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Sulforaphane ameliorates lipid profile in rodents: An updated systematic review and meta-analysis

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Abstract

Sulforaphane (SFN) which is enriched in cabbage and broccoli, a naturally-occurring isothiocyanate, has been provided as food supplements to improve weight management and reduce lipid levels. However, its effects on serum lipid profile are contradictory. In this review, a meta-analysis and systematic review of SFN on lipids reduction and weight control is assessed with mice and rats fed with high-fat diet. The effects of SFN supplementation were evaluated by weighted mean difference (WMD) and the corresponding standard error of body weight, liver weight and concentrations of lipids. A random-effects model was chosen to estimate the overall summary effect. Our analytic results of the meta-analysis revealed that SFN can reduce body weight (WMD: -2.76 g, 95% CI: -4.19, -1.34) and liver weight (WMD: -0.93 g, 95% CI: -1.63, -0.23) significantly from ten trials. Its effects on serum total cholesterol (WMD: -15.62 mg/dL, 95% CI: -24.07, -7.18), low-density lipoprotein cholesterol (WMD: -8.35 mg/dL, 95% CI: -15.47, -1.24) and triglyceride (WMD: -40.85 mg/dL, 95% CI: -67.46, -14.24) were significant except for high-density lipoprotein cholesterol (WMD: 1.05 mg/dL, 95% CI: -3.44, 5.54). The subgroup analytic results from findings unveiled that classifying studies according to species, disease model, duration, SFN dosage as well as administration route could not explain the heterogeneity among studies and change the results. In summary, these findings provide new insights concerning preclinical strategies for treating diseases including obesity, diabetes, hypertension, non-alcoholic fatty liver disease as well as cardiovascular disease with SFN supplements.

Introduction

The prevalence of chronic non-communicable diseases and metabolic syndromes, involving obesity, diabetes, hypertension, hypercholesterolaemia, cardiovascular disease (CVD) and non-alcoholic fatty liver disease (NAFLD)¹⁻³, are increasing due to changes in lifestyle and dietary patterns, thereby triggered modifications in global nutritional and epidemiological characteristics⁴. The lipid profile as well as obesity are risk factors for CVD⁵. A balanced diet and the uptake of natural products supplements have been suggested to lower risks of metabolic syndrome by improving weight management and ameliorating lipid profile^{6,7}.

In the past decades, natural products derived from plant were applied to prevent obesity, diabetes and lipids-associated disorders⁸⁻¹⁰. An epidemiological study including thousands of people suggested that supplementation of adequate plant-derived bioactive compound is beneficial in controlling body weight (BW) and reducing lipid accumulation¹¹. Sulforaphane (SFN), enriched in broccoli and cabbage, was reported to decrease levels of lipid both *in vivo* and *in vitro* models^{6,12,13}. These researches suggest SFN becomes a potential drug in therapy for dyslipidemia. SFN has also been effective in treatment of atherosclerosis, diabetes, and neurodegenerative diseases¹⁴⁻¹⁶.

Two randomized clinical trials (RCTs) show that intake of broccoli sprouts can significantly reduce inflammatory markers and plasma low density lipoprotein cholesterol (LDL-C) of patients in the long term^{17,18}. Animal studies show that phase I & phase II metabolic enzymes and lipid metabolism-related enzymes/proteins can be regulated by SFN¹⁹. Recent studies suggest that SFN plays a role in inducing adipocyte lipolysis and inhibiting adipocyte differentiation²⁰⁻²³. Therefore, one of the possible mechanisms that SFN can improve lipid profile is by increasing adipocyte lipolysis and upregulating the activity of lipid metabolism-related enzymes/proteins.

There are only two RCTs of SFN on the serum lipid profile, so we have focused on the effect of SFN for lipid profile's regulation in the preclinical studies (rats and mice)^{17,18}. Particularly, there is no meta-analysis on SFN single drug effect of using SFN as a mono drug on lipid profile instead of using food. Hence, an update systematic review and a meta-analysis is put into practice to summarize the animal data of SFN effects on lipid profile after year 2013.

