and the mean HbA1c was 8.3 ± 1.1%. The control group included 20 males and 12 females. The mean age was 67.5 ± 6.6 years, and the mean BMI was 26.1 ± 3.0. The mean FPG level was 9.3 ± 1.6 mmol/L, and the mean HbA1c was 8.3 ± 1.0%. There was no significant difference in age, BMI, FPG level or HbA1c level between the 2 groups. The detailed characteristics of diabetes parameters are shown in Table 1.

### 3.2. Food intake and bodyweight

Food intake was estimated by the 2005 Block Food Frequency Questionnaire during the follow-up period. The diet composition did not change much 6-months after DNT intake. The amount of

**Table 1**

**Clinical characteristics of included type 2 diabetes Patients.**

| Characteristics | DNT group | Control group | P |
|---|---|---|---|
| n | 32 | 32 | |
| Gender | | | |
| Male/Female (n) | 21/11 | 20/12 | .794 |
| Age (yr) | 66.1 ± 6.8 | 67.5 ± 6.6 | .421 |
| BMI (kg/m$^2$) | 25.5 ± 2.7 | 26.1 ± 3.0 | .130 |
| Diabetes characteristic | | | |
| Duration of diabetes (year) | 0.7 ± 1.0 | 0.8 ± 1.1 | .903 |
| FPG (mmol/L) | 9.5 ± 1.4 | 9.3 ± 1.6 | .683 |
| HbA1c (%) | 8.3 ± 1.1% | 8.3 ± 1.0% | .990 |
| Patient classification | | | |
| FPG>11.1 (n) | 6 | 4 | |
| FPG between 7 mmol/L and 11.1 mmol/L (n) | 26 | 28 | .491 |
| HbA1c>7% (n) | 28 | 29 | |
| HbA1c between 6.5% and 7% | 4 | 3 | .689 |

Data are mean ± SD. DNT = danning tablet, BMI = body mass index, FPG = fasting plasma glucose, HbA1c = hemoglobin HbA1c.

daily food intake (kcals) was 101 ± 7% of that before intake ($P$ = .612). There was also no significant difference in the food intake in the control group ($P$ = .290).

The BMI of the patients in the DNT group decreased from 25.5 ± 2.7 to 24.3 ± 2.7 ($P$ = .009). The BMI in the control group did not change significantly ($P$ = .261). Moreover, the BMI of the patients in DNT group was less than that of the patients in the control group (24.3 ± 2.7 vs 26.2 ± 2.9, $P$ = .012).

### 3.3. Effect on glucose metabolism

Before oral DNT intake, there was no significant difference in the FPG level ($P$ = .683) and HbA1c ($P$ = .990) between 2 groups. The average FPG and the level of HbA1c in the DNT group were 9.5 ± 1.4 mmol/L and 8.3 ± 1.1%, respectively. After 6 months, the average FPG and HbA1c levels decreased to 8.3 ± 1.6 mmol/L ($P$ < .001) and 7.6 ± 1.0% ($P$ = .001), respectively (Table 2). However, the FPG level increased from 9.3 ± 1.6 mmol/L to 9.7 ± 1.6 mmol/L ($P$ = .003) in the control group, and the HbA1c level increased from 8.3 ± 1.0 mmol/L to 8.8 ± 1.0 mmol/L ($P$ = .001). Therefore, the average FPG ($P$ = .001) and HbA1c levels ($P$ < .001) in the DNT group were lower than those in the control group.

We also classified the patients according to a previous definition of disease progression. In the DNT group, there were 10 patients (31.3%) "in remission", 17 patients (53.1%) "improved," 4 patients (12.5%) "unimproved," and 1 patient (3.1%) in "deteriorated" status. The total effectiveness rate was 84.4%. In the control group, no patient was "in remission," 2 patients (6.3%) were "improved," 3 patients (9.4%) were "unimproved," and 27 patients (84.4%) were considered "deteriorated."

