

Resveratrol Supplementation in Patients with Non-Alcoholic Fatty Liver Disease: Systematic Review and Meta-analysis

Ahmed Elgebaly¹, Ibrahim A. I. Radwan², Mohamed M. AboElnas³, Hamza H. Ibrahim⁴, Moutaz F. M. Eltoomy⁵, Ahmed A. Atta⁶, Hend A. Mesalam¹, Alaa A. Sayed⁷, Amr A. Othman⁸

1) Faculty of Medicine, Al Azhar University, Cairo;
2) Ain Shams University, Faculty of Medicine;
3) Kasr-ALainy Medical School, Cairo University;
4) Faculty of Pharmacy, Alexandria University;
5) Genetic Engineering & Biotechnology Research Institute, University of Sadat City;
6) Faculty of Veterinary Medicine, Cairo University; 7) Faculty of Medicine, Beni Suef University;
8) Department of Pharmaceutics and Pharmaceutical Sciences, Faculty of Pharmacy, Alexandria University, Egypt

Address for correspondence:

Ahmed Saber Elgebaly
Faculty of Medicine,
Al-Azhar University,
Madinet Nasr, Abbassia,
Cairo, Egypt
Ahmedelgebaly94@azhar.edu.eg

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ABSTRACT

Background: Resveratrol is a potential treatment option for management of non-alcoholic fatty liver disease (NAFLD) due to its anti-inflammatory, antioxidant properties, and calorie restriction-like effects. We aimed to synthesise evidence from published randomized clinical trials (RCTs) about the efficacy of resveratrol in the management of NAFLD.

Methods: A computer literature search of PubMed, Scopus, Web of Science, and Cochrane Central was conducted using relevant keywords. Records were screened for eligible studies and data were extracted and synthesized using Review Manager Version 5.3 for windows. Subgroup analysis and sensitivity analysis were conducted.

Results: Four RCTs (n=158 patients) were included in the final analysis. The overall effect estimates did not favor resveratrol group in terms of: serum ALT (MD -2.89, 95%CI [-15.66, 9.88], p=0.66), serum AST (MD -3.59, 95%CI [-13.82, 6.63], p=0.49), weight (MD -0.18, 95%CI [-0.92, 0.55], p=0.63), BMI (MD -0.10, 95%CI [-0.43, 0.24], p=0.57), blood glucose level (MD -0.27, 95%CI [-0.55, 0.01], p=0.05), insulin level (MD -0.12, 95%CI [-0.69, 0.46], p=0.69), triglyceride level (MD 0.04, 95%CI [-0.45, 0.53], p=0.87), and LDL level (MD 0.21, 95%CI [-0.41, 0.83], p=0.51). Pooled studies were heterogeneous.

Conclusion: Current evidence is insufficient to support the efficacy of resveratrol in the management of NAFLD. Resveratrol does not attenuate the degree of liver fibrosis or show a significant decrease in any of its parameters.

Key words: Non-alcoholic fatty liver disease – Resveratrol – steatosis – meta-analysis.

Abbreviations: ALT: Alanine aminotransferase; AMPK: AMP-activated protein kinase; AST: Aspartate aminotransferase; BMI: Body mass index; CK-18: Cytokeratin-18; CRP: C-reactive protein; HC: Head circumference; HDL: High density lipoprotein; IL-6: Interleukin-6; LDL: Low density lipoprotein; MD: Mean difference; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; RCT: Randomized Controlled Trial; RR: Relative risk; SIRT1: Silent information regulation 2 homologue 1; TNF- α : Tumor necrosis factor α ; WC: Waist circumference; WHR: Waist hip ratio.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease worldwide. It refers to a broad spectrum of liver diseases which vary from non-alcoholic steatohepatitis (NASH) to progressive fibrosis and cirrhosis with portal hypertension [1, 2]. The clinical definition of NAFLD depends on the presence of hepatic fat accumulation more than 5% of the liver weight and

the exclusion of other causes of lipid infiltration in the liver (absence of significant alcohol intake, hepatic viral infections, or other specific causes of liver disease) [1].

Different theories have tried to identify the pathogenesis of progressive inflammation and fibrosis in NAFLD. Previously, Day and colleagues proposed the “two-hit theory”, in which there is an impairment in fatty acid metabolism in hepatocytes, leading to a net accumulation of triglycerides within the liver, combined with peroxidation of lipid accumulated within hepatocytes [3]. Recently, Tilg and colleagues [4] suggested the “Multiple Parallel Hits Hypothesis” as a pathogenesis of NASH. Factors as excessive lipolysis, lipopolysaccharide accumulation in the liver, stimulation of Toll-like receptors, and endocrinal function of adipose tissue, are thought to be linked with the degree of steatosis and fibrosis [4].

NAFLD is asymptomatic in most patients. If present, symptoms include right upper quadrant abdominal pain, fatigue, malaise, hepatomegaly and - to a lesser extent - splenomegaly. A mild elevation in the level of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) serum levels is often associated with these symptoms [5]. Although lifestyle modifications, calorie restriction, and weight loss are the general measures for management of NAFLD, compliance to this restricted lifestyle is difficult to be achieved [6].

Resveratrol (3, 5, 4'-trihydroxy-trans-stilbene) is a naturally occurring polyphenol, which activates AMP-activated protein kinase (AMPK) and silent information regulation 2 homologue 1 (SIRT1). Resveratrol has been recently linked to many beneficial actions such as anti-inflammatory, antioxidant, and calorie restriction-like effects [7–9]. All these properties make resveratrol a promising option for management of NAFLD through its inhibitory effects on lipid accumulation.

However, recent clinical trials show controversy over the efficacy of resveratrol for the management of NAFLD [13, 14]. Therefore, we performed a systematic review and meta-analysis study to assess the effectiveness of resveratrol for the management of NAFLD by searching different bibliographic databases for published randomized controlled trials (RCTs).

METHODS

We followed PRISMA statement guidelines during the preparation of this review and meta-analysis [12].

Inclusion and exclusion criteria

We included RCTs using the following criteria: 1) studies which examined the efficacy of resveratrol in NAFLD; 2) studies in which population consisted of patients with a clinical and histological diagnosis of NAFLD; and 3) studies written in English language. In the case of multiple reports for the same study population, we analyzed data of the most complete dataset. Studies were excluded for the following reasons: 1) studies do not provide sufficient data reliable for pooling in the meta-analysis, and 2) thesis and conference papers.

