

Efficacy of resveratrol supplementation in patients with nonalcoholic fatty liver disease: A systematic review and meta-analysis of clinical trials

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease and refers to the accumulation of triglycerides in hepatocytes. Recent studies have showed that resveratrol (antioxidant of grape) can be effective in the treatment of NAFLD through its inhibitory effect on lipid accumulation.

Method: We systematically searched databases including: ISI web of science, Scopus, PubMed and Embase by using related keywords. Then, by considering inclusion and exclusion criteria, appropriate articles were selected. All the analyses were conducted in Review Manager (RevMan) Version 5.3.

Results: Finally, 6 RCTs were included in meta-analysis and systematic review. Our results showed that resveratrol supplementation significantly reduced levels of TNF-alpha ($SMD = -0.46$; 95% CI $(-0.78, 0.14)$; $P = 0.005$) and hs-CRP ($SMD = -0.53$; 95% CI $(-1.01, -0.05)$; $P = 0.030$), but for other markers (BW, BMI, WC, HC, WHR, SBP, DBP, ALT, AST, GGT, ALP, bilirubin, TC, TG, HDL, LDL, LDL to HDL ratio, apo-A1, apo-B, insulin, HOMA-IR, glucose, creatinine and IL-6), no significant change was observed.

Conclusion: Overall, the results of the present study show that resveratrol supplementation does not affect the management of NAFLD although it can improve some inflammatory markers.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease and refers to the accumulation of triglycerides in more than 5–10% of hepatocytes [1]. NAFLD, if left untreated, can turn into non-alcoholic steatohepatitis and even progress to hepatic cirrhosis and hepatic carcinoma [2]. Studies have also shown that the complications of the NAFLD can go beyond the liver and lead to diseases such as cardiovascular disease and type 2 diabetes and chronic kidney disease [3]. According to a review study in 2016, the global prevalence of NAFLD is 25.24%, with the highest and lowest prevalence being in the Middle East and Africa, respectively [4]. Evidence suggests that nutritional, genetic, lipotoxicity, inflammatory, and oxidative stress factors are involved in the pathogenesis and progression of NAFLD [2,5]. To

date, there are no suitable and approved medications for NAFLD and treatments are based on lifestyle changes such as weight loss, dietary changes and increased physical activity [6].

Recent studies have indicated that resveratrol (3,5,4'-trihydroxy-trans-stilbene, natural polyphenol in grapes) can have antioxidant effects on steatohepatitis [7,8]. Also, resveratrol has other features including anticancer, cardioprotective, neuroprotective, anti-inflammatory and antimicrobial effects [9–15]. Recent studies have shown that resveratrol can be effective in the management and treatment of NAFLD through its inhibitory effect on lipid accumulation (by activating Silent information regulator 1 (SIRT1), adenosine monophosphate protein kinase (AMPK) and creating calorie-restricted like conditions) [16–18].

Although there are many randomized clinical trials (RCTs) on

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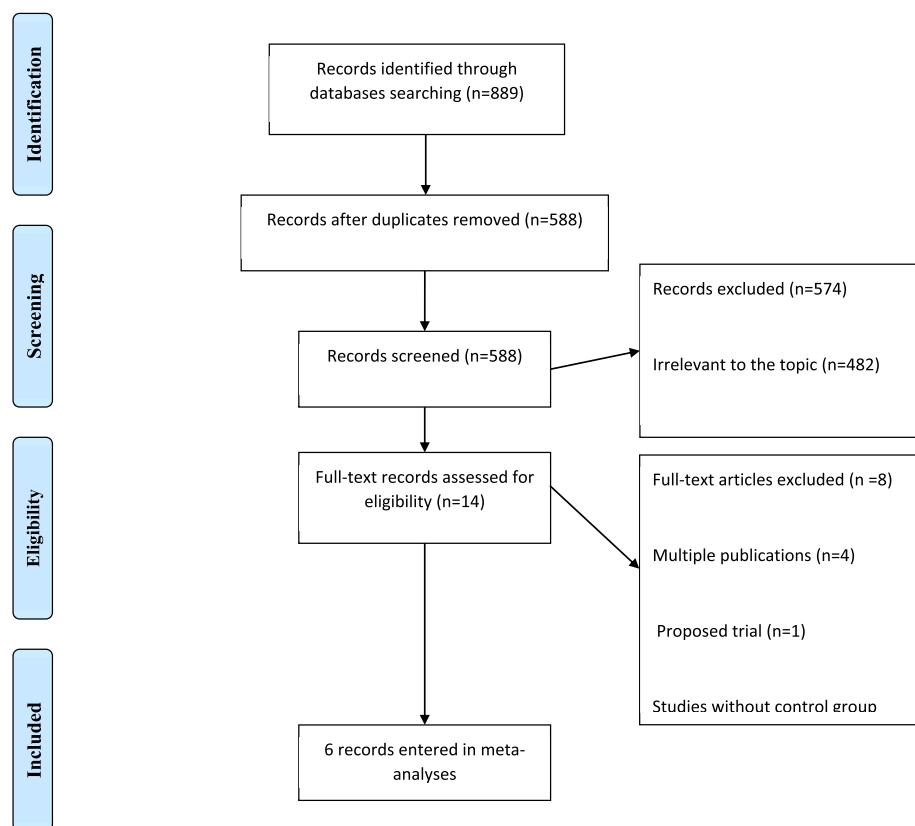
**Fig. 1.** Flow diagram of study selection.

Table 1
Characteristics of included studies.

First author (publication year)	Country	Sample size (M/F)	Target Population	Mean Age	Mean BMI	RCT design (Blinding)	Duration (wks)	Intervention of experimental group	Intervention of control group	Investigated outcomes
Chachay (2014)	Australia	20 (20)	Overweight or obese men with NAFLD	48.15 ± 11.41	31.5 ± 7.60	Parallel (yes)	8	Resveratrol (3000 mg/day)	Placebo (microcellulose)	BMI, Weight, SBP,DBP, ALT, AST, TC, TG, HDL, LDL, Insulin, HOMA-IR, Glucose, Bilirubin, TNFα, Creatinine, IL6
Faghizadeh (2014)	Iran	50 (35/15)	Subjects with NAFLD	45.16 ± 9.77	28.55 ± 3.46	Parallel (yes)	12	Trans-resveratrol (500 mg/day)	Placebo (MCT)	BMI, Weight, HC, WC, WHR, SBP,DBP, ALT, AST, TC, TG, HDL, LDL, LDL/HDL, Insulin, HOMA-IR, Glucose, Bilirubin, Apo-A1, GGT, IL6, hs-CRP
Chen (2015)	China	60 (42/28)	Subjects with NAFLD	44.3 ± 10.5	25.7 ± 2.65	Parallel (yes)	12	Resveratrol (300 mg/day)	Placebo (pullulan and Maltodextrin)	BMI, Weight, HC, WC, WHR, SBP,DBP, ALT, AST, TC, TG, HDL, LDL, Insulin, HOMA-IR, Glucose, TNFα, Apo-A1, Apo-B, GGT, Creatinine
Heeboll (2016)	Denmark	26 (ND)	Overweight patients with NAFLD	43.35	32.05 ± 4.31	Parallel (yes)	24	Resveratrol (1500 mg/day)	Placebo (ND)	BMI, Weight, WHR, SBP, DBP, ALT, AST, ALP, TG, HDL, LDL, Insulin, HOMA-IR, Glucose, Bilirubin, TNFα, GGT
Asghari (2018)	Iran	60 (40/20)	Overweight or obese subjects with NAFLD	39.53 ± 6.66	30.59 ± 3.22	Parallel (No)	12	Trans-resveratrol (600 mg/day)	Placebo (starch)	Weight, BMI, WC,WHR, ALT, AST, TC, TG, HDL, LDL, Insulin, HOMA-IR, Glucose
Farzin (2019)	Iran	50 (35/15)	Overweight or obese subjects with NAFLD	39.24 ± 6.97	30.51 ± 3.29	Parallel (No)	12	Trans-resveratrol (600 mg/day)	Placebo (corn starch)	Weight, BMI, GGT, ALP, LDL/HDL, Apo-A1, Apo-B, hs-CRP

