

Ginger supplementation for the treatment of non-alcoholic fatty liver disease: a meta-analysis of randomized controlled trials

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Abstract

Introduction: The efficacy of ginger supplementation remains controversial for non-alcoholic fatty liver disease. We conduct this meta-analysis to explore the influence of ginger supplementation versus placebo on the treatment of non-alcoholic fatty liver disease.

Methods: We have searched PubMed, EMBASE, Web of Science, EBSCO, and Cochrane library databases through November 2021 and included randomized controlled trials (RCTs) assessing the efficacy of ginger supplementation versus placebo for non-alcoholic fatty liver disease. This meta-analysis was performed using the random-effect model.

Results: Four RCTs involving 177 patients were included in the meta-analysis. Overall, compared with non-alcoholic fatty liver disease, ginger supplementation was associated with significantly reduced alanine aminotransferase (ALT, standard mean difference (SMD)=-0.43; 95% confidence interval [CI]=-0.85 to -0.02; P=0.04), homeostatic Model Assessment of Insulin Resistance (HOMA-IR, SMD=-1.14; 95% CI=-2.05 to -0.22; P=0.02), but revealed no obvious impact on aspartate-aminotransferase (AST, SMD=-0.66; 95% CI=-0.81 to 2.12; P=0.38), total cholesterol (SMD=-0.33; 95% CI=-0.67 to 0.02; P=0.06), low density lipoprotein (LDL, SMD=-0.30; 95% CI=-0.64 to 0.04; P=0.08) or body mass index (BMI, SMD=0; 95% CI=-0.41 to 0.40; P=0.99).

Conclusions: Ginger supplementation benefits to treat non-alcoholic fatty liver disease.

Keywords: ginger; non-alcoholic fatty liver disease; randomized controlled trials; meta-analysis.

DOI: <https://dx.doi.org/10.4314/ahs.v23i1.65>

Cite as: Zhou Q, Peng Y, Chen F, Dai J. Ginger supplementation for the treatment of non-alcoholic fatty liver disease: a meta-analysis of randomized controlled trials. *Afri Health Sci.* 2023;23(1):614-21. <https://dx.doi.org/10.4314/ahs.v23i1.65>

Introduction

Non-alcoholic fatty liver disease was identified by Ludwig in 1980 and accumulation of more than 5% triglyceride in hepatic parenchyma without notable alcohol consumption is defined as non-alcoholic fatty liver disease, which has become one global public health problem¹⁻⁴. This disease is featured by a wide range of liver disorders from hepatocellular steatosis to more severe non-alcoholic steatohepatitis, which may progress to hepatic fibrosis and cirrhosis⁵⁻⁷.

There is still lack of effective treatment for non-alcoholic fatty liver disease, and new therapeutic approaches should be developed to improve the treatment efficacy⁸. Diets containing antioxidants and anti-inflammatory agents showed some benefits in the treating of non-alcoholic fatty liver disease⁹⁻¹¹. Ginger was widely used worldwide as a spice, and demonstrated some efficacy to treat neurological diseases, diabetes, rheumatism, gingivitis, toothache, asthma, constipation, maldigestion, nausea and vomiting because of its roles in immune regulator, tumor inhibition, anti-inflammation, anti-apoptotic and antiemetic effects. There have been more than 40 antioxidant compounds that are identified in ginger¹². Ginger family was reported to suppress nuclear factor-kappa B (NF- κ B), which was the key protein complex for cytokine production and cellular responses to stimuli such as inflammatory cytokines and oxidative stress¹³⁻¹⁵.

In patients with non-alcoholic fatty liver disease, ginger supplement resulted in significant improvement in alanine

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aminotransferase (ALT), total cholesterol, low-density lipoprotein (LDL) and insulin resistance index (HOMA) compared to placebo¹⁶. However, the benefit of ginger supplementation for non-alcoholic fatty liver disease has not been well established. Recently, several studies on the topic have been published, and the results were conflicting¹⁶⁻¹⁸. With accumulating evidence, we therefore searched for eligible randomized controlled trials (RCTs) assessing the efficacy of ginger supplementation versus placebo for non-alcoholic fatty liver disease and perform this meta-analysis using the random-effect model. Sensitivity analysis was also conducted. These aimed to explore the efficacy of ginger supplementation versus placebo for non-alcoholic fatty liver disease.