Literature search strategy

We searched all published RCTs in the following electronic databases: PubMed, Scopus, Web of Science and Cochrane Central. We used Mesh database and the following search queries: ((„resveratrol”[Supplementary Concept] OR „resveratrol”[All Fields]) AND („fatty liver”[MeSH Terms] OR („fatty”[All Fields] AND „liver”[All Fields]) OR „fatty liver”[All Fields])). Three authors screened the title and abstract of retrieved records for eligibility. Full-texts of potentially eligible studies were reviewed, for selecting the eligible studies for meta-analysis.

Data extraction

Three authors extracted the data independently using an online data extraction form. The extracted data included the following: 1) study design; 2) study population; 3) risk of bias domains, and 4) study outcomes: the degree of liver fibrosis, markers of liver damage, lipid profile, anthropometric index, serum cytokines, and glucose metabolism parameters.

Quality assessment

The quality of the retrieved RCTs was assessed according to Cochrane Handbook of systematic reviews of interventions 5.1.0 (updated March 2011). Risk of bias assessment included the following domains: sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias; the authors' judgment is categorized as 'Low risk', 'High risk' or 'Unclear risk' of bias. We used the quality assessment table provided in the same book (part 2, Chapter 8.5) [13].

Measures of treatment effect

The primary outcome measurements in studies assessing the efficacy of resveratrol in NAFLD were:

- 1) treatment effect on liver histology and degree of fibrosis assessed by transient elastography score [14];
- 2) markers of liver damage: serum ALT, serum AST and total bilirubin levels;
- 3) lipid profile: total cholesterol, HDL, LDL and triglyceride levels;
- 4) anthropometric index: body mass index (BMI), waist circumference (WC), head circumference (HC), waist-hip ratio (WHR) and weight (kg);
- 5) glucose metabolic parameters: blood glucose level, insulin level and HOMA2-IR;
- 6) serum cytokines: tumor necrosis factor (TNF- α), cytokeratin-18 (CK-18), interleukin-6 (IL-6) and C-reactive protein (CRP) levels.

Dealing with missing data

In the case of a missing standard deviation (SD) of mean change from baseline, this was calculated from the standard error or 95% confidence interval (CI) according to Altman [15].

Data synthesis

Continuous data was pooled as mean difference (MD) in a meta-analysis model. Dichotomous data was pooled as relative risk (RR) in a random-effect model. We used Review Manager 5.3 for windows.

Assessment of heterogeneity

Heterogeneity was assessed by the visual inspection of the Forest plots and measured by I-square and Chi-square tests. Chi-square test was used to test the existence of significant heterogeneity while I-square quantified this heterogeneity if present. I-Square test was interpreted according to recommendations of Cochrane Handbook of systematic reviews and meta-analysis (0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; and 75% to 100%: considerable heterogeneity). Chi-square $P < 0.1$ was set as a level of significant heterogeneity.

Sensitivity analysis

In order to resolve detected statistical heterogeneity, we performed sensitivity analysis excluding one study in each scenario.

Publication bias

According to Egger and colleagues [16, 17], publication bias assessment is not reliable for less than 10 pooled studies. Therefore, in the present study, we could not assess the existence of publication bias by Egger’s test for funnel plot asymmetry.

RESULTS

Search results

We retrieved 230 unique citations. After the initial title and abstract screening, 19 full texts were retrieved and screened for eligibility: 15 articles were excluded and four RCTs (five reports, n=158 patients) were included in this study (See PRISMA flow diagram, Fig. 1). (Reasons for study exclusion are shown in Supplementary File 1).

Characteristics of included studies

Among the four included RCTs, two trials included only overweight or obese patients diagnosed with NAFLD [10, 18]. In two trials resveratrol was administrated at a dose of 300mg and 500mg for three months [11, 19], in one study at a dose of 1500mg daily for six months [18], and in one study a dose of 3000mg daily was utilized and followed up the patients were followed-up only for two months [10]. One trial recommended a healthy diet and regular exercise for its participants [19], while the remaining trials asked their patients to maintain usual lifestyle and habitual dietary intake. Summary of included studies and their main results are shown in Table I and baseline characteristics of their populations are shown in Table II.

Quality of the included studies

The quality of the included studies is from moderate to high quality according to the Cochrane risk of bias assessment tool. The summary of quality assessment domains of included

studies is shown in Fig.2 (authors’ judgments with justifications are shown in Supplementary File 2).

Liver histology and degree of fibrosis

Only one study assessed the effect of resveratrol on liver histology and degree of fibrosis [19]. The mean change in the degree of fibrosis was -0.84 in the resveratrol group vs. 0.06 in the placebo group. This detected difference was not statistically

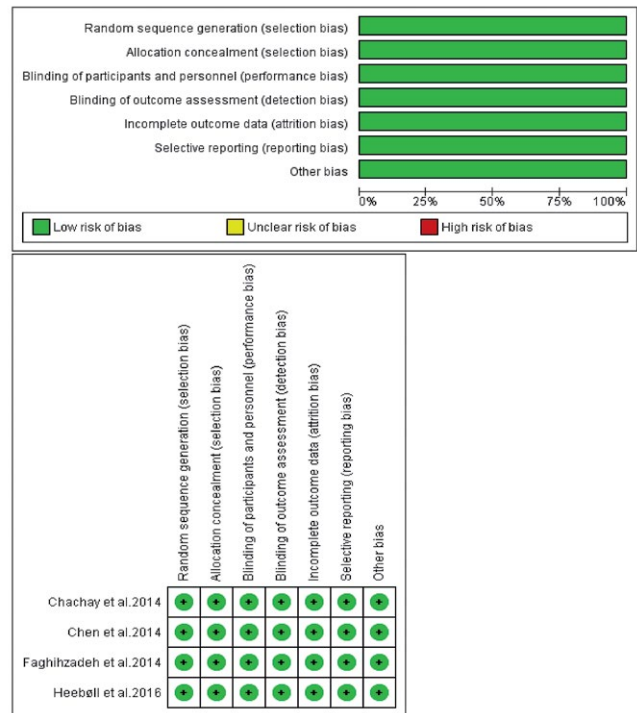


Fig. 2. The risk of bias summary and risk of bias graph according to Cochrane Risk of Bias assessment tool.