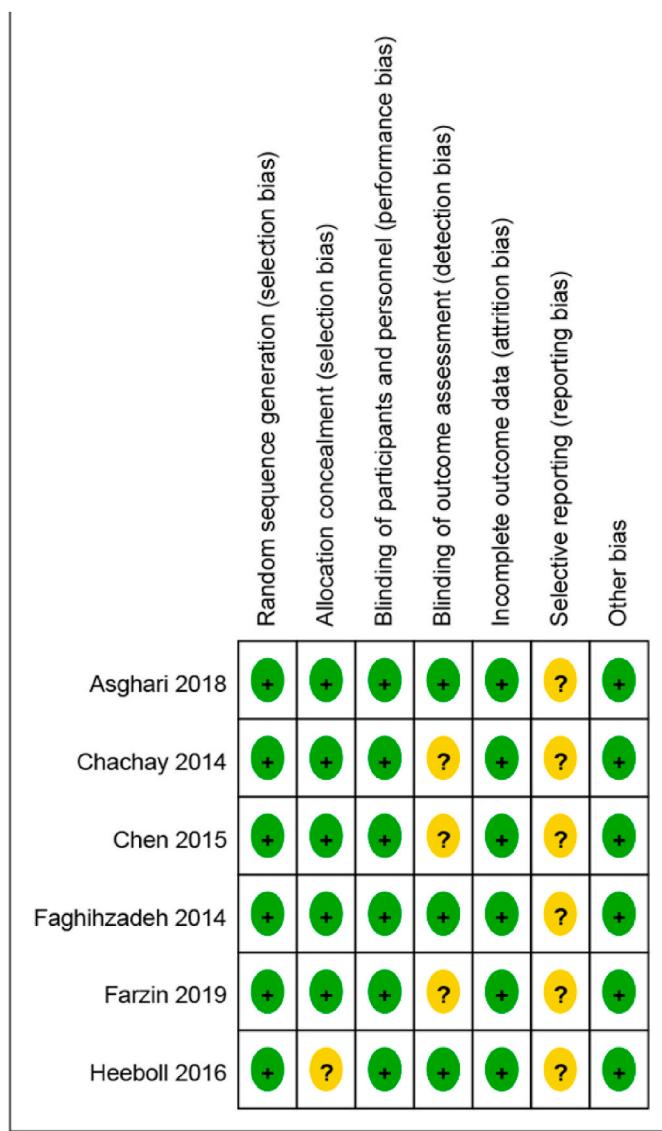


Fig. 2. Risk of bias assessment for included randomized controlled clinical trials.

resveratrol effects on the NAFLD, the results are conflicting. Only in some studies, the positive effects of resveratrol supplementation on non-alcoholic fatty liver disease were observed [19,20], while in other studies no effects were observed [21–24]. Consistently, two meta-analysis studies in 2016 and 2017 involving four RCTs showed that resveratrol supplementation has insignificant effects on NAFLD features [25,26]. Also, in these two studies, factors such as hip circumference, waist to hip ratio, ALP, LDL to HDL ratio, Apo-A1, Apo-B and creatinine were not considered. Therefore, we carried out an update systematic review and meta-analysis to summarize the RCTs data reported in six articles to investigate the effect of resveratrol on NAFLD.

2. Materials and methods

2.1. Search strategy

To find associated articles, we searched databases including: ISI web of science, Scopus, PubMed and Embase until November 2019. We systematically identified articles that studied the efficacy of resveratrol supplementation on NAFLD. We did not limit our search to publication time and language. We used (Resveratrol*[Title/Abstract]) OR

"Resveratrol" [Mesh]) AND ("Fatty liver" [Title/Abstract]) OR NAFLD [Title/Abstract] OR "Fatty Liver" [Mesh] OR "Non-alcoholic Fatty Liver Disease" [Mesh] OR "Non alcoholic Fatty Liver Disease" [Title/Abstract] OR "Nonalcoholic Fatty Liver Disease" [Title/Abstract] OR "Nonalcoholic Steatohepatitis" [Title/Abstract]) as search terms. Furthermore, the references of included literatures and related reviews were screened to define more potential relevant studies. After eliminating the duplicates, remained manuscripts were reviewed based on title, abstract, or full text by two authors (S. R. and H. M.) separately. During the study selection process, discrepancies between researchers were resolved by face-to-face discussion to achieve consensus.

2.2. Inclusion criteria

Original studies with following criteria were considered in our systematic review and meta-analysis: (1) having clinical trials design; (2) considering intervention with resveratrol supplement; (3) conducting on adult participants (aged ≥ 18 years); and (4) considering body weight (BW), body mass index (BMI), waist circumference (WC), hip circumference (HC), waist to hip ratio (WHR), systolic blood pressure (SBP), diastolic blood pressure (DBP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), bilirubin, total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), LDL to HDL ratio, apo-A1, apo-B, insulin, HOMA-IR, glucose, creatinine, tumor necrosis factor alpha (TNF- α), high-sensitivity C-reactive protein (hs-CRP) and Interleukin 6 (IL-6) as the primary or secondary outcomes.

2.3. Exclusion criteria

Studies were excluded if they: (1) used a mixture of resveratrol with other compounds (2) were uncontrolled studies, (3) reported duplicate data; and (4) were reviews, letters, editorial articles, study protocol or case reports.

2.4. Data extraction

After reading title, abstract and considering the inclusion and exclusion criteria appropriate articles were selected. The following information was extracted from articles and recorded in an Excel spreadsheet: publication information ((first author's last name, publication date, and study location), participants' characteristics (total sample size, target population, mean age and mean body mass index (BMI)), details of clinical trial (study design (blinding), trial duration, dose and type of interventions in intervention and placebo group), and final outcomes that investigated.

2.5. Quality assessment

Reviewers (S. R. and H. M.) independently evaluated the quality of the appropriate studies through Cochrane Collaboration's tool including seven domains as follows: (1) random sequence generation (selection bias); (2) allocation concealment (selection bias); (3) blinding of participants and personnel (performance bias); (4) blinding of outcome assessment (detection bias); (5) incomplete outcome data (attrition bias); (6) selective reporting (reporting bias); and (7) other sources of bias (funding declaration). Each domain was categorized to three classes: low risk of bias, high risk of bias and unclear risk of bias. According to the mentioned domains, the overall quality of individual study was considered as good (low risk for more than 2 item), fair (low risk for 2 item), and weak (low risk for less than 2 item) [27].

