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Effects of Resveratrol on Liver Function Tests in Patients with Non-Alcoholic Fatty Liver Disease: a Systematic Review and Meta-Analysis of Randomized Controlled Trials

Pardis Ebrahimpour, Mohammad Karamian, Amrollah Sharifi*

Hamadan University of Medical Sciences, Hamadan, Iran

Background. Some studies have shown that resveratrol may prevent, delay, or treat liver damage. This study aimed to provide up-to-date evidence regarding the effect of resveratrol on the liver enzymes (ALT & AST) in NAFLD patients. We conducted a systematic review and meta-analysis to evaluate the effect of resveratrol on liver enzymes in patients with NAFLD by searching various databases for published RCTs.
Methods. A systematic search in PubMed, Scopus, and Web of Science was performed up to September 2023. This systematic review and meta-analysis included all the RCT studies assessing resveratrol supplements on serum AST and/or ALT in NAFLD patients. The effect was presented as a mean difference and 95 % confidence interval (CI) in a random-effects model.
Results. Finally, six eligible randomized controlled trials consisting of 256 patients were found. Resveratrol had no significant effect on serum ALT (Mean diff = 3.30 IU/L; 95 % CI: –2.34, 8.94; $p = 0.25$) and AST (Mean diff = 0.07 IU/L; 95 % CI: –2.96, 3.10; $p = 0.96$) concentrations. Moreover, subgroup analysis revealed that neither resveratrol dose nor intervention duration had any significant effect on the serum ALT and AST levels.
Conclusion. The current evidence shows that resveratrol supplementation did not affect liver enzymes in NAFLD patients.
Keywords: resveratrol, non-alcoholic fatty liver disease, alanine transaminase, aspartate aminotransferases, meta-analysis
Conflict of interest: the authors declare no conflict of interest.

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Влияние ресвератрола на функциональные пробы печени у пациентов с неалкогольной жировой болезнью печени: систематический обзор и метаанализ рандомизированных контролируемых исследований

П. Эбрагимпур, М. Карамян, А. Шарифи*

Хамаданский университет медицинских наук, Хамадан, Иран

Актуальность. Некоторые исследования показали, что ресвератрол может предотвращать, задерживать или лечить повреждение печени.
Цель исследования: предоставить современные данные о влиянии ресвератрола на ферменты печени (АЛТ и АСТ) у пациентов с НАЖБП. Для оценки влияния ресвератрола на ферменты печени у пациентов с НАЖБП был проведен систематический обзор и метаанализ путем поиска в различных базах данных опубликованных РКИ.
Материалы и методы. Систематический поиск в базах данных PubMed, Scopus и Web of Science проводился до сентября 2023 г. В данный систематический обзор и метаанализ вошли все РКИ, оценивающие влияние добавок ресвератрола на уровень АСТ и/или АЛТ в сыворотке крови у пациентов с НАЖБП. Эффект был представлен как средняя разница и 95 %-ный доверительный интервал (95 % ДИ) в модели случайных эффектов.
Результаты. Были отобраны шесть отвечающих условиям поиска рандомизированных контролируемых исследований с участием 256 пациентов. Ресвератрол не оказывал существенного влияния на уровень концентрации сывороточной АЛТ (среднее значение = 3,30 МЕ/л; 95 % ДИ: –2,34–8,94; $p = 0,25$) и АСТ (среднее значение = 0,07 МЕ/л; 95 % ДИ: –2,96–3,10; $p = 0,96$). Более того, анализ подгрупп показал, что ни доза ресвератрола, ни продолжительность вмешательства не оказали существенного влияния на уровни АЛТ и АСТ в сыворотке.

Вывод. Имеющиеся данные показывают, что прием ресвератрола не влияет на ферменты печени у пациентов с НАЖБП.
Ключевые слова: ресвератрол, неалкогольная жировая болезнь печени, аланинаминотрансфераза, аспартатаминотрансфераза, метаанализ
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

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Introduction

Over the past few decades, liver diseases have rapidly increased and become a global public health problem [1]. Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease, which includes a wide range of steatosis to nonalcoholic steatohepatitis [2–4]. The global prevalence of NAFLD is around 32 %, and it is higher in men than in women [5].