Material and method

Search strategy. To find related articles, we searched databases including: Web of science, PubMed, SCOPUS, medRxiv, bioRxiv and Google Scholar up to Sept. 2020. We searched those databases following MeSH and non-MeSH terms related to lipid profile and sulforaphane: "Lipoproteins, LDL", "Low Density Lipoprotein

Cholesterol”, “Cholesterol LDL”, “LDL triacylglycerol”, “Triglycerides”, “Triacylglycerol”, “Triacylglycerols”, “Lipoproteins, HDL”, “HDL Lipoproteins”, “High Density Lipoproteins”, “High-Density Lipoproteins”, “Lipoproteins, High-Density”, “Lipoproteins, VLDL”, “Cholesterol”, “Cholesterol, VLDL”, “VLDL Cholesterol”, “Very Low Density Lipoprotein Cholesterol”, “Very-Low-Density Lipoproteins”, “Lipoproteins, Very-Low-Density”, “Very Low Density Lipoproteins”, “Lipoproteins VLDL”, “VLDL Lipoproteins”, “Lipoproteins, VLDL”, “total cholesterol”, “TC”, “LDL”, “HDL”, “VLDL”, “TG”, “Lipolysis” and “sulforaphane”²⁴. Initially, we want to focus the research on the clinical trials of SFN. The search only finds two clinical papers of SFN relevant to lipid profile and the researches lack selection like language, dosage of drug, duration of treatment as well as route of administration. Hence, we concentrated on the preclinical studies of SFN which was evaluated in rodents (rats and mice) for lipid profile in this study.

Inclusion criteria. This systematic review and meta-analysis was conducted according to the PRISMA guidelines²⁵. Researches with following criteria may be chosen in our meta-analysis: (i) Original articles; (ii) Focusing on rodent (rats and mice) models; (iii) Using SFN per se in intervention group; (iv) Evaluated systemic metabolic parameters such as lipid profile as an outcome.

Exclusion criteria. After reading the full text of selected articles, we excluded trials if they met the following criteria: A) Using food instead of SFN, B) Using other food supplements with SFN, C) No control group, D) Having unclear data, E) Not using rodents (rats and mice) model, F) Acute SFN action.

Data extraction. After reading the title, abstract and considering inclusion and exclusion criteria, eligible articles were selected. Detailed data includes: the name of the first author, publication year, species and sex, number of animals, age of animals, model method, duration, intervention (including SFN dose, mode of administration), the main outcomes, intergroup difference and results²⁶.

Statistical analysis. Treatment effects were considered as weighted mean difference (WMD) and the corresponding standard error (SE) in BW, LW and concentrations of serum lipids (TC, LDL-C, HDL-C and TG). To estimate the overall summary effect, we used a random-effects model, previously described by DerSimonian and Laird, which considers both within and between-study heterogeneity²⁷. Heterogeneity among the studies was estimated using the I^2 statistic, with values of 0-25%, 25.1-75%, and 75.1-100% representing a low, moderate, and

high degree of heterogeneity, respectively. When standard deviations or SEs were not shown in studies, they were calculated using 95% CI. In addition, when studies have reported median and interquartile range, they were converted to mean and SE using available formulas²⁸. Statistical analyses were done using Stata, version 13 (Stata Corp., College Station, TX, USA). P-values less than 0.05 were considered statistically.

Results

Selection of articles.

A total of 654 studies were involved by our data base search. 279 duplicate articles were removed. After reading the title and abstract of papers, 20 articles were selected to read the full text after removing 355 studies. We considered inclusion and exclusion criteria and then excluded 10 studies owing to prescribing broccoli supplement or broccoli sprout extract instead of SFN (n = 3), acute SFN action (n = 2), RCTs (n = 2), rabbit model (n = 1), alcohol-induced liver steatosis model (n = 1) and lacking of clear data (n = 1) (Figure. 1). Finally, this meta-analysis was conducted on ten trials of rodents²⁹⁻³⁸ (Table 1), including 5 batches of C57BL/6 mice, 4 batches of Wistar rats and 1 batch of Sprague Dawley rats. In terms of gender, all the trials selected male animals aged 4-10 weeks. The methods to build disease model were feeding mice or rats with high-fat diet, high-fructose diet and highly palatable diet or injecting of streptozotocin (STZ) into rodents. Specifically, four trials induced obesity by feeding with high-fat diet, one trial by feeding with high-fructose diet, one trial by feeding with high-fat high-sucrose diet, one trial by feeding with highly palatable diet, two trials adopted diabetes by feeding with high-fat diet and then injecting of STZ and one trail by injection of STZ. The animals were treated with SFN by oral administration, oral gavage, subcutaneous injection and intraperitoneal injection. The intervention duration was 3 to 16 weeks. The dosage of SFN was 0.5 mg/kg to 30 mg/kg.