2.6. Statistical analysis

We calculated the standardized mean difference of change (SMD) with 95% CI for each study. Random effect model based on Inverse-

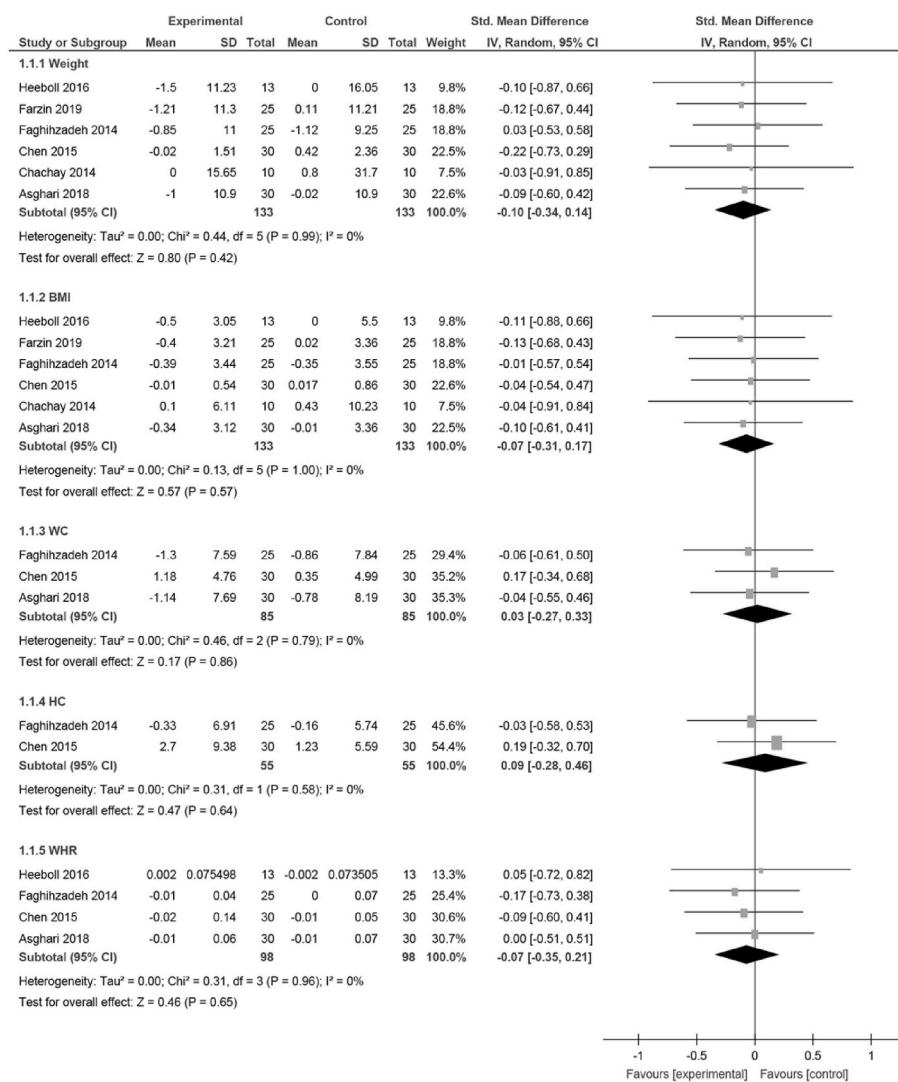


Fig. 3. Forest plot of the effect of resveratrol supplementation on anthropometric indices.

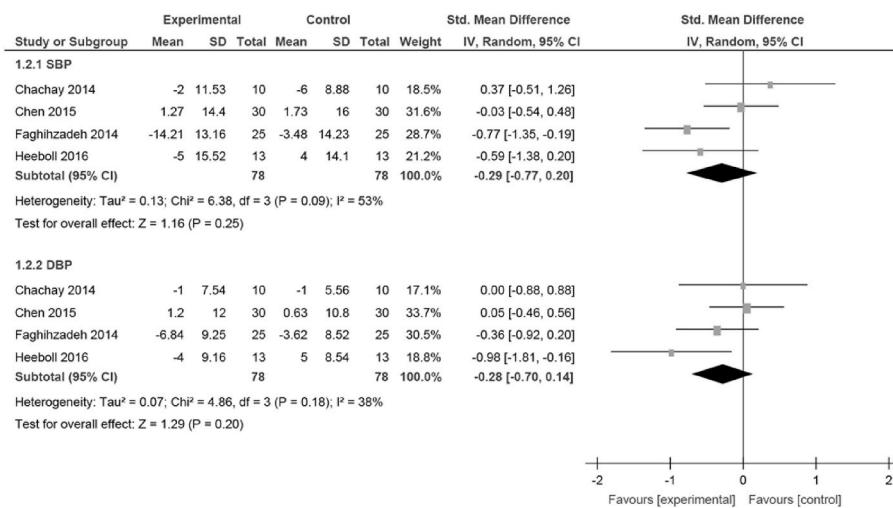


Fig. 4. Forest plot of the effect of resveratrol supplementation on blood pressure.

Variance method was used to pool the data. We assessed and quantified heterogeneity using heterogeneity chi-squared test. P-value less than 0.05 and I^2 statistic over 50% considered as statistically significant

heterogeneity among studies. We visually assessed funnel plots to investigate for small study effects and publication bias towards positive reporting. All the analyses and plots were conducted in Review Manager

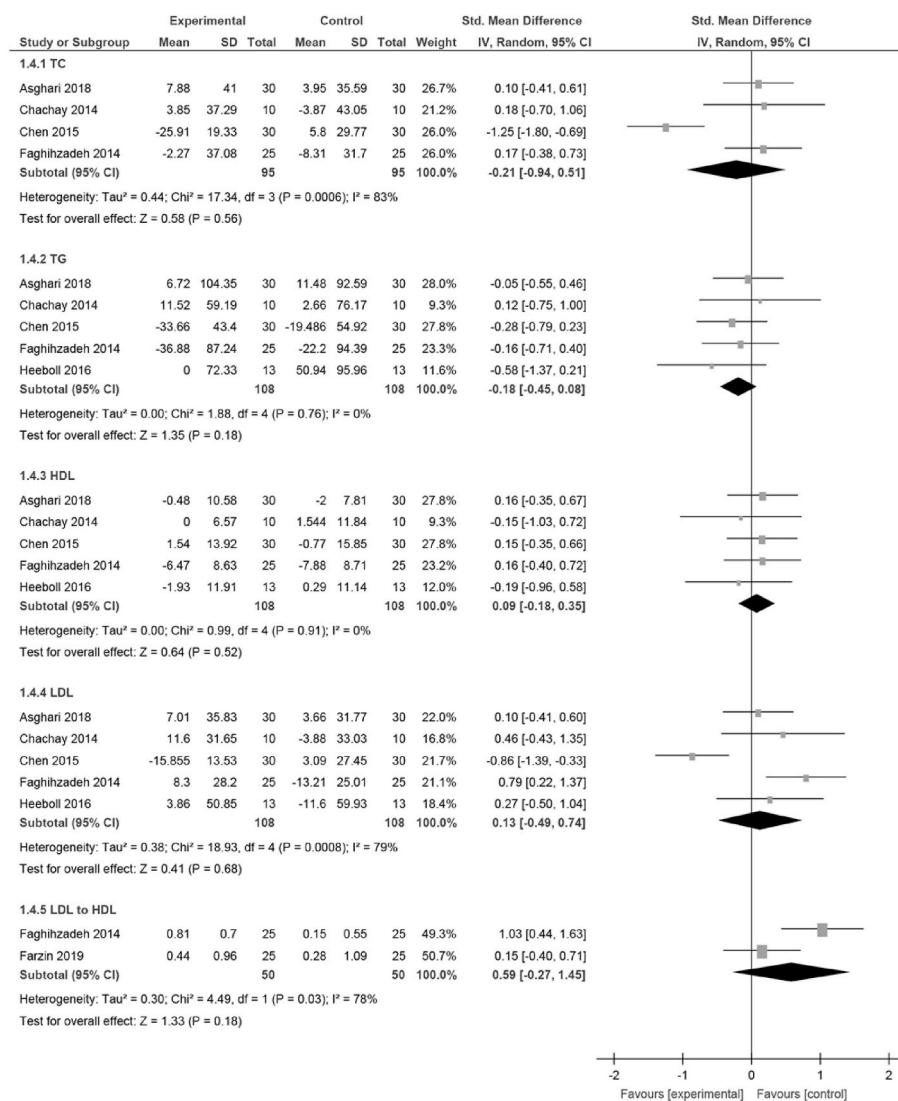


Fig. 5. Forest plot of the effect of resveratrol supplementation on blood lipids.