### 3.4. Effect on lipid metabolism

Before oral DNT intake, there was no significant difference in the TC ($P$ = .406), TG ($P$ = .959), LDL-C ($P$ = .424) and HDL-C ($P$ = .312) level between 2 groups. After 6-months of treatment with DNTs, the average level of TC decreased from 5.16 ± 1.42 mmol/L to 4.43 ± 1.00 mmol/L ($P$ = .024), and the LDL-C level decreased from 4.28 ± 1.76 mmol/L to 3.75 ± 1.92 mmol/L ($P$ = .034). There was no significant difference in the levels of

**Table 2**

**Changes of glucose and lipid metabolism 6 months after taking DNTs.**

| | DNT group | | | Control group | | |
|---|---|---|---|---|---|---|
| Variable | Preoperative | Postoperative | P | Preoperative | Postoperative | P |
| BMI (kg/m$^2$) | 25.5 ± 2.7 | 24.3 ± 2.7 | .009 | 26.1 ± 3.0 | 26.2 ± 2.9 | .261 |
| FPG (mmol/L) | 9.5 ± 1.4 | 8.3 ± 1.6* | .000 | 9.3 ± 1.6 | 9.7 ± 1.6 | .003 |
| HbA1c (%) | 8.3 ± 1.1 | 7.6 ± 1.0* | .001 | 8.3 ± 1.0 | 8.8 ± 1.0 | .001 |
| TC (mmol/L) | 5.16 ± 1.42 | 4.43 ± 1.00* | .024 | 4.93 ± 1.06 | 5.24 ± 1.38 | .072 |
| TG (mmol/L) | 1.76 ± 1.03 | 1.90 ± 0.82 | .122 | 1.72 ± 0.59 | 2.01 ± 0.80 | .020 |
| HDL-C (mmol/L) | 1.13 ± 0.33 | 1.10 ± 0.27* | .508 | 1.04 ± 0.38 | 0.92 ± 0.33 | .028 |
| LDL-C (mmol/L) | 4.28 ± 1.76 | 3.75 ± 1.92* | .034 | 3.98 ± 1.78 | 4.67 ± 1.64 | .013 |
| TBA (μmol/L) | 6.05 ± 2.60 | 5.10 ± 1.83 | .037 | 6.01 ± 2.91 | 6.21 ± 2.58 | .386 |
| GLP-1 (pmol/L) | 6.93 ± 4.94 | 11.25 ± 5.88* | .000 | 7.06 ± 5.42 | 7.86 ± 6.14 | .061 |

DNT = danning tablet, BMI = body mass index, FPG = fasting plasma glucose, GLP-1 = glucagon-like peptide-1, HbA1c = hemoglobin A1c, TC = total cholesterol, TG = triglyceride, HDL-C = high-density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, TBA = total bile acid.

All data are mean ± standard deviation.

* Significant difference compared to the control group ($P$ < .05).

triglycerides (1.76 ± 1.03 mmol/L vs 1.90 ± 0.82 mmol/L, $P = .122$) or HDL-C (1.13 ± 0.33 mmol/L vs 1.10 ± 0.27 mmol/L, $P = .508$).

In the control group, the TG level increased from 1.72 ± 0.59 mmol/L to 2.01 ± 0.80 mmol/L ($P = .020$), the LDL-C level increased from 3.98 ± 1.78 mmol/L to 4.67 ± 1.64 mmol/L ($P = .013$), and the HDL-C level decreased from 1.04 ± 0.38 mmol/L to 0.92 ± 0.33 mmol/L ($P = .028$). There was no significant difference in the level of TC (4.93 ± 1.06 mmol/L vs 5.24 ± 1.38 mmol/L, $P = .072$).

Therefore, the TC level was lower in patients in the DNT group than in patients in the control group ($P = .011$) after 6 months, as was the LDL-C level ($P = .037$). The HDL-C level was higher in the DNT group than in the control group ($P = .025$).

### 3.5. Biochemistry variables

The average level of TBA decreased significantly in the DNT group. It decreased from 6.05 ± 2.60 μmol/L to 5.10 ± 1.83 μmol/L ($P = .037$) after 6 months of treatment with DNTs. Before oral DNT administration, there was no significant difference between 2 groups (6.05 ± 2.60 μmol/L vs 6.01 ± 2.91 μmol/L, $P = .960$). However, the average TBA level in the DNT group was lower than in the control group 6 months afterwards (5.10 ± 1.83 μmol/L vs 6.21 ± 2.58 μmol/L, $P = .015$).

The level of GLP-1 increased from 6.93 ± 4.94 pmol/L to 11.25 ± 5.88 pmol/L in the DNT group ($P < .001$), and was higher in the DNT group than in the control group (7.86 ± 6.14 pmol/L, $P = .027$), although there was no significant difference before DNT intaking (6.93 ± 4.94 pmol/L vs 7.06 ± 5.42 pmol/L $P = .959$).