Effects of SFN Supplementation on Body Weight.

The meta-analysis of BW included 6 publications with 6 effect sizes. We found that SFN supplementation was associated to BW (WMD: -2.76 g, 95% CI: -4.19, -1.34; P = 0.032, I² = 58.9%) (Figure. 2). In the subgroup analyses, the heterogeneity sources were not found when studies were stratified species, disease model, duration and SFN dosage and administration route (Table 2). However, heterogeneity was attenuated in oral administration subgroup (I² = 0.0%), studies which lasted for >10 weeks (I² = 0.0%), diabetes model subgroup (I² = 12.2%), studies whose dosage of SFN ≤0.5 mg/kg/d (I² = 12.2%) and rats subgroup (I² = 24.8%). SFN supplementation significantly decreased BW in mice group (WMD: -2.93 g, 95% CI: -4.34, -1.52; P = 0.015, I² = 76.3%), obesity model of rodents

(WMD: -3.30 g, 95% CI: -4.46, -2.14; $P = 0.096$, $I^2 = 52.7\%$), studies which lasted for ≤ 10 weeks (WMD: -3.18 g, 95% CI: -4.60, -1.75; $P = 0.037$, $I^2 = 64.6\%$), studies whose dosage of SFN >0.5 mg/kg/d (WMD: -3.30 g, 95% CI: -4.46, -2.14; $P = 0.096$, $I^2 = 52.7\%$), oral administration group (WMD: -3.96 g, 95% CI: -4.47, -3.14; $P = 0.392$, $I^2 = 0.0\%$) and injection administration group (WMD: -1.33 g, 95% CI: -4.46, 1.80; $P = 0.107$, $I^2 = 55.2\%$). However, BW significantly increased in rats group (WMD: 1.12 g, 95% CI: -6.87, 9.19; $P = 0.265$, $I^2 = 24.8\%$) and diabetes model of rodents whose dosage of SFN ≤ 0.5 mg/kg/d (WMD: 1.09 g, 95% CI: -4.53, 6.72; $P = 0.286$, $I^2 = 12.2\%$) (Table 2).

Effects of SFN Supplementation on Liver Weight.

The results of liver weight (LW) were calculated in 4 comparisons from 4 studies. As shown in Figure. 3, SFN significantly affected LW of rodents (WMD: -0.93 g, 95% CI: -1.63, -0.23; $P = 0.000$, $I^2 = 93.0\%$). In subgroup analyses by the species, disease model, duration, SFN dosage and administration of rodents, it showed that SFN caused a reduction in levels of LW in obesity group treated with dosage of SFN >0.5 mg/kg/d by oral administration (WMD: -1.26 g, 95% CI: -2.31, -0.39; $P = 0.000$, $I^2 = 95.2\%$), but its effect in diabetes group treated with dosage of SFN ≤ 0.5 mg/kg/d by injection (WMD: 0.00 g, 95% CI: -0.37, 0.37; $P = 0.000$, $I^2 = 95.2\%$) was not significant (Table 2). Results revealed that classifying trails on the basis of species, disease model, duration, SFN dosage as well as administration route could not explain the heterogeneity among studies from the subgroup analysis (Table 2).

Effects of SFN Supplementation on Serum Total Cholesterol.

In total 6 publications with 6 effect sizes, serum total cholesterol concentrations were reported. Overall, it had been found that SFN caused a decrement in serum TC levels significantly from the quantitative meta-analysis (WMD: -15.62 mg/dL, 95% CI: -24.07, -7.18, $P = 0.000$, $I^2 = 92.3\%$) (Figure. 4). Heterogeneity was eliminated in studies which lasted for >10 weeks ($I^2 = 0.0\%$), however, the heterogeneity sources were not found when studies were stratified duration and other subgroups (Table 2). Moreover, in all studies, intake of SFN could lead to a significant decline in serum levels of total cholesterol, particularly in mice (WMD: -23.59 mg/dL, 95% CI: -60.48, 13.30, $P = 0.000$, $I^2 = 97.3\%$), the dosage of SFN >0.5 mg/kg/d (WMD: -22.75 mg/dL, 95% CI: -40.46, -5.04; $P = 0.000$, $I^2 = 95.1\%$) and ≤ 10 weeks' intervention subgroups (WMD: -21.27 mg/dL, 95% CI: -34.67, -7.87; $P = 0.000$, $I^2 = 92.5\%$) (Table 2).