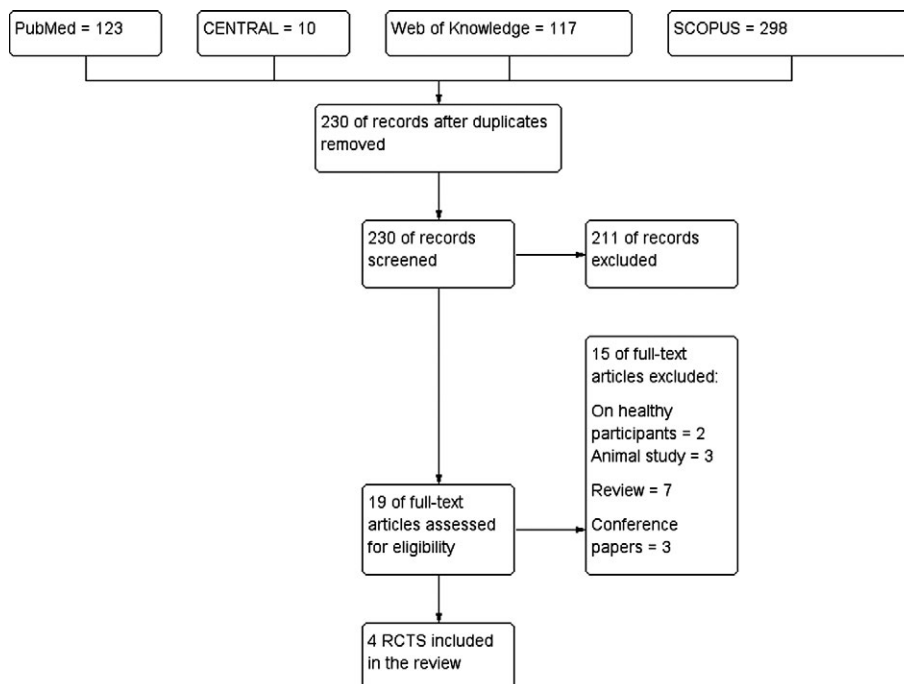


Fig. 1. PRISMA flow diagram of studies’ screening and selection.

Table I. Summary of the included studies

Study ID	Design	Population	Dose/day resveratrol	Sample size (No.)	Follow-up	Results
Chen et al. 2014 [11]	Double-blind RCT	Subjects with NAFLD	300 mg	60	3 months	Resveratrol supplementation may benefit patients with NAFLD.
Chachay et al. 2014 [21]	Double-blind RCT	Overweight or obese men diagnosed with NAFLD	3000 mg	20	8 weeks	Eight weeks administration of resveratrol did not significantly improve any features of NAFLD, compared with placebo
Faghihzadeh et al. 2014 [19]	Double-blind RCT	Subjects with NAFLD	500 mg	50	12 weeks	500 mg resveratrol, along with lifestyle modification, is superior to lifestyle modification alone
Heebøll et al. 2016 [18]	Double-blind RCT	Overweight patients with transaminasemia and histological NAFLD	1500 mg	28	6 months	Resveratrol treatment had no consistent therapeutic effect in alleviating clinical or histological NAFLD, though there might be a small ameliorating effect on liver function tests and liver fat accumulation.

RCT: Randomized controlled trial; NAFLD: non-alcoholic fatty liver disease

significant ($p=0.09$). However, the number of patients with steatosis grade 2/3 was significantly lower in the resveratrol group compared to the placebo group at the end of follow-up ($p=0.02$).

Markers of liver damage

Resveratrol group did not show a statistically significant reduction in serum ALT compared to the placebo group (MD -2.89, 95%CI [-15.66, 9.88], $p=0.66$); pooled studies showed significant heterogeneity which was best resolved by excluding the Chachay et al. trial [10], the only trial that reported significant increase in serum ALT in the resveratrol group. Serum AST did not decrease significantly in the resveratrol group in comparison to the placebo group (MD -3.59, 95%CI [-13.82, 6.63], $p=0.49$); pooled studies were also heterogeneous, which was best resolved by excluding Chachay et al. [10]. The MD in the total bilirubin level did not favor either of the two

groups (MD -0.09, 95%CI [-0.44, 0.26], $p=0.61$); pooled studies were homogeneous ($p>0.1$) (Fig. 3).

Anthropometric index

Overall effect estimate did not favor the resveratrol group in terms of: weight (MD -0.18, 95%CI [-0.92, 0.55], $p=0.63$), BMI (MD -0.10, 95%CI [-0.43, 0.24], $p=0.57$), WHR (MD 0.00, 95%CI [-0.03, 0.04], $p=0.88$), HC (MD -0.27, 95%CI [-1.68, 1.13], $p=0.7$), and systolic blood pressure (SPB) (MD -3.63, 95%CI [-10.39, 3.13], $p=0.29$). Pooled studies were homogeneous (Fig. 4).

Glucose metabolism parameters

Compared to the placebo group, resveratrol did not improve fasting blood glucose level (MD -0.27, 95%CI [-0.55, 0.01], $p=0.05$), insulin level (MD -0.12, 95%CI [-0.69, 0.46],

Table II. Baseline characteristics of the included studies

Study ID	Group	Age	Sex	Height (cm)	Weight	BMI	WC	SBP	Severity of fatty infiltration (No.)			
		Mean (SD)	No. of male (%)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Absent	Mild	Moderate	Severe
Chen et al. 2014 [11]	Resveratrol	45.2 (10)	22 (73.3)	166.1 (7.59)	70.0 (9.15)	25.3 (2.11)	88.4 (7.01)	124.1 (13.1)	0	4	24	2
	Placebo	43.5 (11)	20 (66.6)	165.2 (7.95)	71.6 (10.2)	26.2 (3.08)	88.2 (7.10)	131.7 (21.7)	0	3	24	3
Chachay et al. 2014 [21]	Resveratrol	48.8 (12.2)	10 (100)	NA	105.3 (15.7)	31.8 (5.45)	NA	130 (12)	NA	NA	NA	NA
	Placebo	47.5 (11.2)	10 (100)	NA	110.7 (32.0)	31.2 (9.6)	NA	130 (10)	NA	NA	NA	NA
Faghihzadeh et al. 2014 [19]	Resveratrol	44.04 (10.10)	18 (72)	167.14 (9.85)	79.11 (10.94)	28.35 (3.49)	95.46 (7.78)	NA	0	8	12	5
	Placebo	46.28 (9.52)	17 (68)	167.82 (10.56)	80.63 (9)	28.75 (3.50)	96.24 (7.82)	NA	0	14	9	2
Heebøll et al. 2016 [18]	Resveratrol	43.2	9	NA	97.1 (11.7)	32.1 (3.1)	NA	142 (15)	0	2	3	8
	Placebo	43.5	8	NA	94.7 (16.0)	32.0 (5.4)	NA	136 (15)	0	0	4	9

NA=Not available in the published paper; BMI= Body mass index; WC= Waist circumference; SBP= Systolic blood pressure.

