Effects of fructose epimers on blood lipid profile: A systematic review and meta-analysis of randomized controlled trials

Cuiju Xu  
Yantai University

Shanbin Chen  
Shandong Academy of Agricultural Sciences

Fangling Du  
Shandong Academy of Agricultural Sciences

Aizhen Zong  
Shandong Academy of Agricultural Sciences

Tongcheng Xu (✉ xtc@live.com)  
Shandong Academy of Agricultural Sciences

Yanli You  
Yantai University

Research Article

Keywords: Fructose epimers, Lipid profile, Meta-analysis

Posted Date: November 30th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2311338/v1

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Abstract

OBJECTIVES

The epimers of fructose may have the benefit of regulating lipid metabolism. This systematic review and meta-analysis of randomized controlled trials (RCTs) aimed to assess the effects of fructose epimers on blood lipids, including high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), total cholesterol (TC), triglyceride (TG) and free fatty acids (FFA).

METHODS

PUBMED, EMBASE, Cochrane Library and Web of science databases were retrieved up to November 2022. We included all published RCTs concerning the effects of fructose epimers on fasting or postprandial blood lipid responses. Data were pooled with standardized mean differences (SMD). Subgroup analysis was applied to investigate the heterogeneity. Quality of literature was accessed with version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2).

RESULTS

A meta-analysis of 6 trials including 686 participants was eligible. The pooled data revealed that single dose fructose epimers intervention significantly increase postprandial FFA levels (SMD, 0.64; 95% CI, 0.07 to 1.22; \( P = 0.027 \)) but no effect on postprandial TG. The daily intervention of fructose epimers significantly ameliorated the fasting plasma HDL-C level (SMD, -0.42; 95% CI, -0.83 to -0.01; \( P = 0.046 \)). In addition, fructose epimers showed an obvious but not significant effect on reducing fasting TC level (SMD, -0.13; 95% CI, -0.29 to 0.04; \( P = 0.135 \)). The epimers of fructose have no observable effect on fasting LDL-C and TG levels.

CONCLUSIONS

Fructose epimers intake leads to modest improvements in blood lipid profiles. Strong and long-term randomized controlled trials are needed to confirm the certainty and sustainability of these improvements.

Introduction

Metabolic syndromes such as diabetes and obesity have become a global health care crisis, where the excessive consumption of high fat and high sugar played an important role [1]. In the circumstance where the notion of healthy diet is presumed and the pleasure of sweet is unabandoned, sweetener seems to be the perfect solution. However, artificial sweeteners were reported not so harmless as considered previously. They seemed to alter the host’s microbiome and interference glucose homeostasis, which may contribute to metabolic syndrome and obesity epidemics [2, 3]. While, the natural alternative sweeteners (NAS) can avoid this well. They have been reported to improve energy metabolism and other biological functions [1]. Therefore, NAS becomes a popular research topic.

The epimers of fructose, mainly D-allulose and D-tagatose, are regarded as NAS and have gained increasing attention owing to its excellent properties. D-allulose was reported to be nearly 70% as sweet as sucrose and its heat is only about 10% of sucrose [4, 5]. D-tagatose is extremely similar to sucrose in taste, and it has low calories (~ 1.5 kcal/g) [5]. Hence, D-allulose and D-tagatose were perceived as excellent alternatives to sugar and artificial sweeteners. Furthermore, there has been reports that the epimers of fructose were of benefit to glycemic control and lipid metabolism in animal studies and small-scale clinical trials. Experimental studies in mice show that D-allulose inhibited the absorption of D-glucose and D-fructose, improve insulin sensitivity, increase fat oxidation and reduce fat content, which could help in preventing obesity and type 2 diabetes [6]. D-tagatose was also reported to reduce susceptibility to glucose-induced metabolic disturbances in mice [7]. Moreover, meta-analysis of controlled trials showed that small doses of fructose epimers lead to modest improvements on glucose metabolism [8].