Effects of SFN Supplementation on Serum Low-density Lipoprotein.

In total, the analysis of LDL-C involves 3 publications with 3 effect sizes. A statistically significant reduction effect of SFN supplementation on serum LDL-C (WMD: -8.35 mg/dL, 95% CI: -15.47, -1.24; $P = 0.001$, $I^2 = 85.2\%$) was discovered (Fig. 5).

Effects of SFN Supplementation on Serum High-Density Lipoprotein.

Combining 5 effect sizes from 5 publications, we found SFN was not effective to the levels of serum HDL-C concentration (WMD: 1.05 mg/dL, 95% CI: -3.44, 5.54; $P = 0.000$, $I^2 = 91.2\%$) (Fig. 6). In subgroup analyses, it suggested that SFN played a role in the increment of HDL-C significantly in diabetes subgroup which is injected with SFN (WMD: 4.00 mg/dL, 95% CI: 0.65, 7.35)³³, but it had no significant effect in obesity group by oral administration (WMD: 0.40 mg/dL, 95% CI: -5.42, 6.22; $P = 0.000$, $I^2 = 92.5\%$). In addition, SFN supplementation reduced the level of HDL-C significantly in mice subgroup (WMD: -8.30 mg/dL, 95% CI: -11.94, -4.66). The species, disease model, duration and SFN dosage and administration route of studies were not determined as sources of heterogeneity (Table 2).

Effects of SFN Supplementation on Serum Triglyceride.

There were five effect sizes from 5 publications which met the inclusion and exclusion criteria and were included in the analysis of serum triglyceride. Overall, levels of serum TG were reduced after supplementation of SFN with high degree of study heterogeneity showed by the quantitative meta-analysis (WMD: -40.85 mg/dL, 95% CI: -67.46, -14.24; $P = 0.000$, $I^2 = 97.1\%$) (Fig. 7). The results of the subgroup analysis revealed that the heterogeneity among studies could not be explained when studies were divided by species, disease model, duration and SFN dosage and administration route. In these analysis results, the effect of reducing serum TG concentrations after intake of SFN was significant when researches were performed on rodents, those dosage of SFN ≤ 0.5 mg/kg/d (WMD: -132.41 mg/dL, 95% CI: -231.71, -33.12; $P = 0.000$, $I^2 = 97.5\%$), with an intervention duration of >10 weeks (WMD: -103.25 mg/dL, 95% CI: -128.94, -77.56), and rats group (WMD: -33.14 mg/dL, 95% CI: -60.77, -5.51; $P = 0.000$, $I^2 = 95.3\%$). In addition, SFN supplements were not statistically significant for other subgroups (Table 2).

Publication Bias and Sensitivity Analysis.

There were no evidence for publication bias through Funnel plots and Egger's tests (BW Egger's test: $P = 0.201$, LW Egger's test: $P = 0.386$, TC Egger's test: $P = 0.055$, LDL-C Egger's test: $P = 0.515$, HDL-C Egger's test: $P = 0.836$

and TG Egger's test: $P = 0.230$) (Supplementary Table S1 and Figure S1). Sensitivity analyses revealed that any particular study did not influence the summary effects on BW, LW, TC, LDL-C, HDL-C and TG (Supplementary Figure S2)

Discussion

In this updated meta-analysis, ten articles were contained to assess SFN supplementation's effects on body weight and lipid profile in preclinical animal models. Our analytic results indicated that SFN supplementation significantly decreased BW, LW, TC as well as LDL-C levels apart from HDL-C. This meta-analytic study for the first time summarizes the function of SFN per se instead of mixtures like whole broccoli on lipid profile in rodents with metabolic syndrome. This study suggested that SFN is effective on BW, LW and lipid profile in animal models.

Our results revealed that different disease model (with or without STZ) did not influence the previous results of meta-analysis on lipid-related parameters and weight in rodents after supplementation with SFN. Changing duration and dosage of SFN and administration route has no effect on the result.