Materials and methods

Ethical approval and patient consent were not required because this was a meta-analysis of previously published studies. This meta-analysis was conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)^{19,20}.

Search strategy and study selection

Two investigators have independently searched the following databases (inception to November 2021): PubMed, EMBASE, Web of science, EBSCO and Cochrane library databases. The electronic search strategy was conducted using the following keywords: “non-alcoholic fatty liver disease” OR “steatohepatitis” AND “ginger”. The inclusive selection criteria were as follows: (i) patients were diagnosed with non-alcoholic fatty liver disease; (ii) intervention treatments were ginger supplementation versus placebo; (iii) study design was RCT.

Data extraction and outcome measures

We extracted the following information: author, number of patients, age, female, weight, body mass index and detail methods in each group etc. Data were extracted independently by two investigators, and discrepancies were resolved by consensus. The primary outcomes were alanine aminotransferase (ALT) and aspartate-aminotransferase (AST). Secondary outcomes included homeostatic Model Assessment of Insulin Resistance (HOMA-IR),

total cholesterol, low density lipoprotein (LDL) and body mass index (BMI).

Quality assessment in individual studies

Methodological quality of the included studies was independently evaluated using the modified Jadad scale^{20,21}. There were three items for Jadad scale: randomization (0-2 points), blinding (0-2 points), dropouts and withdrawals (0-1 points). The score of Jadad Scale varied from 0 to 5 points. An article with Jadad score ≤ 2 had low quality. If the Jadad score ≥ 3 , the study was thought to have high quality^{22,23}.

Statistical analysis

We estimated the standard mean difference (SMD) with 95% confidence interval (CI) for continuous outcomes. The random-effects model was used regardless of heterogeneity. Heterogeneity was reported using the I² statistic, and I² > 50% indicated significant heterogeneity²⁴. Whenever significant heterogeneity was present, we searched for potential sources of heterogeneity via omitting one study in turn for the meta-analysis or performing subgroup analysis. All statistical analyses were performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

Results

Literature search, study characteristics and quality assessment

A detailed flowchart of the search and selection results was presented in Figure 1. 184 potentially relevant articles were identified initially and four RCTs were finally included in the meta-analysis^{16-18,25}. The baseline characteristics of four eligible RCTs were summarized in Table 1. The four studies were published between 2016 and 2020, and total sample size was 177. The doses of ginger supplementation ranged from 1000 mg daily to 1500 mg daily. Two studies reported the same patient sample with different outcomes. Among the four studies included here, three studies reported ALT and AST^{16,18,25}, three studies reported HOMA-IR^{16,17,25}, two studies reported total cholesterol and LDL^{16,17} and two studies reported BMI^{16,18}. Jadad scores of the four included studies varied from 3 to 4, and all four studies had high quality.