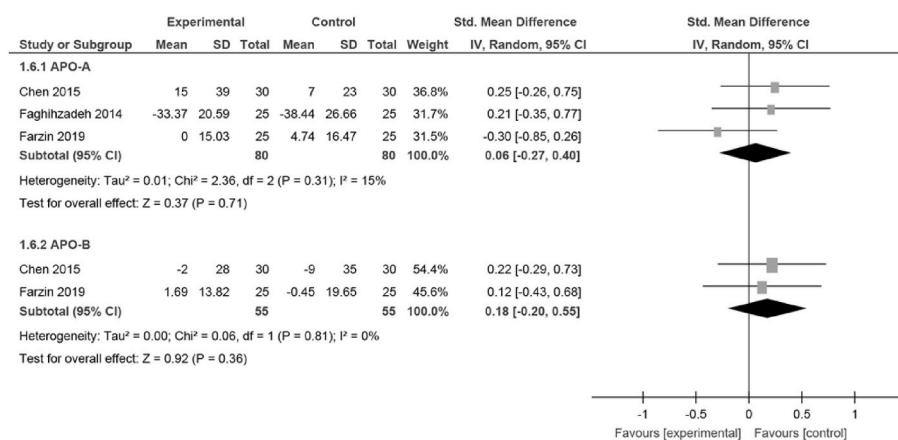


Fig. 6. Forest plot of the effect of resveratrol supplementation on Apo-A and Apo-B.

(RevMan) Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014.

3. Results

3.1. Systematic review

In total we identified 588 non duplicated records in search of

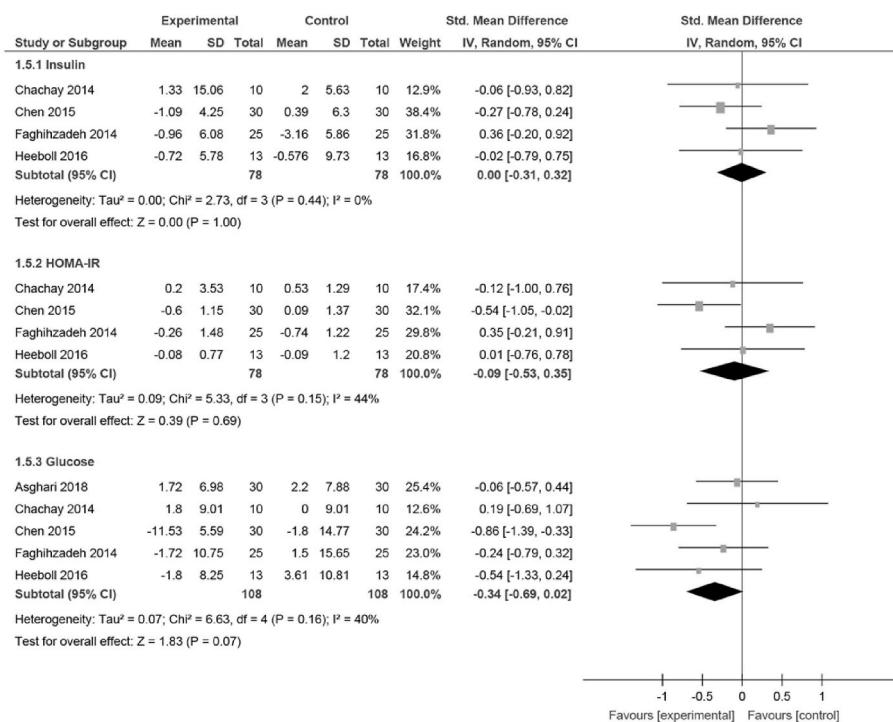


Fig. 7. Forest plot of the effect of resveratrol supplementation on glycemic indices.

electronic databases. Most records ($n = 574$) were excluded after title and abstract screening because they were animal and in vitro studies ($n = 92$) or irrelevant to the topic ($n = 482$). Then full text of 14 potentially related articles were assessed. Finally, 6 trials [19–22,24,28] met all inclusion criteria and included in meta-analyses and systematic review (Fig. 1).

Characteristics of all included studies were summarized in Table 1. Publication date ranged from 2014 to 2019. All trials were parallel and enrolled 266 subjects aged 39–48 years. Except one study was conducted in men [24], other studies were enrolled both gender. Half of investigations were conducted in Iran [20,22,28] and other half were conducted in Australia, China and Denmark [19,21,24]. Except two trials were conducted on NAFLD subjects [19,20], other trials were conducted on overweight or obese subjects with NAFLD [21,22,24,28]. Duration of intervention ranged from 8 to 24 weeks. Dose of resveratrol supplementation varied from 300 to 3000 mg/day. Three studies used trans-resveratrol for supplementation [20,22,28].

M, male; F, female; ND, no data, NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; WC, waist circumference; HP, hip circumference; WHR, waist to hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; GGT, Gamma-Glutamyl Transferase; ALP, Alkaline Phosphatase; TC, total cholesterol; TG, Triglyceride; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; TNF- α , tumor necrosis factor alpha; hs-CRP, high-sensitivity C-reactive protein; IL6, Interleukin 6.

Fig. 2 describes risk of bias assessment based on different quality domains using Cochrane collaboration tool. After evaluating the quality of included studies, all were classified as good quality. All trials present enough information regarding sequence generation. Except one study had unclear risk of bias in allocation concealment [21], other studies had low risk of bias in this domain. In addition, all trials had low risk of bias regarding blinding of participants and personnel. Moreover some of trials had unclear risk of bias in blinding of outcome assessors [19,24,28]. All studies showed respectively low/unclear risk of bias based on incomplete outcome data and selective outcome reporting.