Although our research focuses on effect of SFN as a mono drug on lipid profile, almost all are clinical trials of broccoli and broccoli sprouts instead of SFN per se. However, clinical trials about intake of broccoli enriched with SFN can provide some auxiliary support for research on SFN effect. Take study of Adriana Conzatti et al. for example, clinical research of the supplement of broccoli revealed that broccoli sprouts intervention could improve these parameters related to lipid profile and blood glucose¹³. In one study by Armah et al.¹⁷, plasma LDL-C was downregulated significantly after intake of high glucoraphanin broccoli from one clinical trial. In another study by Armah et al.³⁹, the intervention group with a diet rich in high-glucoraphanin broccoli showed positive changes in lipid and amino acid metabolites. The intervention group with a diet rich in high glucose rapamycin cauliflower reduced changes in lipid and amino acid metabolites. However, according to the result of Sudini et al.⁴⁰, intake of whole Broccoli sprouts lasting for half a week could not improve inflammation and oxidative stress markers although causing a remarkable increment in serum SFN levels. In all related clinical trials, the intervention of subjects was consumption of food like broccoli instead of SFN per se and the intervention needs to be taken for a longer time to get a positive effect for clinical trials.

At the animal and cellular level, cumulative research evidence shows that SFN can improve lipid-related metabolic indicators and cardiovascular disorders^{41,42}. Recently, SFN was reported to attenuate HFD-induced obesity through inhibiting lipogenesis via triggering the AMP-activated protein kinase (AMPK) pathway^{20,29}. Direct evidence has shown that AMPK is essential for the prevention of SFN-mediated cardiomyopathy induced by Type 2

diabetes. Specifically, the reason why SFN plays a positive role in cardiomyopathy is related to regulate antioxidative pathways mediated by NRF2 (nuclear factor, erythroid 2 like 2) and promote lipid metabolism mediated by AMPK^{29,43,44}. Evidence from clinical studies and animal experiments shows that SFN prevention of CVD may also be related to the regulation of Nrf2 activation mechanism⁴⁵. Apart from regulating systemic metabolic parameters, the present findings reveal that glycated hemoglobin as well as fasting blood glucose were reduced by SFN in type 2 diabetes patients^{14,43,46}. What's more, Fu et al.'s work⁴⁷ showed that SFN supplement attenuated production of reactive oxygen species stimulated by glucose, and thereby decreased insulin secretion. Many researches showed the similar results that obesity and insulin resistance could be ameliorated by SFN^{31,48-50}.

It is the most meaningful point that is SFN may lower risks of metabolic syndrome by attenuating associated risk factors by improving weight management and ameliorating lipid profile of this meta-analysis^{12,51}. Our meta-analysis has the following advantages. Our meta-analysis is the first systematic review and meta-analysis that summarizes previous studies of SFN per se on lipid distribution in rodents of metabolic syndrome, rather than whole broccoli. Subgroup analysis has been done based on model method, age, SFN dosage, intervention duration and mode of administration. What's more, the meta-analysis involved 10 studies containing different countries and animal models. It was no limitation on language that existed in our meta-analysis.

As there are no articles on female rats or mice, it is not clear how SFN differs between males and females. Female animals and male animals have different sex hormones, which may affect blood lipids. Therefore, SFN may have different effects on women's blood lipid status. It is necessary to conduct research to evaluate the effect of SFN on the lipid profile of men and women.

When interpreting the results of this meta-analysis, some limitations must be kept in mind. Firstly, it is not clear how SFN differs between males and females as there are seldom articles on female rats or mice. Female animals and male animals have different sex hormones, which may affect serum lipid concentration. It is necessary to conduct research to evaluate the effect of SFN on the lipid profile of males and females. Secondly, our meta-analysis is based on animal experiments rather than RCTs. Animal experimental research is not comprehensive because the results obtained through animal models are not necessarily applicable to humans. Lastly, there is only ten researches which meet our requirements. The number of studies of clear data about metabolic parameters is too small to hinder further subgroup analysis. Most articles were not exclusively on rodents fed with HFD, and using other food supplements with SFN was not as exclusion criteria.

Overwhelming results support that SFN supplements could have a certain effect on BW, LW and lipid profile such as TC, TG, LDL-C from this updated meta-analysis. However, the conclusion of the meta-analysis needs

to be further confirmed by clinical trials. In addition, it is necessary to perform more studies and evaluating assess more comprehensive indicators on patients with dyslipidemic, obesity, CVD, NAFLD and so on.

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Table legends

Table 1. Description of included studies.

Table 2. Subgroup analysis to assess the effect of SFN supplement on lipid profile.

Table 1. Description of included studies.