As the complicate interaction between carbohydrate and lipid metabolism, and the fact that a sucrose rich diet can induce not only hyperglycemia but also hyperlipidemia [9], the notion that fructose epimers may have the potential to improve hyperlipidemia became appealing. However, the results of clinical studies were not consistent. It was reported that D-allulose intake reduces low-density lipoprotein cholesterol (LDL-C) or non-high-density lipoprotein cholesterol [10]. While other studies have found that D-allulose had no significant effect on plasma cholesterol [6, 11] or even increased plasma total cholesterol (TC) and LDL-C [12, 13]. The effect of fructose epimers on plasma lipids has not been demonstrated conclusively. Therefore, it is necessary to do a systematic review and meta-analysis to address inconsistent conclusions, improve estimates of effects, and indicate directions for further studies.

Materials And Methods

Search strategy
Two independent researchers (C.X. and S.C.) searched PubMed, Embase and the Cochrane Library for studies published until August 2022. The following search terms combined with Medical Subject Headings (MeSH) words were used: (“Allulose”, “Psicose”, “Tagatose”, “Fructose” “Fructose epimers” “Fructose isomers” and “Blood lipids”, “Lipid”, “Hypertiglyceridemia”, “Obesity”, “Hyperlipidemia”, “Total cholesterol”, “Triglyceride”, “HDL-C”, “LDL-C”, “FFA”). Randomized controlled trials were retrieved and repetitive studies were deleted. According to the inclusion and exclusion criteria, two researchers independently completed the title and abstract of the screening articles. Moreover, any disagreement between the two researchers can be discussed or consulted by the third author (A.Z.).

**Inclusion And Exclusion Criteria**

Inclusion criteria: 1) The study design was randomized controlled trials. 2) One of the fructose epimers (i.e., D-allulose or D-tagatose) was applied as intervention. 3) Participants did not eat any hypoglycemic and lipid-lowering drugs during fructose epimers intervention, and maintained normal diet and exercise. 4) Fasting and/or postprandial plasma lipids profile (included HDL-C, LDL-C, TG, TC, and FFA) were analyzed. 5) the mean value and standard deviation (SDs) of baseline or endpoint, or equivalent value were presented.

Exclusion criteria: 1) The study design was not randomized controlled trials. 2) There were other interventions or other interference factors during the intervention of fructose epimers in the included population, resulting in inaccurate data.

**Data Extraction**

The two reviewers (C.X. and S.C.) independently extracted the relevant data of the study characteristics and outcomes of HDL-C, LDL-C, FFA, TG and TC. Any differences are resolved by consensus. The mean difference (MD) and standard deviation (SD) between the baseline and the endpoint in both control and intervention groups or equivalent value were extracted. When data is only represented in the diagram, the values are extracted from the available graph digitizer (https://apps.automeris.io/wpd/).

**Quality Of The Included Studies**

Article quality evaluation was assessed by two researchers (C.X. and S.C.) using the new revised Cochrane risk-of-bias tool for randomized trials. Articles were judged as high, low, or unclear in the following areas: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result and overall bias. Assessment was conducted according to the signaling questions which aim to elicit information about features relevant to risk of bias of the trial. Overall bias of each study was further classified to low or high risk of bias, or some concerns. Any disagreement in deviation risk was reconciled through consensus.

**Data Synthesis And Statistical Analysis**

All the analyses were conducted with STATA 12.0 (Statacorp LP, College Station, TX, USA). Changes from baseline to endpoint were used for the analysis of HDL-C, LDL-C, FFA, TG and TC. When the SD was not reported, it was derived from the available data 95% CI, p-values, or SE using the method suggested by the Handbook for Systematic Review of Interventions [14]. When needed, the SD for changes from baseline was imputed using a pooled correlation coefficient according to a published procedure, where the constant R = 0.5. If trials compared multiple intervention groups with the same control group, the shared control group was considered as two or more groups [15]. Standardized mean difference (SMD) with 95% CI between the intervention group and the control group was applied to evaluate the effect of fructose isomers on plasma lipids. $P < 0.05$ was considered statistically significant. The heterogeneity between the test results was evaluated by Q test and $I^2$ statistic, $P < 0.1$ or $I^2 \geq 50\%$ indicated a significant level of heterogeneity. When $I^2 \geq 50\%$, the random effect model was adopted. Sensitivity analysis was used to recalculate its effect by deleting each study. Subgroup analysis was used to assess the impact of certain factors, including kind of fructose epimer, BMI, intervention duration, and intervention dose. Begg's test and Egger's test were used to test for publication bias, and significant publication bias was defined as $P < 0.05$.