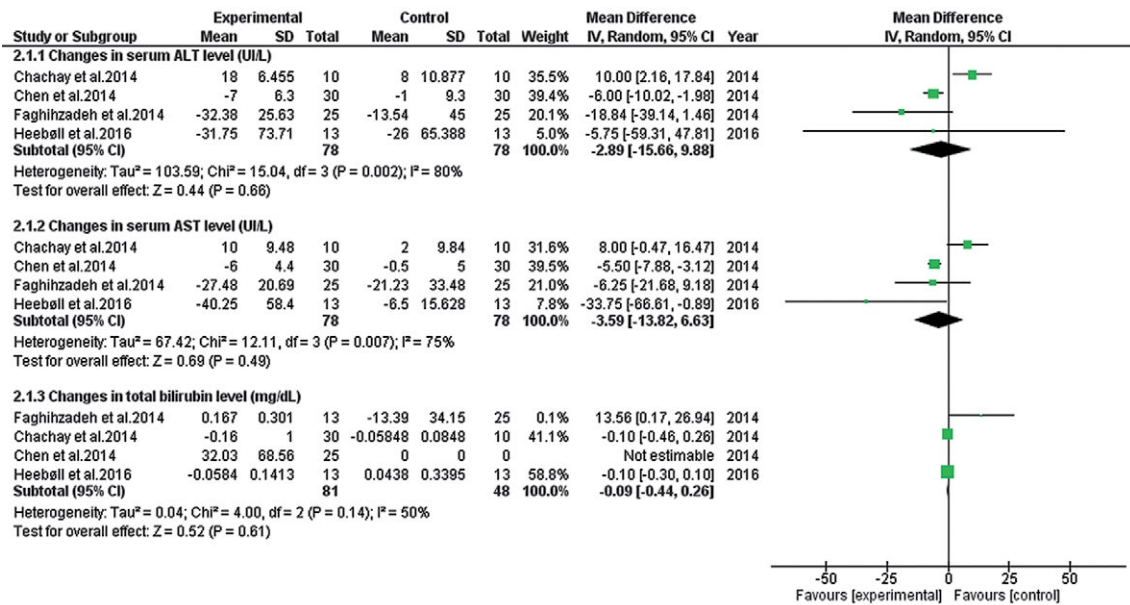


Fig. 3. Forest plot of mean difference of changes in markers of liver damage. MD: mean difference, IV: inverse variance, CI: confidence interval

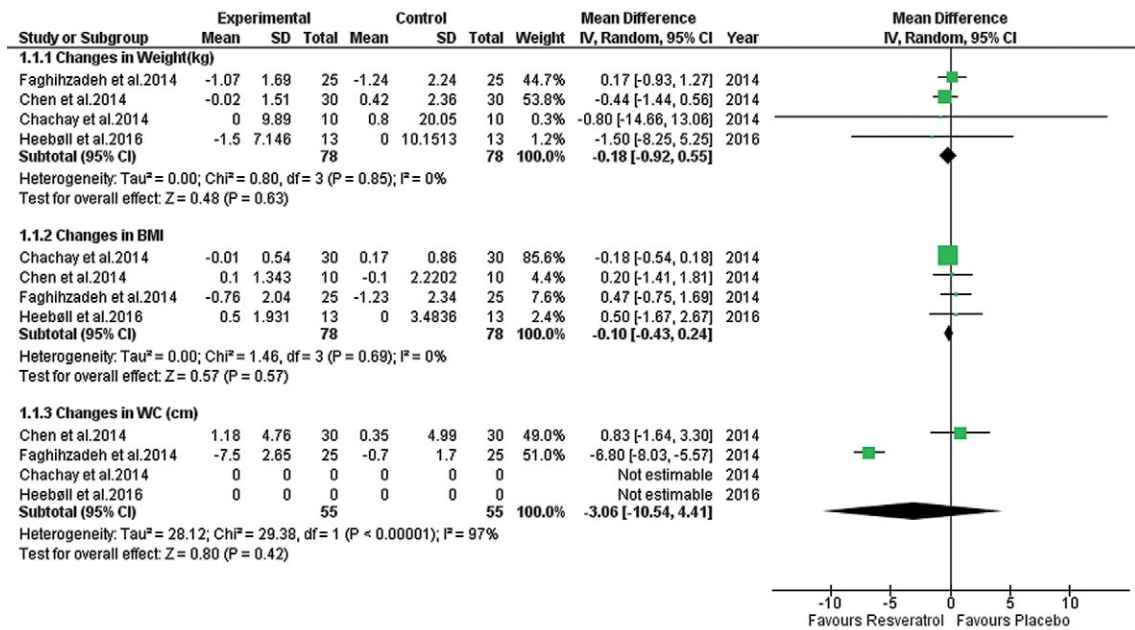


Fig. 4. Forest plot of mean difference of changes in the anthropometric index. (Abbrev.: see Fig. 3)

p=0.69), HOMA-IR level (MD -0.27, 95%CI [-0.55, 0.01], p=0.05). Pooled studies showed significant heterogeneity which was best resolved by excluding Chachay et al. [10] (Fig. 5).

Serum cytokines

In terms of inflammatory markers, the overall effect estimate did not favor the resveratrol group in terms of: TNF- α (MD -0.62 [-1.91, 0.67], p=0.34), CK-18 (MD -18.23, 95%CI [-41.97, 5.50], p=0.13), IL-6 (MD -11.69, 95%CI [-30.11, 6.73], p=0.21), CRP (MD -10.45, 95%CI [-32.42, 11.51], p=0.35) (Fig. 6).

Lipid profile

Overall effect estimate did not favor resveratrol group in terms of: triglyceride level (MD 0.04, 95%CI [-0.45, 0.53], p=0.87), total cholesterol level (MD -0.07, 95%CI [-0.57, 0.42],

p=0.87), HDL level (MD 0.01, 95%CI [-0.04, 0.07], p=0.65), and LDL level (MD 0.21, 95%CI [-0.41, 0.83], p=0.51). Pooled studies were not homogeneous (Fig. 7).

Sensitivity analysis

Statistically significant heterogeneity was detected in most of the pooled outcomes, and it was best resolved by excluding Chachay et al. [10] in the following outcomes: serum ALT, serum AST, glucose level, HOMA-IR level, CK-18 level, and triglyceride level. Moreover, after removing Chachay et al. study, the overall effect estimate favored the resveratrol group in the following outcomes: serum ALT, glucose level, HOMA-IR level, and CK-18 level. Chachay et al. was a double-blinded RCT using resveratrol at a dose of 3000 mg for 8 weeks only and required its patients to maintain their usual lifestyle and habitual dietary intake (Supplementary File 3).