First author, year	Species	No. of animals (intervention/ control group)	Age (Weight)	Model method (time)	Duration	Intervention	The main outcomes	Intergroup difference	Results
1 Choi K.M. (2014) ²⁹	Male C57BL/6N mice	10/10	4 weeks	High-fat diet (6w)	6 weeks	1 g/kg diet SFN, oral administration	1.BW	1.P<0.01	BW and serum TC, decreased significantly, but serum TG, HDL-C, LDL-C, liver TC, and TG didn't change in SFN group
							2.TC (Serum)	2.P<0.05	
							3.TG (Serum)	3.P>0.05	
							4.HDL-C	4.P>0.05	
							5.LDL-C	5.P>0.05	
							6.TC (Liver)	6.P>0.05	
							7.TG (Liver)	7.P>0.05	
2 Lei P. (2019) ⁵²	Male Wistar rats	6/6	4-6 weeks (160-200 g)	High-fat diet (10w)	10 weeks	20 mg/kg, 3 days a week SFN, oral gavage	1.LW	1.P<0.05	LW, serum TC, TG, LDL-C, liver TG and LDs decreased significantly, but serum HDL-C, and liver TC didn't change in
							2.TC (Serum)	2.P<0.05	
							3.TG (Serum)	3.P<0.05	
							4.HDL-C	4.P>0.05	

3	Shawky N.M. (2019) ³¹	Male Sprague Dawley rats	8/10	8 weeks (150-200 g)	High-fructose diet (9w)	6 weeks	0.5 mg/kg/day SFN, oral gavage	5.LDL-C	5.P<0.05	SFN group
								6.TC (Liver)	6.P>0.05	
								7.TG (Liver)	7.P<0.05	
								8.LDs (Liver)	8.P<0.01	
								9.FFA (Liver)	9.P<0.01	
								1.BW	1.P>0.05	AUC _{OGTT} , HOMA-IR, serum HDL-C and LDL-C ameliorated significantly, but BW, AUC _{ITT} , serum TC and TG didn't change in SFN group
								2.AUC _{OGTT}	2.P<0.05	
								3. AUC _{ITT}	3.P>0.05	
								4.HOMA-IR	4.P<0.05	
								5.TC (Serum)	5.P>0.05	
4	Shawky N.M. (2016) ³²	Male C57BL/6 J mice	11/11	8 weeks	High-fat high- sucrose diet (8w)	3 weeks	0.5 mg/kg/day SFN, subcutaneous injection	6.TG (Serum)	6.P>0.05	BW, HOMA-IR, AUC _{IPGTT} , plasma TG, HDL-C, FFA and Non-HDL-C ameliorated significantly, but plasma TC,
								7.HDL-C	7.P<0.05	
								8.LDL-C	8.P<0.05	
								1.BW	1.P<0.05	
								2.HOMA-IR	2.P<0.05	
								3.AUC _{IPGTT}	3.P<0.05	
								4.TC (Plasma)	4.P>0.05	

5	Souza C.G. (2016) ³³	Male Wistar rats	8/7	8 weeks	injection of STZ	3 weeks	0.5 mg/kg/day SFN, intraperitoneal injection	5.TG (Plasma)	5.P<0.05	LDL-C didn't change in SFN group
								6.HDL-C (Plasma)	6.P<0.05	
								7.LDL-C (Plasma)	7.P>0.05	
								8.FFA (Plasma)	8.P<0.05	Serum TC, Non-HDL-C, TG, AUC _{IPIRT} decreased significantly, but LW, HDL-C, ALT, and AST didn't change in SFN group
								9.Non-HDL-C (Plasma)	9.P<0.05	
								1.LW	1.P>0.05	
								2.TC (Serum)	2.P<0.05	
								3.HDL-C (Serum)	3.P>0.05	
								4.Non-HDL-C	4.P<0.05	
								5.TG (Serum)	5.P<0.05	
								6.ALT	6.P>0.05	
6	Souza C.G. (2013) ³⁴	Male Wistar rats	7/7	8 weeks	Highly Palatable diet (24w) (enriched sucrose diet)	16 weeks	1 mg/kg/day SFN, oral gavage	7.AST	7.P>0.05	Lipid parameters didn't change significantly in SFN group
								8.AUC _{IPIRT}	8.P<0.05	
								1.BW	1.P>0.05	
								2.LW	2.P>0.05	
								3.TC (Serum) 4.HDL-C	3.P>0.05	
								5.TAG (Serum)	4.P>0.05	