**Results**

**Literature search**

Figure 1 shows the systematic retrieval and selection of literature. In total, we identified 3133 records, of which 3127 were excluded based on the inclusion and exclusion criteria. The final analysis consisted of 6 randomized controlled trials, including 598 participants. Of which, five trials studied the effect of D-allulose [16–20] and one studied D-tagatose [21].

**Characteristics Of The Included Studies**

All the included trials met the PICOS (population, intervention, comparison, outcome, study design) criteria. Table 1 provides the subdivision of experimental research characteristics. The age of the study populations ranged from 18 to 75 years, and the BMI ranged from 20 to 45 kg/m$^2$. The treatment duration ranged from 12 to 48 weeks. Two studies investigated the effects of single dose intervention of fructose epimers on postprandial
indicators (FFA, TG, TC, HDL-C and LDL-C) [17, 19]. As fructose epimers were rapidly metabolized and excreted from the body after ingestion, and its effect on lipid metabolism was intermediate in rats, the data at 4 hours after meal were extracted for postprandial indicators analysis [22, 23]. In the daily intervention trials, the postprandial TC, HDL-C or LDL-C and the fasting FFA were only studied in one trial, so these indicators were not meta-analyzed.

Four daily intervention studies the long-term effect on plasma lipid profile, of which six comparisons examined fasting TC, HDL-C and LDL-C, three comparisons examined fasting TG [17, 18, 20, 21].

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Participants</th>
<th>Gender</th>
<th>Age, year</th>
<th>BMI, kg/m²</th>
<th>Physical status</th>
<th>Study Design</th>
<th>Duration (weeks)</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Intervention manner</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. Tanaka, 2020</td>
<td>Japan</td>
<td>8 8 F</td>
<td>Healthy</td>
<td>R,C,SB</td>
<td>NA</td>
<td>D-allulose</td>
<td>sucrase</td>
<td>SI, 1.8g added in chocolate, substitute equivalent amount of sucrose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. Tanaka, 2020</td>
<td>Japan</td>
<td>8 8 F</td>
<td>Healthy</td>
<td>R,C,SB</td>
<td>NA</td>
<td>D-allulose</td>
<td>sucrase</td>
<td>SI, 3.6g added in chocolate, substitute equivalent amount of sucrose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. Tanaka, 2020</td>
<td>Japan</td>
<td>8 8 F</td>
<td>Healthy</td>
<td>R,C,SB</td>
<td>NA</td>
<td>D-allulose</td>
<td>sucrase</td>
<td>SI, 12.6g added in chocolate, substitute equivalent amount of sucrose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T. Kimura, 2017</td>
<td>Japan</td>
<td>13 13 M/F</td>
<td>Healthy</td>
<td>R,C,SB</td>
<td>NA</td>
<td>D-allulose</td>
<td>10 mg Aspartame</td>
<td>SI, 5g in 200mL tea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. Tanaka, 2019</td>
<td>Japan</td>
<td>28 27 M/F</td>
<td>Healthy</td>
<td>R,C,SB</td>
<td>NA</td>
<td>D-allulose</td>
<td>5g×1 times/d in beverage prior to breakfast</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. Tanaka, 2020</td>
<td>Japan</td>
<td>28 27 M/F</td>
<td>Healthy</td>
<td>R,C,SB</td>
<td>NA</td>
<td>D-allulose</td>
<td>5g×1 times/d in beverage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y. Han, 2018</td>
<td>Korea</td>
<td>40 40 M/F</td>
<td>Healthy</td>
<td>R,C,SB</td>
<td>12</td>
<td>D-allulose</td>
<td>5g×1 times/d in beverage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y. Han, 2018</td>
<td>Korea</td>
<td>40 41 M/F</td>
<td>Healthy</td>
<td>R,C,SB</td>
<td>12</td>
<td>D-allulose</td>
<td>5g×1 times/d in beverage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N. Hayashi, 2010</td>
<td>Japan</td>
<td>9 8 M/F</td>
<td>Healthy</td>
<td>RPDB</td>
<td>12</td>
<td>D-allulose</td>
<td>Splenda with equivalent sweetness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. Enser, 2015</td>
<td>America, India</td>
<td>184 172 M/F</td>
<td>Healthy</td>
<td>RPDB</td>
<td>40</td>
<td>D-tagatose</td>
<td>4.5g/d in water with meals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Con, Control; Trt, Treatment; R, Randomized; P, parallel; C, crossover; SB, Single Blind; DB, Double Blind; SI, Single dose Intervention; DI, Daily Intervention.
The assessment on the individual and summary risk of bias is shown in Fig. 2A&B according to the Cochrane Collaboration risk of bias tool version 2. Six studies specifically described the randomized method. Six studies specifically described the detailed method of allocation concealment. In most of the studies, both participants and researchers were blind when adopting a double-blind design. All studies described the methods of blind implementation. Bias due to deviations from the intended interventions, missing outcome data or measurement of the outcome was low, except for one study in which lost to follow-up and switching to non-assigned intervention occurred. 2 studies had some concerns in selection of the reported result, as they had no pre-specified analysis plan. Overall, no serious risk of bias was found.