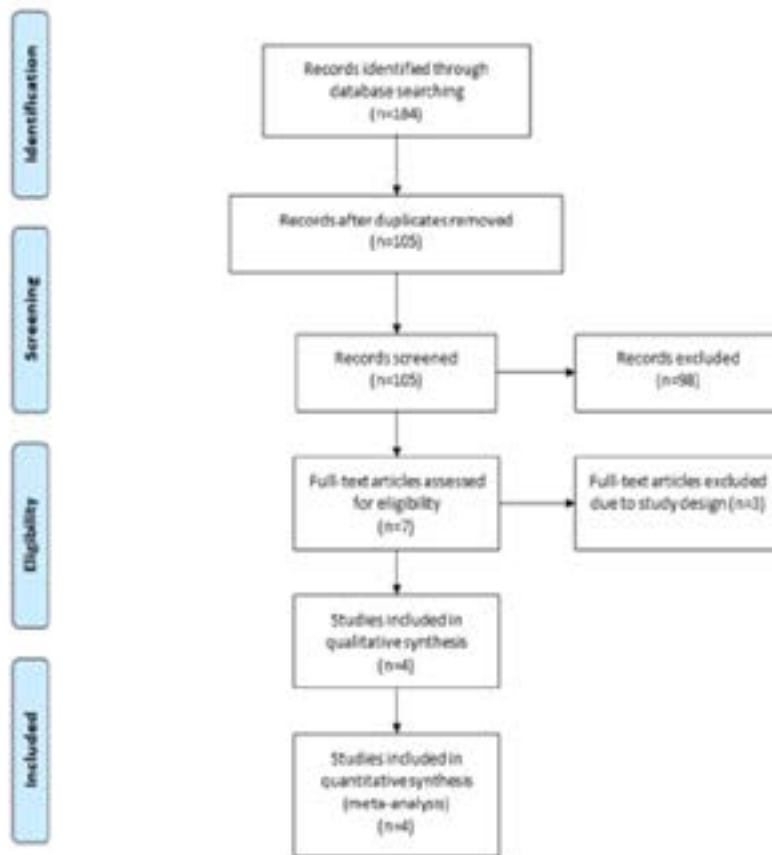


Figure 1: Flow diagram of study searching and selection process.

Table 1: Characteristics of included studies

N O.	Author , year	Ginger group					Control group					Jada scor es		
		Num ber	Age (years)	Fem ale (n)	Weight (kg)	Body mass index (kg/m ²)	Method s	Num ber	Age (years)	Fema le (n)	Weight (kg)		Body mass index (kg/m ²)	Metho ds
1	Rafie 2020	23	50.04 ± 10.26	13	-	31.70±3 .75	1500 mg ginger powder daily for 12 weeks	23	47.95 ± 9.24	13	-	30.94±1 .98	placeb o	4
2	Danes hi- Masko oni 2019	43	45.5±8. 9	16	85.2±11 .3	30.5±2. 4	two 500 mg capsule s (green cardam om from ginger family) three times per day for 3 months	44	45.0± 7.7	17	88.6±13 .2	30.7±3. 2	placeb o	4
3	Danes hi- Masko oni 2018	43	45.5±8. 9	16	85.2±11 .3	30.5±2. 4	two 500 mg capsule s (green cardam om from ginger family) three times per day for 3 months	44	45.0± 7.7	17	88.6±13 .2	30.7±3. 2	placeb o	4
4	Rahiml ou 2016	23	45.45±2 .31	11	86.47±3 .59	30.55±0 .95	500 mg ginger capsule s twice daily for 12 weeks	21	45±2. 14	13	81.38±2 .96	31.53±0 .47	placeb o	3

Primary outcomes: ALT and AST

These outcome data were analysed with the random-effects model, and compared to control group for non-alcoholic fatty liver disease, ginger supplementation was associated with significantly reduced ALT (SMD=-0.43;

95% CI=-0.85 to -0.02; P=0.04) with low heterogeneity among the studies (I²=44%, heterogeneity P=0.17, Figure 2), but showed no obvious influence on AST (SMD=-0.66; 95% CI=-0.81 to 2.12; P=0.38) with significant heterogeneity among the studies (I²=95%, heterogeneity P=0.38, Figure 3).

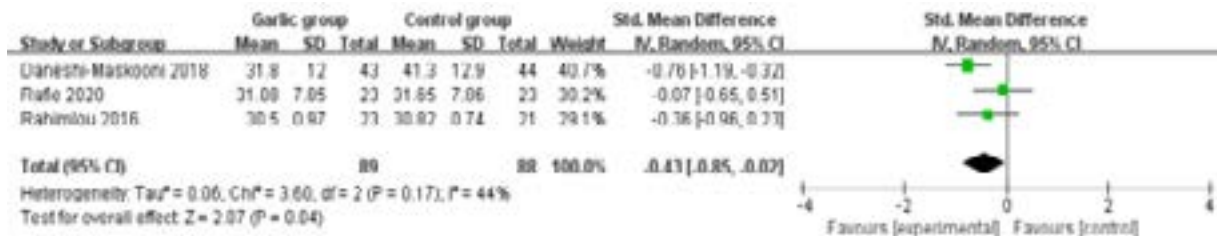


Figure 2: Forest plot for the meta-analysis of ALT.