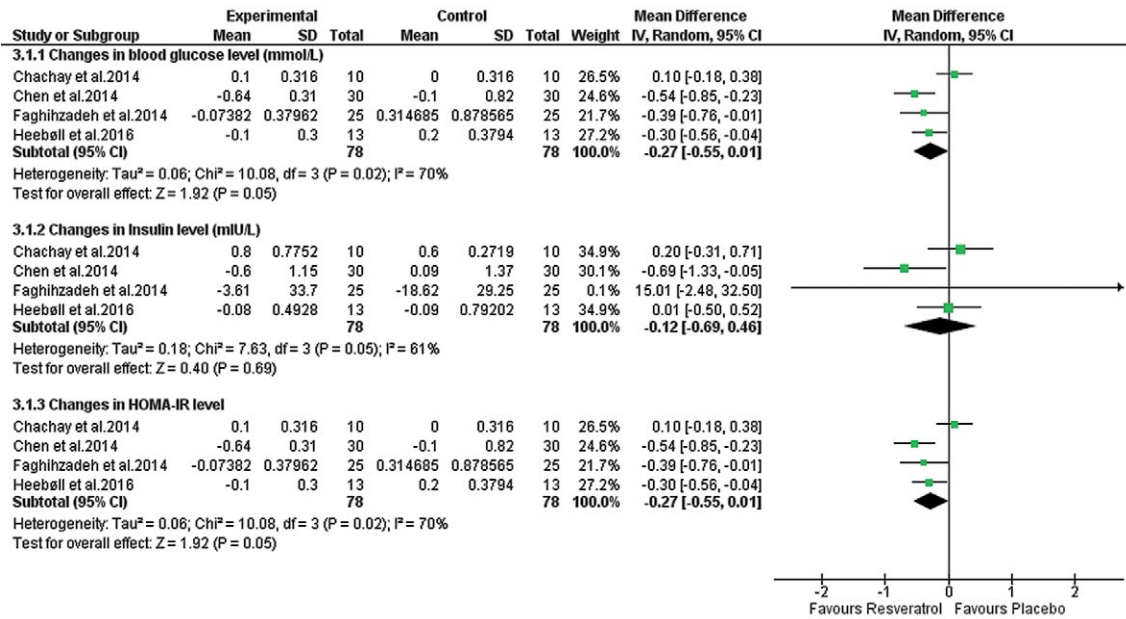


Fig. 5. Forest plot of mean difference of changes in glucose metabolic parameters. (Abbrev.: see Fig. 3)

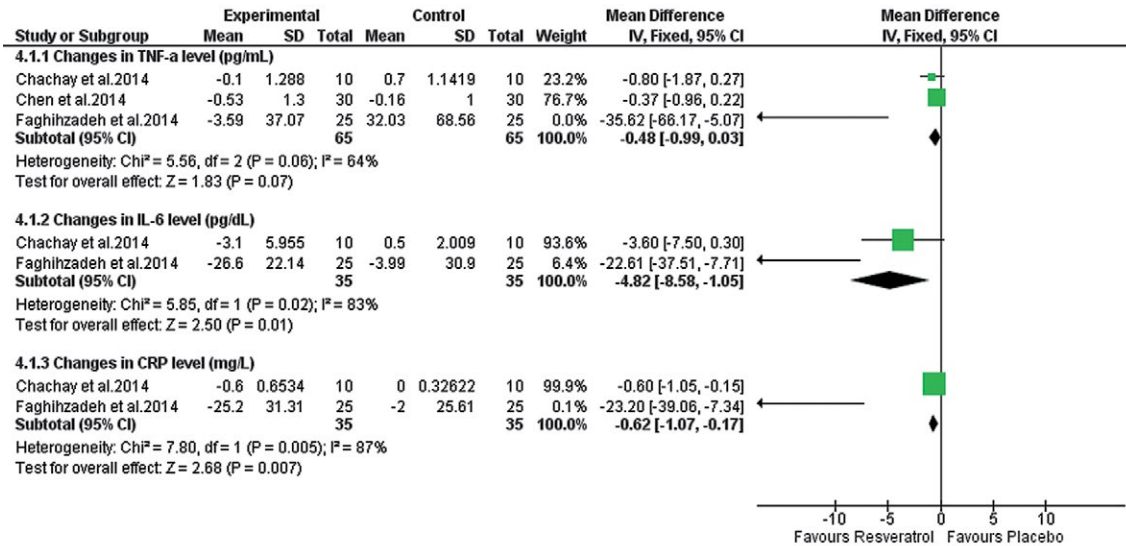


Fig. 6. Forest plot of mean difference of changes in serum cytokines level. (Abbrev.: see Fig. 3)

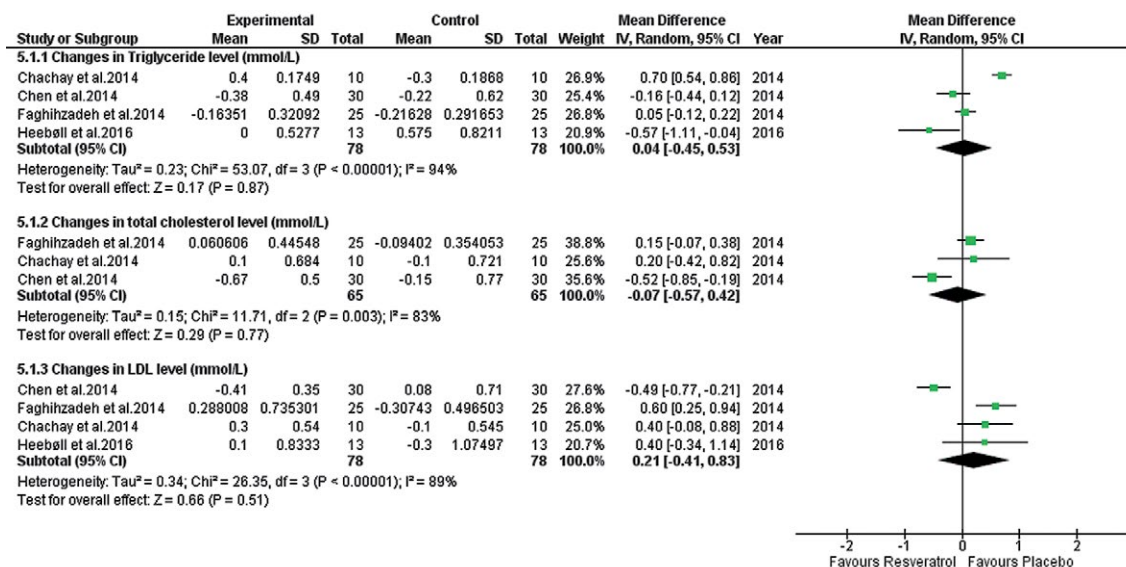


Fig. 7. Forest plot of mean difference of changes in lipid profile. (Abbrev.: see Fig. 3)

DISCUSSION

Summary of the main results

Resveratrol (3, 5, 4'-trihydroxy-trans-stilbene) is a naturally occurring polyphenol, which activates AMPK and SIRT1; thereby, it mimics a condition of caloric restriction as shown in a number of *in vitro* and *in vivo* studies [20, 21]. The presented meta-analysis shows that there is no sufficient evidence to support the efficacy of resveratrol in the management of NAFLD, as resveratrol did not show a significant reduction in the degree of fibrosis, or in the level of markers of liver damage and inflammatory markers.