**Effects Of Single Dose Fructose Epimers Intervention On Postprandial Plasma FFA And TG Level**

Figure 3 shows the effect of fructose epimers on postprandial FFA levels and TG levels. Four comparisons with 58 subjects reported postprandial FFA and TG outcomes [16, 19]. The combined effect showed that the epimers of fructose significantly increased postprandial FFA levels (Fig. 3A, SMD, 0.64; 95% CI, 0.07 to 1.22; P= 0.027). In the heterogeneity test for postprandial FFA, was determined as 0.0%, with P> 0.1, which indicated low heterogeneity. The results of funnel plots and Begg's and Egger's tests indicated no publication bias (Figure S1, P_{Begg} = 0.497, P_{Egger} = 0.332). In the sensitivity analysis, removal of individual trials in the epimers of fructose did not alter the statistical significance of the total effect value, which indicate that the effect was robust (Figure S2). The epimers of fructose had no effect on postprandial TG levels (Fig. 3B, SMD, 0.02; 95% CI, -0.54 to 0.57; P= 0.958). The test and Q test indicated low heterogeneity (I² = 0.0%, P> 0.1). No significant evidence on publication bias was observed (Figure S3, P_{Begg} = 0.497, P_{Egger} = 0.76). And the sensitivity analysis showed robustness of the result (Figure S4).

**Effect of daily fructose epimers intervention on fasting lipid profile**

**Fasting TG**

Three studies with 494 subjects reported the effect of fructose epimers on fasting plasma TG outcomes [18, 20]. The pooled results indicated no significant influence of the fructose epimers on fasting plasma TG level (Figure 4A, SMD, 0.37; 95% CI, -1.18 to 1.92; P = 0.639). The heterogeneity was high (I²=97.4%, P < 0.1), and no publication bias was observed (Figure S5, P_{Begg}=0.497, P_{Egger}=0.111). Subgroup analysis showed overt difference between D-allulose and D-tagatose. Three trials evaluated the effect of D-allulose, and found a decrease in fasting TG level. While one trial investigated the effect of D-tagatose, and found a significant increase in fasting TG level. Data from sensitivity analysis shows that the result was stable and robust in the D-allulose subgroup (Figure S6).