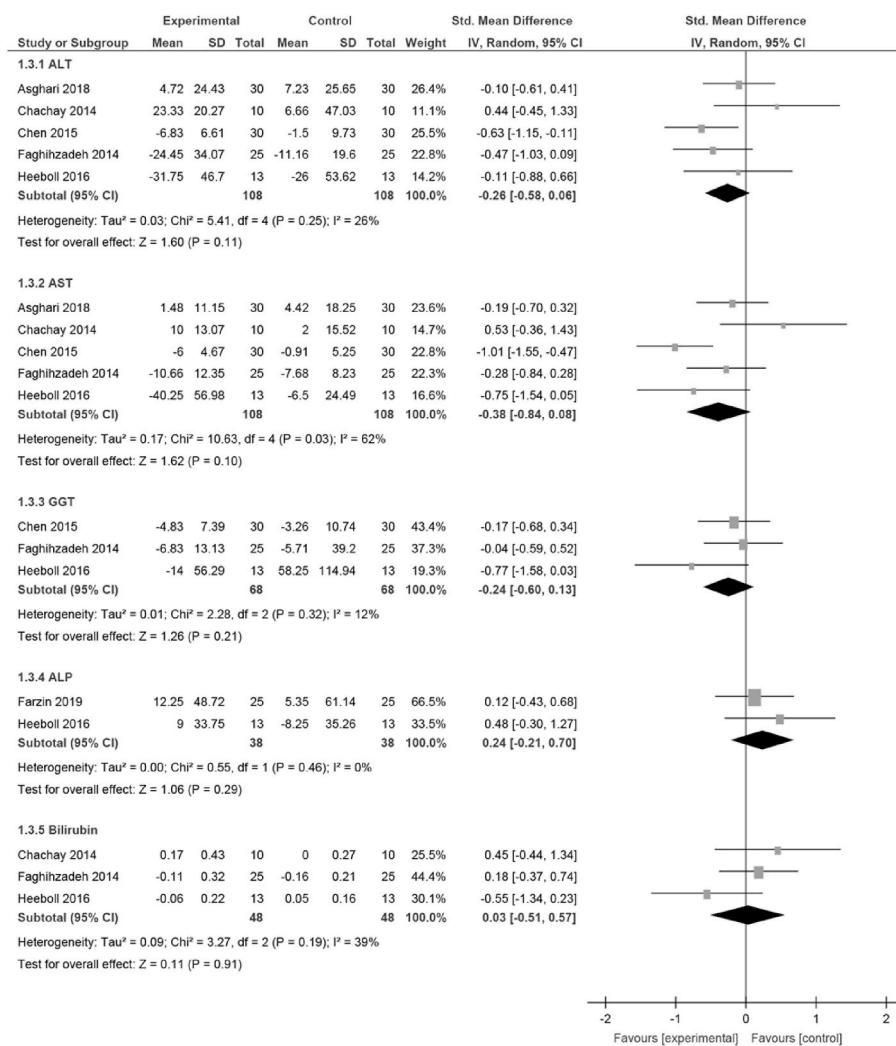
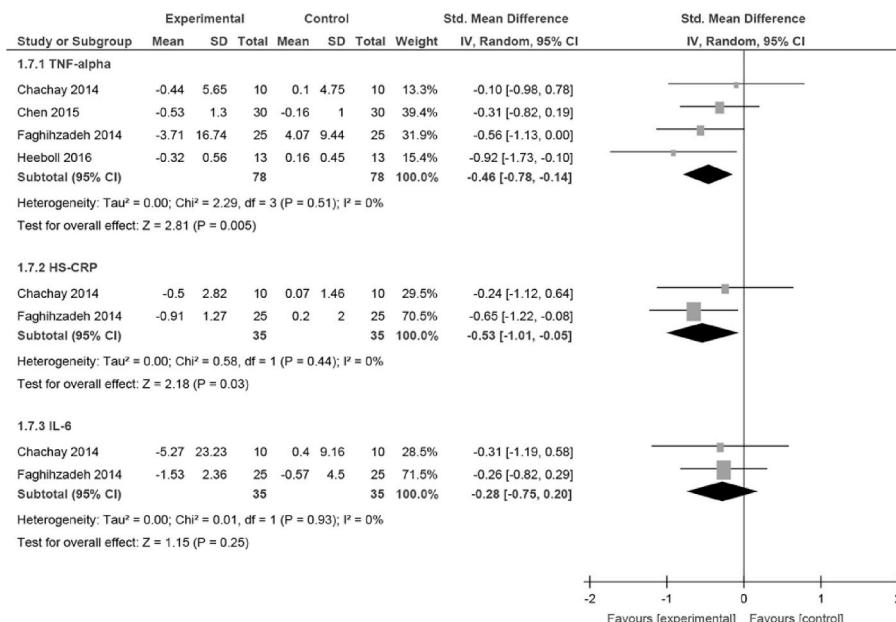
The effect of resveratrol supplementation on anthropometric indices.

Forest plots of comparison of BW, BMI, WC, HC and WHR between the resveratrol and control groups are shown in Fig. 3. Pooled effect size from the random-effects model revealed that change in weight (SMD = -0.10; 95% CI (-0.34, 0.14); $P = 0.420$), BMI (SMD = -0.07; 95% CI (-0.31, 0.17); $P = 0.570$), WC (SMD = 0.03; 95% CI (-0.27, 0.330); $P = 0.86$), HC (SMD = 0.09; 95% CI (-0.28, 0.46); $P = 0.640$) and WHR (SMD = -0.07; 95% CI (-0.35, 0.21); $P = 0.650$) were not statistically significant. No significant heterogeneity was detected across the studies for all anthropometric indices including weight ($Tau^2 = 0$, $I^2 = 0.0\%$, $P = 0.990$), BMI ($Tau^2 = 0$, $I^2 = 0.0\%$, $P = 1.00$), WC ($Tau^2 = 0$, $I^2 = 0.0\%$, $P = 0.790$), HC ($Tau^2 = 0$, $I^2 = 0.0\%$, $P = 0.580$) and WHR ($Tau^2 = 0$, $I^2 = 0.0\%$, $P = 0.960$).

Forest plots of comparison of SBP and DBP between the resveratrol and control groups are shown in Fig. 4. Pooled effect size from the random-effects model indicated that change in SBP (SMD = -0.29; 95% CI (-0.77, 0.20); $P = 0.250$) and DBP (SMD = -0.28; 95% CI (-0.70, 0.14); $P = 0.200$) were not statistically significant. No significant heterogeneity was found between studies for both SBP ($Tau^2 = 0.13$, $I^2 = 53\%$, $P = 0.090$) and DBP ($Tau^2 = 0.07$, $I^2 = 38\%$, $P = 0.180$).

Forest plots of comparison of TC, TG, HDL, LDL and LDL to HDL ratio between the resveratrol and control groups are shown in Fig. 5. Pooled effect size from the random-effects model revealed that change in TC (SMD = -0.21; 95% CI (-0.94, 0.51); $P = 0.560$), TG (SMD = -0.18; 95% CI (-0.45, 0.08); $P = 0.180$), HDL (SMD = 0.09; 95% CI (-0.18, 0.350); $P = 0.520$), LDL (SMD = 0.13; 95% CI (-0.49, 0.74); $P = 0.680$) and LDL to HDL ratio (SMD = 0.59; 95% CI (-0.27, 1.45); $P = 0.180$) were not statistically significant. No significant heterogeneity was detected across the studies for TG ($Tau^2 = 0$, $I^2 = 0.0\%$, $P = 0.76$) and HDL ($Tau^2 = 0$, $I^2 = 0.0\%$, $P = 0.910$), whereas the inter-study heterogeneity was significant for TC ($Tau^2 = 0.44$, $I^2 = 83\%$, $P = 0.006$), LDL ($Tau^2 = 0.38$, $I^2 = 79\%$, $P = 0.008$) and LDL to HDL ratio ($Tau^2 = 0.30$, $I^2 = 78\%$, $P = 0.030$).

Forest plots of comparison of Apo-A and Apo-B between the resveratrol and control groups are shown in Fig. 6. Pooled effect size from the random-effects model indicated that change in Apo-A (SMD = 0.06; 95% CI (-0.27, 0.40); $P = 0.710$) and Apo-B (SMD = 0.18; 95% CI (-0.20, 0.55); $P = 0.360$) were not statistically significant. No significant

**Fig. 8.** Forest plot of the effect of resveratrol supplementation on liver function test.**Fig. 9.** Forest plot of the effect of resveratrol supplementation on inflammatory markers.

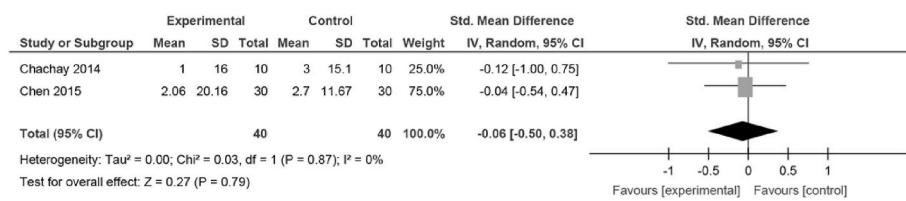


Fig. 10. Forest plot of the effect of resveratrol supplementation on creatinine.

heterogeneity was detected across the studies for Apo-A ($Tau^2 = 0.010$, $I^2 = 15\%$, $P = 0.31$) and Apo-B ($Tau^2 = 0$, $I^2 = 0.0\%$, $P = 0.81$).

Forest plots of comparison of insulin, HOMA-IR and glucose between the resveratrol and control groups are shown in Fig. 7. Pooled effect size from the random-effects model revealed that change in insulin (SMD = 0.00; 95% CI (-0.31, 0.32); $P = 1.00$), HOMA-IR (SMD = -0.09; 95% CI (-0.53, 0.35); $P = 0.690$) and glucose (SMD = -0.34; 95% CI (-0.69, 0.02); $P = 0.520$) were not statistically significant. No significant heterogeneity was found between studies for HOMA-IR ($Tau^2 = 0.09$, $I^2 = 44\%$, $P = 0.150$) and glucose ($Tau^2 = 0.07$, $I^2 = 40\%$, $P = 0.160$) and insulin ($Tau^2 = 0$, $I^2 = 0\%$, $P = 0.440$).