7	Sun Y. (2020) ³⁵	Male C57BL/6 J mice	5/5	8 weeks	High-fat diet (12w,24w), injection of STZ	12 weeks	0.5 mg/kg, 5 days a week SFN, intraperitoneal injection	6.TAG (Liver)	5.P>0.05	BW and Cardiac LDs didn't change significantly in SFN group treated by HFD for 12 weeks, but both of them decreased significantly in SFN group treated by HFD for 24 weeks
								7.TC (Liver)	6.P>0.05	
								8.ALT	7.P>0.05	
								9.AST	8.P>0.05	
								10.AUC _{IPGTT}	9.P>0.05	
8	Tian S. (2017) ³⁶	Male Wistar rats	10/10	4-6 weeks (160-200 g)	High-fat diet (10w)	10 weeks	5, 10, 20 mg/kg, 3 days a week SFN, oral gavage	1.BW	1.P>0.05, P<0.05	Plasma TC, TG decreased significantly, but liver TC, TG didn't change significantly in low-doses-SFN group; All of
								2.LDs (Cardiac)	2.P>0.05, P<0.05	
								1.TC (Plasma)	1.P<0.05,	
								2.TG (Plasma)	P<0.05,	
								3.TC (Liver)	P<0.0001	
								4.TG (Liver)	2.P<0.0001,	

								P<0.05,	plasma TC, TG, liver TC and TG
								P<0.0001	decreased significantly in middle-
								3.P>0.05,	doses-SFN and high-doses-SFN
								P<0.01,	group
								P<0.0001	
								4.P>0.05,	
								P<0.0001,	
								P<0.0001	
							1.LW	1.P<0.05	
							2.TC (Liver)	2.P<0.05	
							3.TG (Liver)	3.P<0.05	Lipid parameters
9	Male C57BL/6	8/8	5 weeks	High-fat diet	9 weeks	30 mg/kg/day SFN,	4.FFA (Liver)	4.P<0.05	change significantly in
Yang G. (2016) ³⁷	mice			(9w)		oral gavage	5.ALT	5.P<0.05	SFN group
							6.AST	6.P<0.05	
							7.HOMA-IR	7.P<0.05	
10	Male	6/6	8–10 weeks	High-fat diet	16 weeks	0.5 mg/kg, 5 days a	1.TC (Plasma)	1.P>0.05	Plasma TG and cardiac LDs
Zhang Z. (2014) ³⁸	C57BL/6J mice			(12w), injection		week SFN,	2.TG (Plasma)	2.P<0.05	decreased significantly, but

of STZ

subcutaneous

3.AUC_{IPGTT}

3.P>0.05

plasma TC and AUC_{IPGTT} didn't

injection

4.LDs (Cardiac)

4.P<0.05

change significantly in SFN

group

^aALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the curve; FFA, free fatty acids; GTT, glucose tolerance test; HOMA-IR: an index of insulin resistance; IP, intraperitoneally; IRT, the insulin responsiveness test; LDs, lipid droplets; O, oral; w, weeks.

Table 2. Subgroup analysis to assess the effect of SFN supplement on lipid profile.

	Effect size, n	WMD	95% CI	I-squared (%)	P for heterogeneity	P for between subgroup heterogeneity
Body weight						
Overall effect	6	-2.76	-4.19, -1.34	58.9	0.032	
Species						0.471
Mice	3	-2.93	-4.34, -1.52	76.3	0.015	
Rats	3	1.12	-6.87, 9.10	24.8	0.265	
Disease model						0.122
Obesity (without STZ)	4	-3.30	-4.46, -2.14	52.7	0.096	
Diabetes (with STZ)	2	1.09	-4.53, 6.72	12.2	0.286	
Duration						0.122
≤10 weeks	4	-3.18	-4.60, -1.75	64.6	0.037	
>10 weeks	2	-0.45	-3.68, 2.79	0.0	0.37	
SFN dosage						0.292
≤0.5 mg/kg/d	2	1.09	-4.53, 6.72	12.2	0.286	
>0.5 mg/kg/d	4	-3.30	-4.46, -2.14	52.7	0.096	
Administration route						0.391
Oral	3	-3.96	-4.47, -3.14	0.0	0.392	
Injection	3	-1.33	-4.46, 1.80	55.2	0.107	
Liver weight						
Overall effect	4	-0.93	-1.63, -0.23	93.0	0.000	
Species						0.712
Mice	1	-0.54	-0.75, -0.33	\	\	
Rats	3	-1.11	-2.31, 0.09	95.2	0.000	
Disease model						0.363
Obesity (without STZ)	3	-1.26	-2.13, -0.39	93.3	0.000	
Diabetes (with STZ)	1	0.00	-0.37, 0.37	\	\	