**Fasting Tc**

Six trials with 577 subjects examined the fasting plasma TC outcomes [17, 18, 20, 21]. Compared with the placebo, the epimers of fructose had a decrease effect on fasting plasma TC levels, but this decreased difference wasn't significant (Fig. 4B, SMD, -0.13; 95% CI, -0.29 to 0.04; P = 0.135). The heterogeneity was low (I² = 0.0%, P = 0.758), and no publication bias was observed (Figure S7, P_{Begg}=0.602, P_{Egger}=0.861). Sensitivity analysis suggested that the result was stable and robust (Figure S8).

**Fasting Hdl-c**

Six trials with 577 subjects reported plasma HDL-C outcomes [17, 18, 20, 21]. Figure 4C shows the pooled effect of fructose epimers on fasting plasma HDL-C levels. Compared with the control diets, the epimers of fructose had a significant decrease on fasting HDL-C levels (SMD, -0.42; 95% CI, -0.83 to -0.01; P= 0.046). But heterogeneity for fasting plasma HDL-C was obvious (I² = 71.9%, P < 0.1). No publication bias was observed (Figure S9, P_{Begg} = 0.348, P_{Egger} = 0.127). The effect of fructose epimers on fasting plasma HDL-C levels was stable and robust (Figure S10).

A subgroup analysis of fasting HDL-C level was also conducted (Table 2). D-allulose was effective at ameliorating plasma HDL-C level (SMD, -0.55; 95% CI, -0.93 to -0.13; P= 0.011), while the effect of D-tagatose on HDL-C wasn't significant (SMD, 0.01; 95% CI, -0.20 to 0.20; P= 0.948). In the sub-analysis stratified by dosage, fructose epimers intervention at dosage less than 10g (SMD, -0.87; 95% CI, -1.38 to -0.36; P= 0.001) was more favorable for ameliorating plasma HDL-C level than fructose epimers more than 20 g (SMD, -0.14; 95% CI, -0.46 to 0.17; P= 0.365). According to the hierarchical analysis of health status, fructose epimers significantly ameliorated the level of plasma HDL-C in population with the BMI value between 18 and 24 kg/m² (SMD, -0.58; 95% CI, -1.00 to -0.16; P= 0.006). The plasma HDL-C level was significantly ameliorated for intervention of 48 weeks (SMD, -0.66; 95% CI, -1.13 to -0.20; P= 0.005), while the intervention for a shorter duration of 12 weeks did not significantly affect the plasma HDL-C level. Therefore, the subgroup analysis showed that D-allulose of less than 10g/d was effective on the normal BMI intervention for 48 weeks in ameliorating plasma HDL-C.
Table 2
The subgroup analysis of fructose epimers on fasting HDL-C

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>N</th>
<th>SMD</th>
<th>CI</th>
<th>I² (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugar</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-allulose</td>
<td>5</td>
<td>-0.55</td>
<td>-0.97 to -0.13</td>
<td>52.4</td>
<td>0.078</td>
</tr>
<tr>
<td>D-tagatose</td>
<td>1</td>
<td>0.01</td>
<td>-0.20 to 0.21</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10 g d⁻¹</td>
<td>2</td>
<td>-0.87</td>
<td>-1.38 to -0.36</td>
<td>27.1</td>
<td>0.241</td>
</tr>
<tr>
<td>&gt; 20 g d⁻¹</td>
<td>4</td>
<td>-0.14</td>
<td>-0.46 to 0.17</td>
<td>36.0</td>
<td>0.196</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 18 and &lt; 24</td>
<td>3</td>
<td>-0.58</td>
<td>-1.00 to -0.16</td>
<td>0.0</td>
<td>0.703</td>
</tr>
<tr>
<td>&gt; 24</td>
<td>3</td>
<td>-0.33</td>
<td>-0.97 to 0.30</td>
<td>84.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48wk</td>
<td>2</td>
<td>-0.66</td>
<td>-1.13 to -0.20</td>
<td>0.0</td>
<td>0.735</td>
</tr>
<tr>
<td>40wk</td>
<td>1</td>
<td>0.01</td>
<td>-0.20 to 0.21</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>12wk</td>
<td>3</td>
<td>-0.47</td>
<td>-1.22 to 0.29</td>
<td>74.7</td>
<td>0.019</td>
</tr>
</tbody>
</table>

NA, not applicable.