Forest plots of comparison of ALT, AST, GGT, ALP and bilirubin between the resveratrol and control groups are shown in Fig. 8. Pooled effect size from the random-effects model revealed that change in ALT (SMD = -0.26; 95% CI (-0.58, 0.06); $P = 0.110$), AST (SMD = -0.38; 95% CI (-0.84, 0.08); $P = 0.100$), GGT (SMD = -0.24; 95% CI (-0.60, 0.13); $P = 0.210$), ALP (SMD = 0.24; 95% CI (-0.21, 0.70); $P = 0.290$) and bilirubin (SMD = 0.03; 95% CI (-0.51, 0.57); $P = 0.910$) were not statistically significant. No significant heterogeneity was found between studies for ALT ($Tau^2 = 0.03$, $I^2 = 26\%$, $P = 0.250$), bilirubin ($Tau^2 = 0.09$, $I^2 = 39\%$, $P = 0.190$), ALP ($Tau^2 = 0$, $I^2 = 0\%$, $P = 0.29$) and GGT ($Tau^2 = 0.01$, $I^2 = 12\%$, $P = 0.320$). whereas a significant heterogeneity was detected across the studies for AST ($Tau^2 = 0.17$, $I^2 = 62\%$, $P = 0.030$).

Forest plots of comparison of TNF-alpha, hs-CRP and IL-6 between the resveratrol and control groups are shown in Fig. 9. Pooled effect size from the random-effects model revealed that resveratrol supplementation significantly decreased the level of TNF-alpha (SMD = -0.46; 95%

CI (-0.78, 0.14); $P = 0.005$) and hs-CRP (SMD = -0.53; 95% CI (-1.01, -0.05); $P = 0.030$), whereas the change in IL-6 level was not statistically significant (SMD = -0.28; 95% CI (-0.75, 0.20); $P = 0.250$). No significant heterogeneity was detected across the studies for all inflammatory markers including TNF-alpha ($Tau^2 = 0$, $I^2 = 0.0\%$, $P = 0.510$), hs-CRP ($Tau^2 = 0$, $I^2 = 0.0\%$, $P = 0.440$) and IL-6 ($Tau^2 = 0$, $I^2 = 0.0\%$, $P = 0.930$).

Forest plots of comparison of creatinine level between the resveratrol and control groups are shown in Fig. 10. Pooled effect size from the random-effects model revealed that change in creatinine level (SMD = -0.06; 95% CI (-0.50, 0.38); $P = 0.790$) was not statistically significant. No significant heterogeneity was detected across the studies ($Tau^2 = 0$, $I^2 = 0.0\%$, $P = 0.870$).

3.2. Publication bias

We identified clear asymmetry in the funnel plot (supplementary figure 1) for almost all factors except for SBP and DBP, which may be associated with either publication bias in comparison of resveratrol and control group or few number of included studies.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgements

None.

Supplementary.

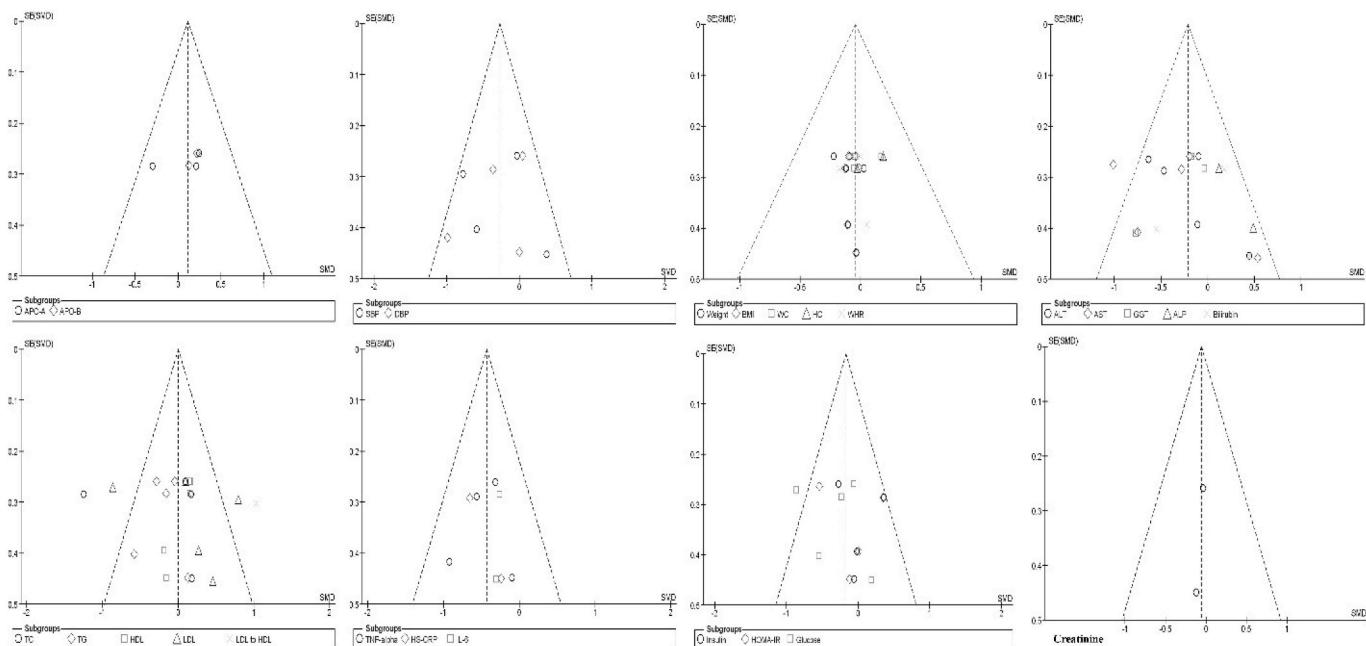


Fig. S1. Funnel plot of the effect of resveratrol supplementation on selected outcomes.

4. Discussion

To date, there are no suitable and approved medications for NAFLD [6]. Recently, alternative medicine has been considered as a possible approach to treat the disease [29]. Recent studies have shown that resveratrol can be effective in the management and treatment of NAFLD through its inhibitory effect on lipid accumulation (by activating SIRT1, AMPK and creating calorie-restricted like conditions) [16–18]. Also, Studies have shown that resveratrol supplementation can decrease liver enzymes, inflammatory markers, and alleviate hepatic steatosis [19,20,30,31]. Accordingly, an updated systematic review and meta-analysis of available clinical trials can characterize the most reliable evidence of resveratrol supplementation efficacy. This updated meta-analysis contains 6 articles studying the effects of resveratrol supplementation on NAFLD. Indices such as HC, WHR, ALP, LDL to HDL ratio, Apo-A1, Apo-B and creatinine are also included in this study, whereas previous meta-analysis did not include these parameters that have underling role on NAFLD patients. Present meta-analysis showed that resveratrol supplementation had no significant effects on NAFLD management. But inflammatory markers such as TNF-alpha and hs-CRP were significantly reduced.

It has been indicated that anthropometric indices such as BMI, WC and WHR are associated with Steatohepatitis and fibrosis in NAFLD patients [32, 33]. In this study, anthropometric indices (BW, BMI, WC, HC and WHR) were unaffected after resveratrol supplementation, which is consistent with other studies [19–22,24,28]. For systolic and diastolic blood pressure, our results showed that resveratrol supplementation had no significant effects, which is in contrast to the study reported by Faghihzadeh et al. and Heeboll et al. [10,12]. Also, in meta-analysis of Liu et al. decreasing effects of higher dose of resveratrol supplementation on SBP was observed, which is in contradiction with the results of the present study [34]. These contradictory results may be due to the use of different dosage of resveratrol and treatment duration in different studies. Therefore, studies with higher sample size and high quality are needed to determine the dose-dependent effects of resveratrol.