In addition, current published evidence shows a significant heterogeneity. Two included RCTs showed a beneficial effect of resveratrol in comparison with the lifestyle modification alone [11, 19]. In contrast, the other two RCTs reported that resveratrol has no consistent therapeutic benefit in the management of NAFLD [10, 18]. We could not perform a further subgroup analysis based on patients' characteristics due to the unavailability of relevant data.

Serum ALT, AST and total bilirubin levels become elevated with liver damage and biliary obstruction, and are therefore used as indicators of the progression of NAFLD [22, 23]. AboZaid et al. [24] reported a significant reduction in the levels of ALT, AST and GGT in induced-NAFLD rats medicated with resveratrol for 6 weeks. Moreover, in terms of the anti-oxidative effect of resveratrol, Schmatz et al. [25] demonstrated that resveratrol significantly prevented the rise of AST, ALT and GGT activities in diabetic rats' groups. In contrast to animal studies, published human trials showed no consistent therapeutic benefits in terms of serum ALT and AST. Our pooled results showed that resveratrol neither attenuates the level of liver damage nor protects against fibrosis.

Obesity is considered as a major risk factor for severe hepatic fibrosis. Chang et al. [26] found that BMI categories are positively correlated with an increased incidence of NAFLD, suggesting that obese patients might have an increased risk of developing NAFLD. Previous studies in rodent models have shown that resveratrol can inhibit NAFLD by decreasing body weight, as well as other obesity-related complications such as blood glucose and LDL-cholesterol [23, 27]. According to the mentioned studies, anthropometric indexes have a crucial role in assessing resveratrol efficacy. None of the included RCTs in this review showed significant differences between the resveratrol and placebo groups in terms of anthropometric index, which runs in accordance with our pooled results. Regarding glucose metabolism, the previous animal study showed a significant decrease in blood glucose level in mice treated with resveratrol [20, 28]. Our pooled analysis showed no beneficial effect of resveratrol on glucose metabolism parameters, which is consistent with all published relevant RCTs except Chen et al. study, which reported a significant decrease in the blood glucose level.

Cytokines as TNF- α , IL6 and serum CK-18 play a key role in the pathogenesis of many metabolic diseases through either its inhibitory or a pro-inflammatory action [29, 30]. Seo et al. conducted a 4-year longitudinal study and found significantly higher levels of TNF- α in subjects who developed NAFLD compared to those who did not [31]. In

addition, IL-6 expression level was found to be positively correlated with the degree of inflammation, fibrosis, and systemic inflammatory response in patients with NAFLD [30]. Because of resveratrol anti-inflammatory properties, it is assumed that resveratrol supplementation might be effective in managing NAFLD and restraining its progression. Previous animal studies showed that resveratrol protects the liver against steatosis and fibrosis via activation of Sirt1, leading to the inactivation of NF- κ B and inhibition of TNF- α [32, 33]. In contrast, available evidence was not sufficient to show a beneficial effect of resveratrol in decreasing the cytokines level among NAFLD patients, the trial by Chen et al. [11] was the only published clinical trial which demonstrated a significant reduction in TNF- α and IL-6 in the resveratrol group. Our pooled results did not favor the resveratrol group for any inflammatory markers.

Overall completeness

Of the total of 158 patients in the four RCTs, there were 7 discontinuations (resveratrol group = 5 and placebo group = 2). Reasons included adverse events, and consent withdrawn. However, we believe that this is not likely to affect the study outcomes because of the very low rate of discontinuations.

Quality of the evidence

We performed all steps in strict accordance to the Cochrane Handbook of systematic reviews for interventions and followed the PRISMA checklist. This evidence is based on RCTs, search methods and eligibility criteria were well defined.

Limitations

We acknowledge that our analysis has certain limitations, related to the design of the included studies. The primary outcomes used in this review were only biochemical and "proxy markers" of liver damage or metabolic control in NAFLD. Although the use of liver enzymes as markers in NAFLD is controversial, there are no other commonly established non-invasive biomarkers for use in clinical NAFLD/NASH trials. Only one included RCT assessed the effect of resveratrol on liver histology and degree of fibrosis by the transient elastography score. All included RCTs administered resveratrol at different doses, followed up patients for variable periods of time, and recommended different dietary habits. Those methodological heterogeneities led to significant statistical heterogeneity, sensitivity and subgroup analysis failed to resolve the heterogeneity. Variables as sex, race, and severity of fatty infiltration were not investigated in the previous literature, so it is hard to generalize the results of our analysis beyond the characteristics of the included population.

CONCLUSIONS

Current evidence is insufficient to support the efficacy of resveratrol in the management of NAFLD. Resveratrol neither attenuates liver fibrosis nor shows a significant decrease in any of the parameters of NAFLD. Further larger and longer duration trials are required to study the correlation between lifestyle and dietary modifications and the efficacy of resveratrol.

Conflicts of interest. All authors confirm no financial or personal relationship with a third party whose interests could be positively or negatively influenced by the article's content.

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Authors' contribution: A.E., I.R., and M.A. designed the study. A.E., H.I., M.E., and A.A. performed the internet search. A.S., H.M., M.E., I.R., M.A., and A.O. extracted the data from eligible studies and performed quality assessment. A.E. performed the statistical analysis. A.E., M.E., M.A., A.S., and H.M. wrote the manuscript. All authors read and agreed on the final version of the manuscript.