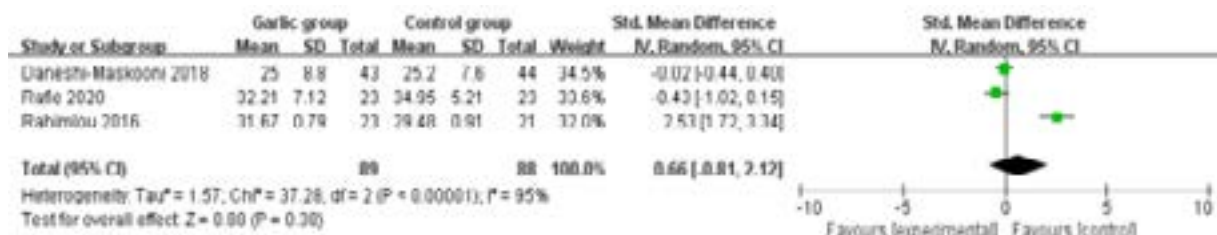


Figure 3: Forest plot for the meta-analysis of AST.

Sensitivity analysis

Significant heterogeneity was observed among the included studies for the AST. As shown in Figure 3, the study conducted by Rahimlou showed the results that were almost out of range of the others and probably contributed to the heterogeneity²⁵. After excluding this study, the results suggested that ginger supplementation also demonstrated no significant impact on AST (SMD=-0.17; 95% CI=-0.56 to 0.21; P=0.37), and low heterogeneity remained (I²=19%, P=0.27).

Secondary outcomes

In comparison with control group for control group for non-alcoholic fatty liver disease, ginger supplementation substantially reduced HOMA-IR (SMD=-1.14; 95% CI=-2.05 to -0.22; P=0.02; Figure 4), but unravelled no obvious influence on total cholesterol (SMD=-0.33; 95% CI=-0.67 to 0.02; P=0.06; Figure 5), LDL (SMD=-0.30; 95% CI=-0.64 to 0.04; P=0.08; Figure 6) or BMI (SMD=0; 95% CI=-0.41 to 0.40; P=0.99; Figure 7).

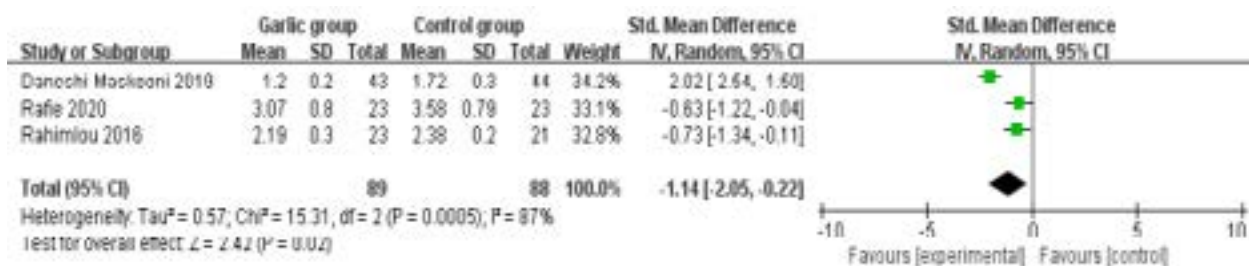


Figure 4: Forest plot for the meta-analysis of HOMA-IR

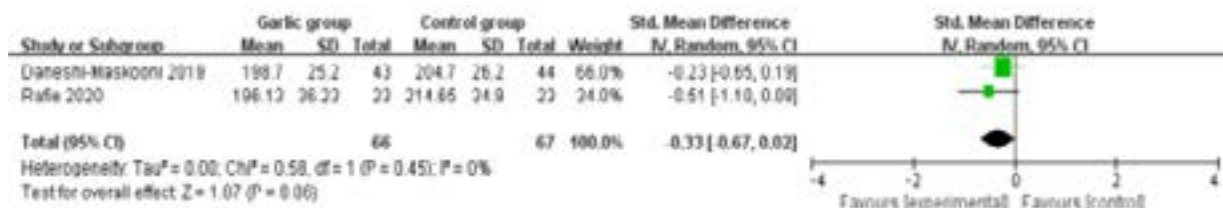


Figure 5: Forest plot for the meta-analysis of total cholesterol.