For blood lipids, we evaluated TC, TG, HDL, LDL and LDL to HDL ratio, Apo-A and Apo-B and found that none of them were changed after resveratrol supplementation. These findings are in accordance with those of some previous studies [21,22,24,28]. Furthermore, the results of the Hariri et al. meta-analysis study confirm the results of the present study. Also, in this study, resveratrol supplementation had no effects on glycemic control markers (insulin, HOMA-IR and glucose), which is in conflict with the results of Chen et al. [19]. Moreover, Liu et al. reported that resveratrol significantly develops glycemic measure and insulin sensitivity in diabetic patients but does not affect in nondiabetic persons [35].

Serum levels of ALT, AST, ALP, GGT and bilirubin are associated with liver diseases and biliary obstruction, and are consequently used as indicators of the NAFLD development [36]. In this study, liver function test (ALT, AST, GGT, ALP and bilirubin) were unchanged after resveratrol supplementation, which is in consistent with most of previous studies [20–22,24,28].

Evidences have indicated that elevated TNF-alpha and hs-CRP levels can be use as predictors of NAFLD development [37–39]. Moreover, studies have shown that Sirt1 plays an important role in inflammation and its activation by resveratrol, which is one of its agonists, can efficiently suppress inflammatory processes [40]. For inflammatory marker (TNF-alpha, hs-CRP and IL-6), results of the study indicated that TNF-alpha and hs-CRP significantly reduced after resveratrol supplementation but for IL-6, the changes were not significant. These results are in accordance with some previous studies [20,21]. Creatinine level was unchanged after resveratrol supplementation, which is in confirmation of Chen et al. and Chachay et al. [19,24].

This study has some of limitation that should be consider. First of all, results of the present study based on a relatively small number of studies, consequently, it should be interpreted with more carefulness. Secondly, dissimilarities in resveratrol dosage and duration of supplementation may also affect the accuracy of the results. Third, half of the studies were from Iran, which limits the ability to extend the results to the whole world.

5. Conclusion

However, existing evidence could not support the hypothesis of the efficacy of resveratrol supplementation in the management of NAFLD, but resveratrol indicated beneficial effects on levels of TNF-alpha and hs-CRP. Subsequently, RCTs with high sample size and elongated period are needed to evaluation of resveratrol supplementation on NAFLD management.

Author contribution

GH. A. and H. M. contributed to the conception of research. S. R. and H. M. searched databases, screened articles and extracted data. and E. S performed statistical analysis. A. GH. contributed to the revision of manuscript, and all authors contributed to the writing and revision of the manuscript.

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References

- [1] J.C. Simeone, J.P. Bae, B.J. Hoogwerf, Q. Li, A. Haupt, A.K. Ali, M.K. Boardman, B. L. Nordstrom, Clinical course of nonalcoholic fatty liver disease: an assessment of severity, progression, and outcomes, *Clin. Epidemiol.* 9 (2017) 679–688.
- [2] J. Yang, M. Fernández-Galilea, L. Martínez-Fernández, P. González-Muniesa, A. Pérez-Chávez, J.A. Martínez, M.J. Moreno-Aliaga, Oxidative stress and non-alcoholic fatty liver disease: effects of omega-3 fatty acid supplementation, *Nutrients* 11 (4) (2019) 872.
- [3] I. Mikolasevic, S. Milic, T. Turk Wensveen, I. Grgic, I. Jakopcic, D. Stimac, F. Wensveen, L. Orlic, Nonalcoholic fatty liver disease - a multisystem disease? *World J. Gastroenterol.* 22 (43) (2016) 9488–9505.
- [4] Z.M. Younossi, A.B. Koenig, D. Abdelatif, Y. Fazel, L. Henry, M. Wymer, Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes, *Hepatology (Baltimore, Md)* 64 (1) (2016) 73–84.
- [5] R.M. Carr, A. Oranu, V. Khungar, Nonalcoholic fatty liver disease: pathophysiology and management, *Gastroenterol. Clin. N. Am.* 45 (4) (2016) 639–652.
- [6] M.-S. Kwak, D. Kim, Non-alcoholic fatty liver disease and lifestyle modifications, focusing on physical activity, *Korean J. Intern. Med. (Korean Ed.)* 33 (1) (2018) 64–74.