Supplementary material: To access the supplementary material visit the online version of the *J Gastrointest Liver Dis* at www.jgld.ro/wp/archive/y2017/n1/a12 and <http://dx.doi.org/10.15403/jgld.2014.1121.261.ely>

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Supplementary File no.1: Reasons for exclusion

Author, Year	Reason
Abd El-Haleim et al., 2016 [1]	Animal study
Choi et al., 2014[2]	Invivo study
Dyson et al. 2014[3]	Review
Faghihzadeh et al. 2015[4]	Review
Heebøll et al., 2015[5]	Conference paper
Lula et al. 2014[6]	Review
Musso et al. 2015[7]	Review
Onyekwere et al. 2015[8]	Review
Pan et al. 2014[9]	Pan
Poulsen et al. 2015[10]	Conference paper
Sanyal et al. 2014[11]	Review
Shang et al., 2008[12]	Animal study
Timmers et al. 2008[13]	Not in NAFLD patients
Poulsen et al., 2013[14]	Not in NAFLD patients

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Supplementary File no.2

Author's Judgment on The Quality of Included Studies.

Author, Year	Domain	Author Judgment
Chachay et al. 2014 [1]	Random sequence generation (selection bias)	Low – “a computer-generated randomization list”
	Allocation concealment (selection bias)	Low - “a computer-generated randomization list”
	Blinding of participants and personnel (performance bias)	Low - “Double-blinded”
	Blinding of outcome assessment (detection bias)	Low - “Double-blinded”
	Incomplete outcome data (attrition bias)	Low - ITT
	Selective reporting (reporting bias)	Low - All outcomes mentioned in the protocol was measured and reported in the paper .
	Other bias	Low - Supported by the Princess Alexandra Research Foundation, the Lions Medical Research Foundation, and the National Health and Medical Research Council of Australia.

Author, Year	Domain	Author Judgment
Chen et al. 2015[2]	Random sequence generation (selection bias)	Low - “computer-generated randomization”
	Allocation concealment (selection bias)	Low - “Patients were randomly assigned by an in-house validated randomization system (RANDALL)”
	Blinding of participants and personnel (performance bias)	Low - “Double-blinded”
	Blinding of outcome assessment (detection bias)	Low - “Double-blinded”
	Incomplete outcome data (attrition bias)	Low - ITT
	Selective reporting (reporting bias)	Low - All outcomes mentioned in the protocol was measured and reported in the paper.
	Other bias	Low – “This study was supported by the National Natural Science Foundation of China (No. 30972469; No. 81273059), the Science and Technology Key Project Foundation of Chongqing (No. CSTC, 2011AB5040), and the National Science-technology Support Plan Projects Foundation of China (No. 2012BAI35B02).”

Author, Year	Domain	Author Judgment
Faghihzadeh et al. 2014[3]	Random sequence generation (selection bias)	Low- “Stratified randomisation lists were computer generated .”
	Allocation concealment (selection bias)	Low -“Stratified randomisation lists were computer generated.”
	Blinding of participants and personnel (performance bias)	Low- “Double-blinded”
	Blinding of outcome assessment (detection bias)	Low- “Double-blinded”
	Incomplete outcome data (attrition bias)	Low - ITT
	Selective reporting (reporting bias)	Low - All clinically important outcomes was reported
	Other bias	Low – “This work was financially supported by the Iran National Science Foundation (A. H., grant number 90008014), and the National Nutrition and Food Technology Research Institute (A. H., grant number 046468). None of the funders had any role in the design, analysis or writing of this article”.

Author, Year	Domain	Author Judgment
Heebøll et al. 2016 [4]	Random sequence generation (selection bias)	Low- "A block randomization of four was generated (using www.randomization.com), by the hospital pharmacist at study start."
	Allocation concealment (selection bias)	Low- "Both investigators and participants were blind to the assigned treatment until completion of study and data collection, upon which the allocation sequence was handed over from the hospital pharmacist to the investigators."
	Blinding of participants and personnel (performance bias)	Low- "Double-blinded"
	Blinding of outcome assessment (detection bias)	Low- "Double-blinded"
	Incomplete outcome data (attrition bias)	Low - Less than 15% of participants was lost during followup
	Selective reporting (reporting bias)	Low - All outcomes mentioned in the protocol was measured and reported in the paper .
	Other bias	Low- "This study was supported by Aarhus University (2010-218/2-82); the Danish Council for Independent Research, Medical Sciences (no. 11-107912); and the Danish Strategic Research Council, (no. 10-093499 and 10-092797). This study was also supported by grants to H Grønbæk from The NOVO Nordisk Foundation and from "Savværksejer Jeppe Juhl og hustru Ovita Juhls mindelegat". Resveratrol was provided by Evolva SA (Basel, Switzerland), free of charge. The funders had no role in study design, data collection and analysis, or preparation of the manuscript.

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Supplementary File no.3

Results of Sensitivity analysis

Figure 1 shows forest plots of mean difference of changes in markers of liver damage after excluding Chachay et al. study.