Fasting LDL-c

Although previous non-RCT reported significant increases in LDL-C after 12 weeks of D-allulose intake,[24], our meta-analysis of six randomized controlled trials with 577 subjects did not support this finding. The forest plot showed that the epimers of fructose had almost no effect on fasting LDL levels (Fig. 4D, SMD, -0.01; 95% CI, -0.49 to 0.47; P = 0.975). The heterogeneity was obvious (I² = 77.3%, P < 0.001). This heterogeneity mainly came from that of D-allulose studies. Only one trial evaluated the effect of D-tagatose on fasting LDL-C and found an obvious but not significant decrease. Funnel plots and Begg’s and Egger’s tests indicated no publication bias (Figure S11, P_Begg=0.348, P_Egger=0.669). And the sensitivity analysis showed that the result was stable (Figure S12).

Discussion

The epimers of fructose have the most similar sweetness to sucrose and extremely low calories, so they have been a high profile as new generation of natural sweetener. They also have been reported to exert multiple biological functions. However, their effect on plasma lipids were not fully evaluated. This work systematically reviewed and meta-analyzed the influence of the routine intake of the fructose epimers on fasting TG, fasting TC, fasting HDL-C, fasting LDL-C, and the real-time effect of single dose intervention of the fructose epimers on postprandial TG, postprandial FFA level. The pooled results suggested that daily intakes of fructose epimers could significantly decreased fasting HDL-C, obviously reduced fasting TC, but did not affect fasting TG and fasting LDL-C. And fructose epimers intake instantly enhanced postprandial FFA but not postprandial TG. The findings from this analysis have also demonstrated the potential benefits of fructose epimers on blood lipid profile.

The meta-analysis showed that the epimers of fructose had an obviously decrease effect on fasting HDL-C levels. Although HDL-C was considered the “good cholesterol” and used as a clinical biomarker of cardiovascular disease risk, the decrease effect of fructose epimers on HDL-C levels should not be considered as an adverse event. As we all known, HDL-C plays a role in the collection of redundant lipids from peripheral tissues, such as the vascular wall, to the liver, generally termed reverse cholesterol transport. This process was associated with preventing and potentially reversing the peripheral accumulation of lipids in arteries which contributed to atherosclerotic vascular disease.[25]. It has been observed that D-allulose may enhance the liver’s uptake of HDL-C by increasing scavenger receptor class B type 1 expression, an HDL-C receptor, which is one of key protein associated with reverse cholesterol transport. Hence D-allulose enhanced the reverse cholesterol transport, and thereby reduced the circulating HDL-C.[26]. In addition, TG, LDL-C was not increased and TC was slightly decreased during fructose epimers intervention. These was far from the classic situation such as dyslipidemia in type 2 diabetes where elevated circulating TG, TC, or LDL-C accompanied by decreased HDL-C.[27]. In general, epimers of fructose promoted the reverse cholesterol transport and then decrease circulating HDL-C level.

As described by the subgroup analysis of HDL-C stratified by specific fructose epimers, the influence of D-allulose was consistent with that of fructose epimers in total, while D-tagatose showed no effect in our analysis. It had to be noted that only one RCT evaluated the HDL-C after D-tagatose intervention. Although the author of this RCT study claimed D-tagatose intervention lowered the fasting HDL-C level by directly comparing the HDL-C
value of intervention group with that of the placebo, the baseline difference of HDL-C level between the group was not took into consideration [21]. By comparing the change from the baseline, we believed no effect of D-tagatose on fasting HDL-C level as the subgroup analysis showed. However, this result was analyzed from only one trial, more high quality RCTs are needed for more consolidated conclusion. And, it was worth noting that the lowering effect on HDL-C was quite different between epimers of fructose. This difference might be related to the property of suppressing the hepatic lipogenic activity and stimulate hepatic fat oxidation found in D-allulose but not D-tagatose [28, 29]. And the pooled effect of fructose epimers on postprandial FFA level also supported this idea.