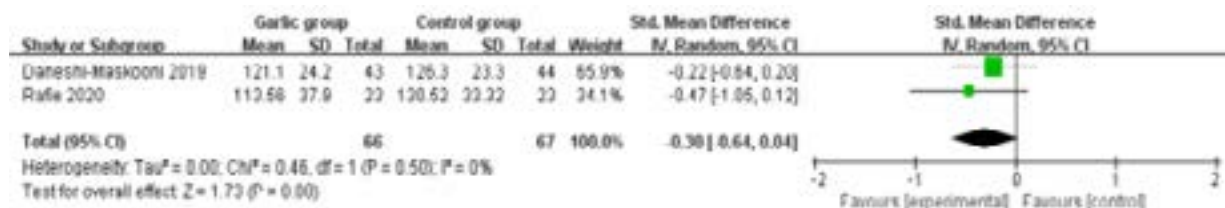


Figure 6: Forest plot for the meta-analysis of LDL.

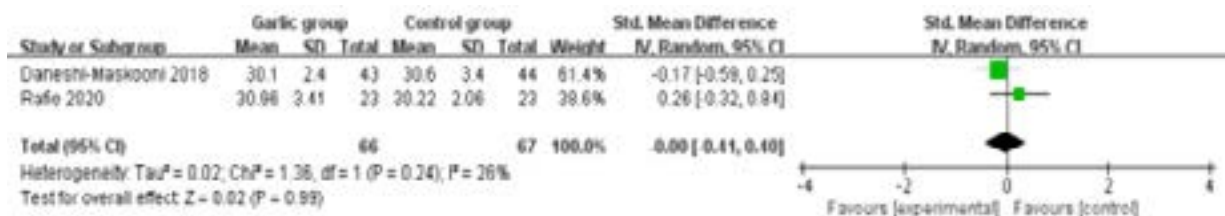


Figure 7: Forest plot for the meta-analysis of BMI.

Discussion

Inhibition of inflammatory and oxidative stress factors in patients with non-alcoholic fatty liver disease plays an important role in slowing the rate of progression and reducing the risk of cardiovascular disorders²⁶⁻²⁸. Ginger has potential antioxidant activities due to its polyphenolic compounds as gingerol and curcumin, and thus inhibits lipid peroxidation²⁹. Our meta-analysis included four eligible RCTs and 177 patients, and the results confirmed that ginger supplementation exerted important beneficial effect on hepatic function and insulin resistance for non-alcoholic fatty liver disease, as evidenced by the significantly reduced ALT and HOMA-IR.

Two-hit hypothesis are widely accepted to cause non-alcoholic fatty liver disease. First hit is defined as insulin resistance that stimulates the synthesis of liver fatty acids and accumulation of fat in the liver and steatosis, and the liver is more susceptible to the second hit (i.e. oxidative stress from different sources)¹⁶. Insulin resistance was substantially improved by ginger supplementation in our study. Insulin resistance, severe disorders of lipid metabolism, oxidative stress and inflammation play important roles in the pathogenesis of non-alcoholic fatty liver disease, and thus potential therapeutic agents are designed to target one or some of these pathological events. The fundamental role of insulin resistance is found in fat accumulation of liver, and the increase in insulin sensitivity is very promising against non-alcoholic fatty liver disease^{16, 30-32}.

Several reasons may account for the beneficial effect of ginger supplementation on non-alcoholic fatty liver disease. Firstly, ginger has substantial ability to improve insulin sensitivity to adipocytes³³. Secondly, biosynthesis of cholesterol can be inhibited and more the transformation of cholesterol to bile acids is promoted by ginger treatment³⁴. Thirdly, ginger can inhibit arachidonic acid metabolism with the suppression of cyclooxygenase and lipoxygenase enzymes, thereby acting as an anti-inflammatory agent¹⁶.

Regarding the sensitivity analysis, significant heterogeneity remained for AST. After excluding the study conducted by Rahimlou et al.²⁵, only low heterogeneity was found (I²=19%, P=0.27), and this heterogeneity was caused by the substantial difference in baseline AST²⁵. Our meta-analysis also has some important limitations. Firstly, our analysis is based on four RCTs, and all of them have a relatively small sample size (n<100). Overestimation of the treatment effect is more likely in smaller trials compared with larger samples. Secondly, although there is significant heterogeneity, different doses and forms of ginger supplementation may produce some bias. Thirdly, different etiologies and severity levels of non-alcoholic fatty liver disease may affect the efficacy assessment of ginger supplementation.

Conclusions

Ginger supplementation provides additional benefits to treat non-alcoholic fatty liver disease.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Acknowledgements

None.

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