## 4. Discussion

A previous study verified that DNTs could activate FXR. FXR is a nuclear BA receptor, that is ubiquitously expressed in various tissues and organs, including the liver, pancreas, intestine, kidney, adipose tissue, and vascular system.[5,8] Activated FXR is involved in the regulation of various biochemical reactions, such as BA metabolism, glucose metabolism, and lipid metabolism. Bile acids are synthesized from cholesterol by the liver, emptied into the small intestine, efficiently re-absorbed and sent back to the liver for re-secretion into bile. This is an intact enterohepatic circulation, which facilitates digestion and absorption of dietary lipids, regulates cholesterol, lipid and glucose homoeostasis. Activated FXR activation can reduce BA synthesis, mainly via a rate limiting enzyme (cholesterol 7-α hydroxy-lase) and the cholesterol 27-α hydroxy-lase alternative pathway. They can also reduce BA intestinal reabsorption by downregulation of sodium taurocholate co-transporting polypeptide and organic-anion-transporting polypeptide, and promote BA secretion by upregulation of apical bile acid efflux transporters.[8] Therefore, the TBA level of the patients in the DNT group decreased after treatment with DNTs, and was also lower than that of the control group. This negative feedback maintains BA homeostasis, prevents BA accumulation, and protects organs from the toxic effects of BAs.[13]

Our study also showed that an FXR agonist improved glucose homeostasis and lipid metabolism, which was consistent with previous findings.[14] The improvement in glucose metabolism was verified in asymptomatic T2DM patients that were treated with DNTs. The total effectiveness rate of glucose control was 84.4%, and the FPG and HbA1c concentrations fell significantly

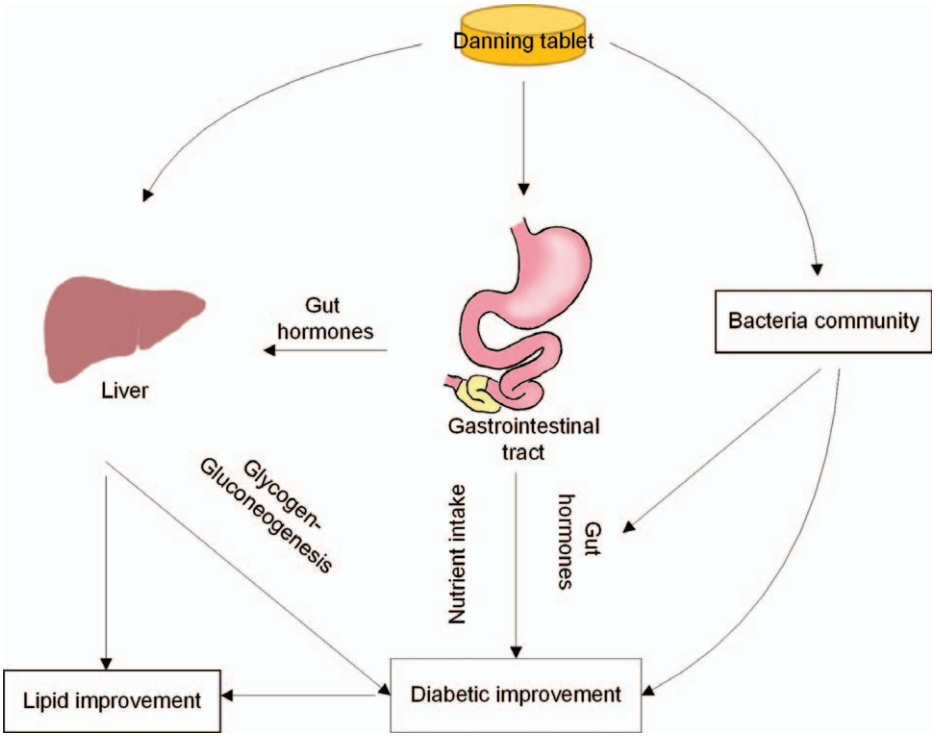


**Figure 1.** The possible mechanism by which Danning tablets improve parameters of diabetes and dyslipidemia. Danning tablets could activate farnesoid X receptors, which exist in the liver and gastrointestinal tract and affect glucose and lipid metabolism. Danning tablets promote bile acid secretion, which could affect the bacterial community and improve health parameters of diabetes.