- [7] J.A. Baur, K.J. Pearson, N.L. Price, H.A. Jamieson, C. Lerin, A. Kalra, V.V. Prabhu, J.S. Allard, G. Lopez-Lluch, K. Lewis, P.J. Pistell, S. Poosala, K.G. Becker, O. Boss, D. Gwinn, M. Wang, S. Ramaswamy, K.W. Fishbein, R.G. Spencer, E.G. Lakatta, D. Le Couteur, R.J. Shaw, P. Navas, P. Puigserver, D.K. Ingram, R. de Cabo, D. A. Sinclair, Resveratrol improves health and survival of mice on a high-calorie diet, *Nature* 444 (7117) (2006) 337–342.
- [8] J.A. Baur, D.A. Sinclair, Therapeutic potential of resveratrol: the in vivo evidence, *Nat. Rev. Drug Discov.* 5 (6) (2006) 493–506.
- [9] A. Bishayee, Cancer prevention and treatment with resveratrol: from rodent studies to clinical trials, *Cancer prevention research* 2 (5) (2009) 409–418. Philadelphia, PA.
- [10] L.M. Hung, J.K. Chen, S.S. Huang, R.S. Lee, M.J. Su, Cardioprotective effect of resveratrol, a natural antioxidant derived from grapes, *Cardiovasc. Res.* 47 (3) (2000) 549–555.
- [11] A.Y. Sun, Q. Wang, A. Simonyi, G.Y. Sun, Resveratrol as a therapeutic agent for neurodegenerative diseases, *Mol. Neurobiol.* 41 (2–3) (2010) 375–383.
- [12] Z.X. Zhou, S.F. Mou, X.Q. Chen, L.L. Gong, W.S. Ge, Anti-inflammatory activity of resveratrol prevents inflammation by inhibiting NFκB in animal models of acute pharyngitis, *Mol. Med. Rep.* 17 (1) (2018) 1269–1274.
- [13] F. Zhang, J. Liu, J.S. Shi, Anti-inflammatory activities of resveratrol in the brain: role of resveratrol in microglial activation, *Eur. J. Pharmacol.* 636 (1–3) (2010) 1–7.
- [14] L. Paulo, S. Ferreira, E. Gallardo, J.A. Queiroz, F. Domingues, Antimicrobial activity and effects of resveratrol on human pathogenic bacteria, *World J. Microbiol. Biotechnol.* 26 (8) (2010) 1533–1538.
- [15] B. Salehi, A.P. Mishra, M. Nigam, B. Sener, M. Kilic, M. Sharifi-Rad, P.V.T. Fokou, N. Martins, J. Sharifi-Rad, Resveratrol: a double-edged sword in health benefits, *Biomedicines* 6 (3) (2018) 91.
- [16] M. Lagouge, C. Argmann, Z. Gerhart-Hines, H. Meziane, C. Lerin, F. Daussin, N. Messadeq, J. Milne, P. Lambert, P. Elliott, B. Geny, M. Laakso, P. Puigserver, J. Auwerx, Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1 alpha, *Cell* 127 (6) (2006) 1109–1122.
- [17] J.H. Um, S.J. Park, H. Kang, S. Yang, M. Foretz, M.W. McBurney, M.K. Kim, B. Viollet, J.H. Chung, AMP-activated protein kinase-deficient mice are resistant to the metabolic effects of resveratrol, *Diabetes* 59 (3) (2010) 554–563.
- [18] R.I. Tennen, E. Michishita-Kioi, K.F. Chua, Finding a target for resveratrol, *Cell* 148 (3) (2012) 387–389.
- [19] S. Chen, X. Zhao, L. Ran, J. Wan, X. Wang, Y. Qin, F. Shu, Y. Gao, L. Yuan, Q. Zhang, M. Mi, Resveratrol improves insulin resistance, glucose and lipid metabolism in patients with non-alcoholic fatty liver disease: a randomized controlled trial, *Digestive and liver disease, off. J. Ital. Soc. Gastroenterol. Ital. Assoc. Study Liver* 47 (3) (2015) 226–232.
- [20] F. Faghizadeh, P. Adibi, R. Rafiei, A. Hekmatdoost, Resveratrol supplementation improves inflammatory biomarkers in patients with nonalcoholic fatty liver disease, *Nutr. Res. (N.Y.)* 34 (10) (2014) 837–843.
- [21] S. Heeboll, M. Kreuzfeldt, S. Hamilton-Dutoit, M. Kjaer Poulsen, H. Stokilde-Jorgensen, H.J. Moller, N. Jessen, K. Thorsen, Y. Kristina Hellberg, S. Bonlokke Pedersen, H. Gronbaek, Placebo-controlled, randomised clinical trial: high-dose resveratrol treatment for non-alcoholic fatty liver disease, *Scand. J. Gastroenterol.* 51 (4) (2016) 456–464.
- [22] S. Asghari, M. Asghari-Jafarabadi, M.H. Somi, S.M. Ghavami, M. Rafraf, Comparison of calorie-restricted diet and resveratrol supplementation on anthropometric indices, metabolic parameters, and serum sirtuin-1 levels in patients with nonalcoholic fatty liver disease: a randomized controlled clinical trial, *J. Am. Coll. Nutr.* 37 (3) (2018) 223–233.
- [23] S. Asghari, M. Rafraf, L. Farzin, M. Asghari-Jafarabadi, S.M. Ghavami, M.H. Somi, Effects of pharmacologic dose of resveratrol supplementation on oxidative/antioxidative status biomarkers in nonalcoholic fatty liver disease patients: a randomized, double-blind, placebo-controlled trial, *Adv. Pharmaceut. Bull.* 8 (2) (2018) 307–317.
- [24] V.S. Chachay, G.A. Macdonald, J.H. Martin, J.P. Whitehead, T.M. O'Moore-Sullivan, P. Lee, M. Franklin, K. Klein, P.J. Taylor, M. Ferguson, J.S. Coombes, G. P. Thomas, G.J. Cowin, C.M. Kirkpatrick, J.B. Prins, I.J. Hickman, Resveratrol does not benefit patients with nonalcoholic fatty liver disease, *Clin. Gastroenterol. Hepatol. Off. Clin. Pract. J. Am. Gastroenterol. Assoc.* 12 (12) (2014), 2092–20103 e1–6.
- [25] C. Zhang, W. Yuan, J. Fang, W. Wang, P. He, J. Lei, C. Wang, Efficacy of resveratrol supplementation against non-alcoholic fatty liver disease: a meta-analysis of placebo-controlled clinical trials, *PloS One* 11 (8) (2016), e0161792.
- [26] A. Elgebaly, I.A. Radwan, M.M. AboElnas, H.H. Ibrahim, M.F. Eltoomy, A.A. Atta, H.A. Mesalam, A.A. Sayed, A.A. Othman, Resveratrol supplementation in patients with non-alcoholic fatty liver disease: systematic review and meta-analysis, *J. Gastrointest. Liver Dis. : JGLD* 26 (1) (2017) 59–67.
- [27] J. Higgins, D. Altman, P. Gotzsche, P. Juni, D. Moher, A. Oxman, J. Savovic, K. Schulz, L. Weeks, J. Sterne, The Cochrane Collaboration's tool for assessing risk of bias in randomised trials, *BMJ* 343 (2011) d5928, Link: <https://goo.gl/nDj3sa>.
- [28] L. Farzin, S. Asghari, M. Rafraf, M. Asghari-Jafarabadi, M. Shirmohammadi, No beneficial effects of resveratrol supplementation on atherogenic risk factors in patients with nonalcoholic fatty liver disease, *Internationale Zeitschrift Fur Vitamin- und Ernahrungsfororschung. J. Int. Vitaminol. Nutr.* (2019) 1–11.
- [29] B.J. Perumpail, A.A. Li, U. Iqbal, S. Sallam, N.D. Shah, W. Kwong, G. Cholankeril, D. Kim, A. Ahmed, Potential therapeutic benefits of herbs and supplements in patients with NAFLD, *Diseases* 6 (3) (2018) 80.
- [30] J.M.O. Andrade, A.F. Paraíso, M.V.M. de Oliveira, A.M.E. Martins, J.F. Neto, A.L. S. Guimarães, A.M. de Paula, M. Qureshi, S.H.S. Santos, Resveratrol attenuates hepatic steatosis in high-fat fed mice by decreasing lipogenesis and inflammation, *Nutrition* 30 (7) (2014) 915–919.
- [31] M. Rahimlou, H. Ahmadnia, A. Hekmatdoost, Dietary supplements and pediatric non-alcoholic fatty liver disease: present and the future, *World J. Hepatol.* 7 (25) (2015) 2597–2602.
- [32] R. Rocha, H.P. Cotrim, F. Carvalho, A. Siqueira, H. Braga, L. Freitas, Body mass index and waist circumference in non-alcoholic fatty liver disease, *J. Hum. Nutr. Diet.* 18 (5) (2005) 365–370.
- [33] R.-D. Zheng, Z.-R. Chen, J.-N. Chen, Y.-H. Lu, J. Chen, Role of body mass index, waist-to-height and waist-to-hip ratio in prediction of nonalcoholic fatty liver disease, *Gastroenterol. Res. Pract.* (2012) 1–6.
- [34] Y. Liu, W. Ma, P. Zhang, S. He, D. Huang, Effect of resveratrol on blood pressure: a meta-analysis of randomized controlled trials, *Clin. Nutr.* 34 (1) (2015) 27–34.
- [35] K. Liu, R. Zhou, B. Wang, M.-T. Mi, Effect of resveratrol on glucose control and insulin sensitivity: a meta-analysis of 11 randomized controlled trials, *Am. J. Clin. Nutr.* 99 (6) (2014) 1510–1519.
- [36] P. Hall, J. Cash, What is the real function of the liver 'function' tests? *Ulster Med. J.* 81 (1) (2012) 30–36.
- [37] J. Lee, K. Yoon, S. Ryu, Y. Chang, H.-R. Kim, High-normal levels of hs-CRP predict the development of non-alcoholic fatty liver in healthy men, *PloS One* 12 (2) (2017), e0172666.
- [38] M.R. Ajmal, M. Yaccha, M.A. Malik, M.U. Rabbani, I. Ahmad, N. Isalm, N. Abdali, Prevalence of nonalcoholic fatty liver disease (NAFLD) in patients of cardiovascular diseases and its association with hs-CRP and TNF- α , *Indian Heart J.* 66 (6) (2014) 574–579.
- [39] Y.Y. Seo, Y.K. Cho, J.-C. Bae, M.H. Seo, S.E. Park, E.-J. Rhee, C.-Y. Park, K.-W. Oh, S.-W. Park, W.-Y. Lee, Tumor necrosis factor- α as a predictor for the development of nonalcoholic fatty liver disease: a 4-year follow-up study, *Endocrinol. Metab.* 28 (1) (2013) 41–45.
- [40] X. Zhu, Q. Liu, M. Wang, M. Liang, X. Yang, X. Xu, H. Zou, J. Qiu, Activation of Sirt1 by resveratrol inhibits TNF- α induced inflammation in fibroblasts, *PloS One* 6 (11) (2011) e27081–e27081.