Duration						0.992
≤10 weeks	3	-0.93	-1.89, 0.03	94.9	0.000	
>10 weeks	1	-1.00	-1.40, -0.60	\	\	
SFN dosage						0.363
≤0.5 mg/kg/d	1	0.00	-0.37, 0.37	\	\	
>0.5 mg/kg/d	3	-1.26	-2.13, -0.39	93.3	0.000	
Administration route						0.363
Oral	3	-1.26	-2.13, -0.39	93.3	0.000	
Injection	1	0.00	-1.63, -0.23	\	\	
Total cholesterol						
Overall effect	6	-15.62	-24.07, -7.18	92.3	0.000	
Species						0.511
Mice	2	-23.59	-60.48, 13.30	97.3	0.000	
Rats	4	-12.77	-21.41, -4.14	89.2	0.000	
Disease model						0.752
Obesity (without STZ)	4	-17.49	-30.34, -4.64	93.7	0.000	
Diabetes (with STZ)	2	-12.92	-28.45, 2.61	94.3	0.000	
Duration						0.261
≤10 weeks	4	-21.27	-34.67, -7.87	92.5	0.000	
>10 weeks	2	-6.17	-9.01, -3.34	0.0	0.525	
SFN dosage						0.338
≤0.5 mg/kg/d	3	-9.66	-20.10, 0.78	90.6	0.000	
>0.5 mg/kg/d	3	-22.75	-40.46, -5.04	95.1	0.000	
Administration route						0.752
Oral	4	-17.49	-30.34, -4.64	93.7	0.000	
Injection	2	-12.92	-28.45, 2.61	94.3	0.000	

HDL-C

Overall effect	5	1.05	-3.44, 5.54	91.2	0.000	
Species						0.199
Mice	1	-8.30	-11.94, -4.66	\	\	
Rats	4	3.31	-1.18, 7.80	88.0	0.000	
Disease model						0.747
Obesity (without STZ)	4	0.40	-5.42, 6.22	92.5	0.000	
Diabetes (with STZ)	1	4.00	0.65, 7.35	\	\	
Duration						0.878
≤10 weeks	4	1.63	-6.44, 9.70	93.4	0.000	
>10 weeks	1	0.00	-0.40, 0.40	\	\	
SFN dosage						0.102
≤0.5 mg/kg/d	2	8.26	-0.71, 17.22	85.9	0.008	
>0.5 mg/kg/d	3	-3.13	-8.38, 2.12	90.1	0.000	
Administration route						0.747
Oral	4	0.40	-5.42, 6.22	92.5	0.000	
Injection	1	4.00	0.65, 7.35	\	\	

Triglyceride

Overall effect	5	-40.85	-67.46, -14.24	97.1	0.000	
Species						0.659
Mice	2	-41.49	-161.29, 78.30	98.7	0.000	
Rats	3	-33.14	-60.77, -5.51	95.3	0.000	
Disease model						0.092
Obesity (without STZ)	3	-1.34	-18.69, 16.01	95.1	0.000	
Diabetes (with STZ)	2	-212.55	-436.50, 11.40	97.1	0.000	
Duration						0.898
≤10 weeks	4	-18.05	-42.06, 5.96	96.4	0.000	
>10 weeks	1	-103.25	-128.94, -77.56	\	\	
SFN dosage						0.305

≤0.5 mg/kg/d	3	-132.41	-231.71, -33.12	97.5	0.000	
>0.5 mg/kg/d	2	4.85	-22.42, 32.13	97.1	0.000	
Administration route						0.092
Oral	3	-1.34	-18.69, 16.01	95.1	0.000	
Injection	2	-212.55	-436.50, 11.40	94.9	0.000	

Figure Legends

Figure 1. Flow diagram of database searches and study selection.

Figure 2. Forest plot showing effects of SFN on body weight levels

Figure 3. Forest plot showing effects of SFN on liver weight levels

Figure 4. Forest plot showing effects of SFN on serum total cholesterol.

Figure 5. Forest plot showing effects of SFN on serum low density lipoprotein levels.

Figure 6. Forest plot showing effects of SFN on Serum High-Density Lipoprotein.

Figure 7. Forest plot showing effects of SFN on Serum Triglyceride.

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Figures

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