after oral DNT intake. Considering that there was no significant change in food intake amount after oral DNT intake, increased GLP-1 levels might contribute to the change in glucose metabolism (Fig.1). GLP-1 secretion is mainly stimulated by the ingestion of nutrients. The L-cell is an "open-type" cell with an apical cytoplasmic process that is in direct contact with nutrients that arrive in the intestinal lumen. Glucose, products of protein degradation, BAs, and even the gut microbiota are stimulators of GLP-1 release.[15,16] The sympathetic nerve also affects GLP-1 secretion.[17] Intestinal GLP-1 can enter circulation, slow gastrointestinal motility and transit, drive the secretion of insulin to regulate postprandial glucose levels and suppress appetite and energy intake.[18] Moreover, increased GLP-1 levels could also improve insulin sensitivity, glucose metabolism and lipid metabolism.[19,20]

FXR is expressed by the murine L-cell line, GLUTag. An FXR agonist, GW4064, blunted the GLP-1 response to short-chain fatty acids in both GLUTag and NCI-H716 cell lines.[21] However, oral intake and vascular perfusion of GW4064 in rats failed to affect GLP-1 levels.[22] Of note, oral administration of another FXR agonist, fexaramine, in mice was reported to enhance GLP-1 secretion and improve insulin sensitivity and the lipid profile.[16] The increased GLP-1 level might be a composite result of factor competition in vivo. Our study also showed that the GLP-1 level in the DNT group increased, which is consistent with the result in mice.

Moreover, FXR activation delays intestinal glucose absorption, increases glycogen synthesis and improves insulin sensitivity by overexpressing of aldo-keto reductase 1B7.[16,23] In addition, the anti-inflammatory effect and adipocyte differentiation induced by FXR have been shown to improve insulin sensitivity by promoting peroxisome proliferator-activated receptor-γ activity and inhibiting the Wnt/β-catenin pathway.[24,25] Activated FXR also improves glucose metabolism by increasing the expression of fibroblast growth Factor 19, which is able to cross the blood-brain barrier and, reduce agouti-related protein/nerve peptide Y neuron activation in the arcuate nucleus.[14] Hepatic overexpression of FXR improves hyperglycemia in diabetic mice, whereas FXR deficiency leads to glucose intolerance and insulin resistance.[26]

Meanwhile, dyslipidemia in T2DM patients was also remitted, and TC and LDL-C concentrations significantly decreased after DNT intake. The HDL-C level was higher than that of the control group after 6 months of DNTs intake. FXR regulates multiple steps in lipid homeostasis including lipid uptake, oxidation, transport, clearance and hepatic lipogenesis. Activated FXR suppresses cholesterol 7 alpha-hydroxylase, very low density lipoprotein receptor and sterol regulatory element binding protein 1c, which can subsequently influence lipid absorption.[27] It also inhibits the expression of acyl-CoA synthetize short chain family member 2 and induces the expression of peroxisome proliferator-activated receptor α and hepatic fibroblast growth Factor 21, both of which are involved in fatty acid oxidation.[28] Lipoprotein transport of fat or other lipids is controlled by FXR through upregulation of ApoE, phospholipid transfer protein, and very low density lipoprotein receptor.[29] FXR has a beneficial effect on lipid metabolism by restoring the expression of *SREBP1* and reducing hepatic inflammation.[14] FXR deficiency is associated with markedly elevated serum and hepatic triglyceride and cholesterol levels, whereas treatment with a selective agonist of FXR lowers hyperlipidemia in db/db mice.[26] In addition, the lipid metabolism is intricately related to glucose metabolism. Hyperinsulinemia is believed to be the main trigger for diabetic dyslipidemia and is involved at all stages of very low-density lipoprotein production and secretion.[30] Improvement of lipid metabolism protects human islet cells from lipid-induced metabolic stress.[31] Therefore, lipid metabolism was improved with the improvement of glucose metabolism.

Our study is a cohort investigation, and there are a few limitations. The basic data between the 2 groups were hard to match precisely, but the PS-matched comparison was used to reduce possible bias. After PS matching, there was no significant difference in the fasting glucose level and hemoglobin A1c level between groups. And the number of patients was limited because this was a preliminary trial. Although further mechanistic investigations are required, our preliminary results show improvement in glucose and lipid metabolism after DNT intake, possibly through the activation of FXR and increased GLP-1 levels. Since DNTs can improve glucose and lipid metabolism, they may be a more suitable option for cholestasis patients with T2DM and provide a new treatment strategy for T2DM.

## 5. Conclusions

The results of our study show that DNT intake improved glucose and lipid metabolism in asymptomatic T2DM patients.

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## Author contributions

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**Supervision:** Xiaodong He.
**Writing – original draft:** Weijie Chen.
**Writing – review & editing:** Xiaodong He.

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