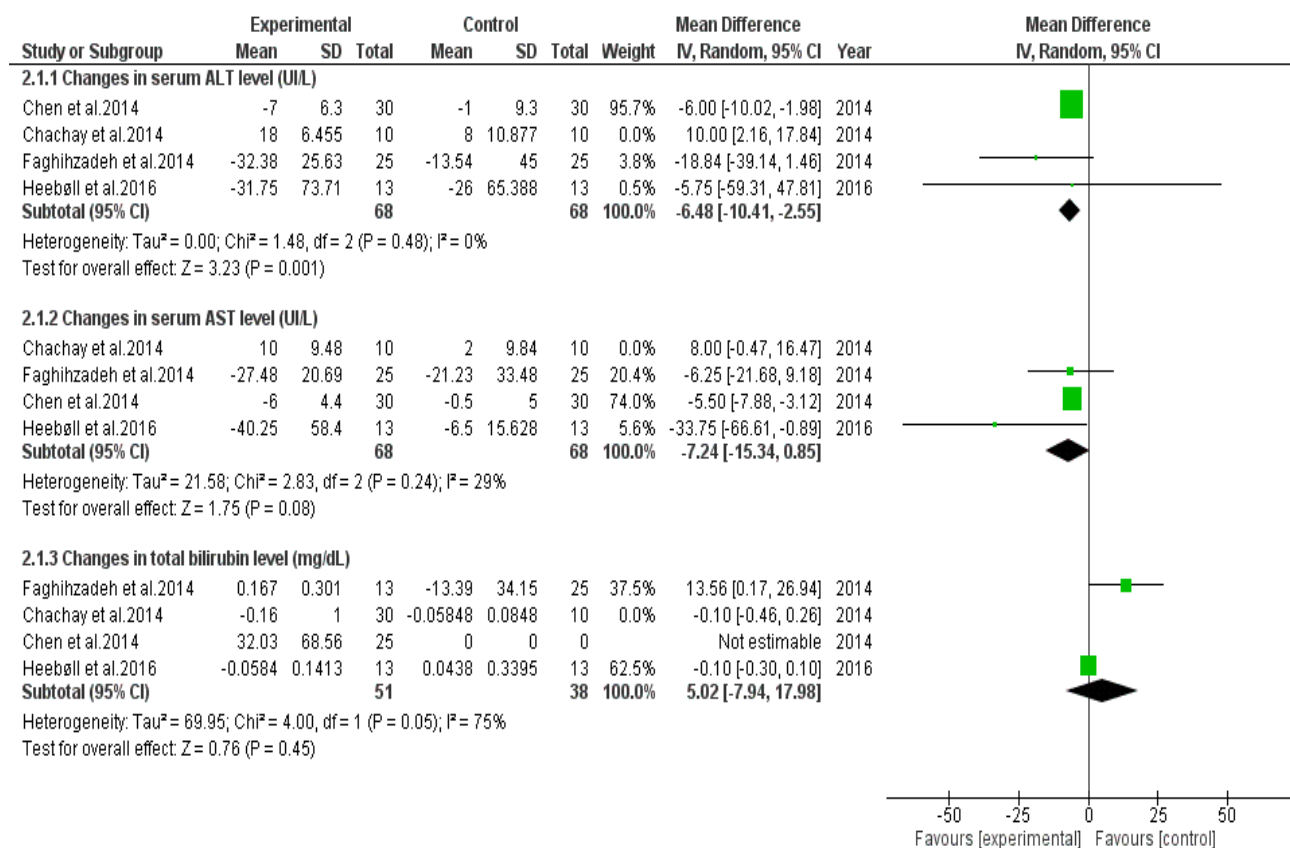


Figure 2 shows forest plots of mean difference of changes in glucose metabolic parameters after excluding Chachay et al. study.

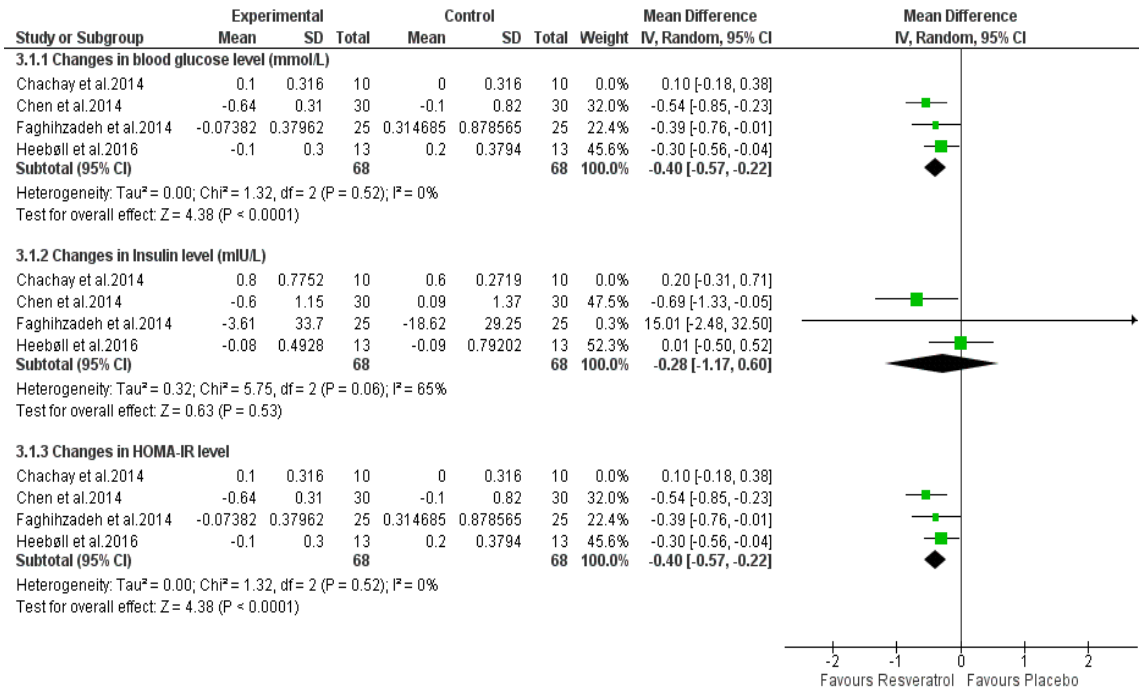


Figure 3 shows forest plots of mean difference of changes in serum cytokines level after excluding Chachay et al. study.

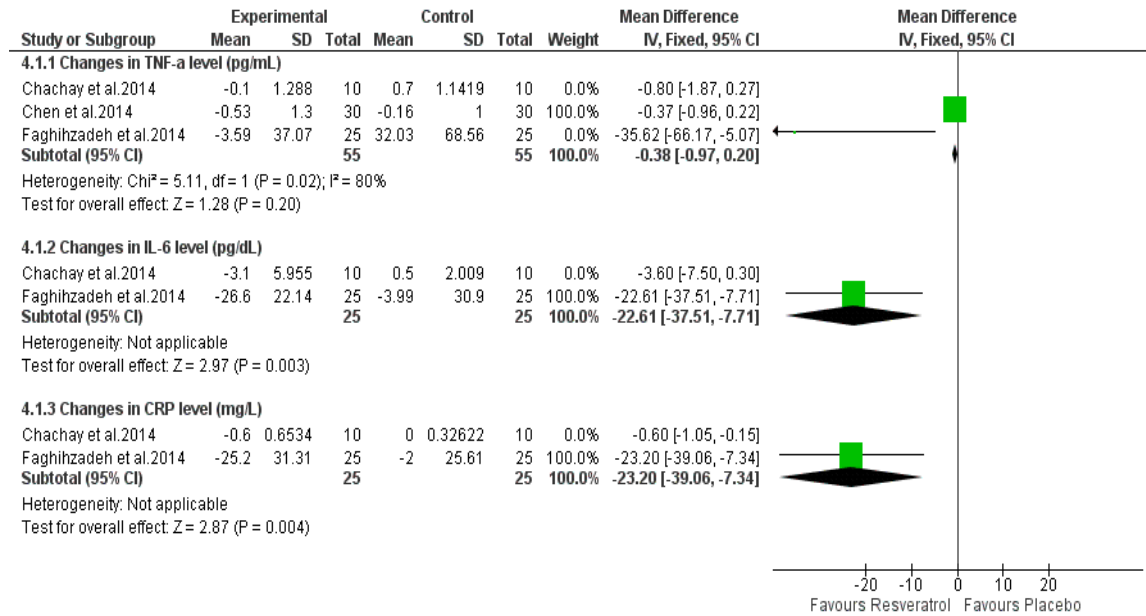


Figure 4 shows forest plots of mean difference of changes in lipid profile after excluding Chachay et al. study.