Epimers of fructose had an increase effect on postprandial FFA levels. Only the studies of D-allulose reported the postprandial FFA levels. The possible mechanism maybe associated with its ability to modulate lipid metabolism. D-allulose was reported to stimulate fat oxidation by increasing the expression of carnitine palmitoyl transferase, and to suppressed fat synthesis by inhibiting expression of acetyl-coA carboxylase and fatty acid synthase [30]. These properties might also relate to the effect of lowering fasting TC and TG levels as this meta-analysis observed. These results were supported by the energy metabolism assessed by a breath-by-breath method, which demonstrated that D-Allulose enhances postprandial fat oxidation in healthy humans [19]. Therefore, D-allulose intervention can ultimately reduce body fat and adipocyte volume as Han et al observed in the RCT [20]. D-tagatose was reported to reduce acetyl-CoA by inhibiting glycolysis, hence reduce cholesterol synthesis [6]. This effect may contribute to the observed reduction in serum TC and LDL-C, which can reduce the risk of cardiovascular and cerebrovascular diseases, such as atherosclerosis. One study conducted in diabetes population found that fasting TG level was increased by D-tagatose intervention. Although this result was not reproduced in the per protocol analysis [21], it was worth noting that it conflicted with previous non-controlled trial or preclinical study [13, 30].

Strengths And Limitations

To our knowledge, this is the first meta-analysis to examine the effects of fructose epimers on plasma lipids. Our systematic review and meta-analysis have the following strengths. First, we performed a comprehensive and reproducible search and selection process of the literature to investigate the effect of fructose to epimers on plasma lipids. Second, all available evidence from the six RCT experiments was collated and synthesized. Third, we assessed the overall quality of the study using the revised Cochrane risk-of-bias tool for randomized trials. However, there are some limitations in our article too. First, although this study included as many as possible trials, eligible trials for further analysis were relative in small quantities. Therefore, the number of articles that can be included in the study of FFA and TG indexes is small, even some indexes were less studied and could not be meta-analyzed. Secondly, the total number of people included in the study is not large, the population characteristics are scattered, and the number of people with each population characteristic is also small, which cannot explain the problem pertinently.

Conclusion

In summary, the present meta-analysis demonstrated that intakes of fructose epimers significantly reduced the fasting HDL-C and increased postprandial FFA levels. Fructose epimers, especially D-allulose, also showed an obvious but not significant decrease in fasting TG and TC levels. Fructose epimers had no effect on fasting LDL-C levels. But more high quality RCTs are required to consolidate this conclusion, especially the clinical trial on D-tagatose.

Declarations


All authors read and approved the final version. All authors agreed to their individual contributions. All authors had full access to all data (primary publications, trials registry entries, trial author communications, data extractions and assessments of risk of bias, and analyses) and take responsibility for the integrity and accuracy of the data. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: This study has been carried out with financial support from the National Key R & D Project (2021YFD2100403), the National Natural Science Foundation of China (32001690), the Agricultural Scientific and Technological Innovation Project of Shandong Academy of Agricultural Sciences (CXGC2022B05), the Key R&D Program of Shandong Province (2021CXGC010807).

Competing Interests: The authors declare no conflict of interest.

Ethical Approval and Consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: The data supporting the findings of this study are available within the published articles.

Acknowledgements: We appreciated funders for their financial support.
References


**Figures**

![Flowchart](chart.png)

**Figure 1**

Literature search.
Figure 2
Quality assessment of included studies. (A) overall exhibition of study quality, (B) risk of bias of individual trial.

Figure 3
The effects of fructose epimers single dose intervention on (A) FFA, (B) TG. FFA = Free Fatty Acids; TG = Triglyceride; SMD = Standardized Mean Differences.
Figure 4

The effects of fructose epimers daily intervention on (A) TG, (B) TC, (C) HDL-C, (D) LDL-C. TG = Triglyceride; TC = Total Cholesterol; HDL-C = High Density Lipoprotein-cholesterol; LDL-C = Low Density Lipoprotein-cholesterol.

Supplementary Files

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- FIGURESupplementary.zip