The complete mechanism of NAFLD pathogenesis is still unclear. Obesity, insulin resistance, and oxidative stress are the most known risk factors. Lifestyle and dietary habits also play a substantial role in the pathogenesis of NAFLD [6]. Common treatments for managing NAFLD include lifestyle modification and weight loss through diet and exercise [6]. NAFLD is often associated with a mild increase in serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) [4].

No effective drug treatment is known for NAFLD [7]. Evidence has shown that adjunctive therapies, including antioxidant compounds and flavonoids, can effectively improve NAFLD [6]. Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a polyphenol compound with antioxidant and anti-inflammatory properties that is found in various plant species, such as black grape skins, berries, and peanuts [6–8]. It may protect against ischemic stroke, heart failure, atrial fibrillation, metabolic syndrome, type 2 diabetes, hepatic steatosis, aging, Alzheimer's disease, viral infections, inflammatory diseases, and cancer [1, 9]. Resveratrol increases insulin sensitivity, improves exercise tolerance, and prevents hepatic steatosis [10–12].

Some studies have shown that resveratrol may prevent or delay liver damage [3, 8, 13–15]. At the same time, it had no effect in some other studies [16, 17]. This contrast may be due to the difference in the duration of administration and formulation and dosage of resveratrol, sample size, and patient's primary metabolic conditions [6].

We conducted a systematic review and meta-analysis to evaluate the effect of resveratrol on liver enzymes in patients with NAFLD by searching various databases for published RCTs up to September 2023.

Materials and methods

Search strategy

This study was done based on the guidelines of the PRISMA-2009 (Preferred Reporting Items for Systematic Reviews and Meta-Analysis). Two investigators (AS, PE) independently searched electronic databases, including PubMed, Web of Science, and Scopus, in September 2023 to find published RCTs evaluating the effects of resveratrol on ALT and AST in patients with NAFLD. No publication time or language filters were used.

The search queries included the following terms in all parts of the papers:

– PubMed: ("Resveratrol"[MeSH]) AND ("Liver Function Tests"[MeSH] OR "Aspartate Aminotransferases"[MeSH] OR "Alanine Transaminase"[MeSH] OR "Non-alcoholic Fatty Liver Disease"[MeSH] OR "Fatty Liver"[MeSH]);

– Scopus: ("Resveratrol") AND ("Liver Function Tests" OR "Aspartate Aminotransferases" OR "AST" OR "ALT" OR "SGPT" OR "SGOT" OR "Alanine Transaminase") AND ("Non-alcoholic Fatty Liver Disease" OR "Nonalcoholic Fatty Liver Disease" OR "Fatty Liver") AND (LIMIT-TO (SRCTYPE,"j")) AND (LIMIT-TO (DOCTYPE,"ar"));

– Web of Science: ALL=(("Resveratrol") AND ("Liver Function Tests" OR "Aspartate Aminotransferases" OR "AST" OR "ALT" OR "SGPT" OR "SGOT" OR "Alanine Transaminase") AND ("Non-alcoholic Fatty Liver Disease" OR "Fatty Liver")).

We also checked the references of the final studies to find further relevant articles.

Inclusion and exclusion criteria

Studies with the following properties were included:

1) designed as randomized controlled trials (RCTs) using either a parallel or cross-over design;

2) the studies focused on examining the impact of resveratrol on liver function tests in patients with NAFLD;

3) the studies provided data on the mean and standard deviation (SD) of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations for both the treatment group (receiving resveratrol) and the placebo/control group.

Studies with unclear criteria for inclusion and exclusion, improper control or placebo groups in the research design, and insufficient information regarding the study methodology were not included.

Data extraction

The following information was provided from the eligible articles: the title and DOI of the study; the name of the first author; the country where the study was conducted; the publication date (year); the sample size in both the treatment and placebo groups; the dosage of resveratrol; the duration of the intervention; the mean and SD of serum ALT and AST levels in both the treatment and placebo groups at the beginning and end of the study; the details required for calculating the Jadad scale, which includes information on randomization, blinding, and reporting the outcomes of all the patients.

In cases where instead of the SD, the standard error (SE) or 95 % confidence interval (95 % CI) was reported, the methods suggested in the Cochrane Handbook [18] were used for conversion to SD. The proposed methods by X. Wan et al. [19] were also used to estimate mean and SD, where median and interquartile range (IQR) or minimum and maximum were reported.

Quality assessment

The Jadad scale [20] was used for the quality assessment of the eligible studies. This scale assesses the clinical trial's methodological quality and

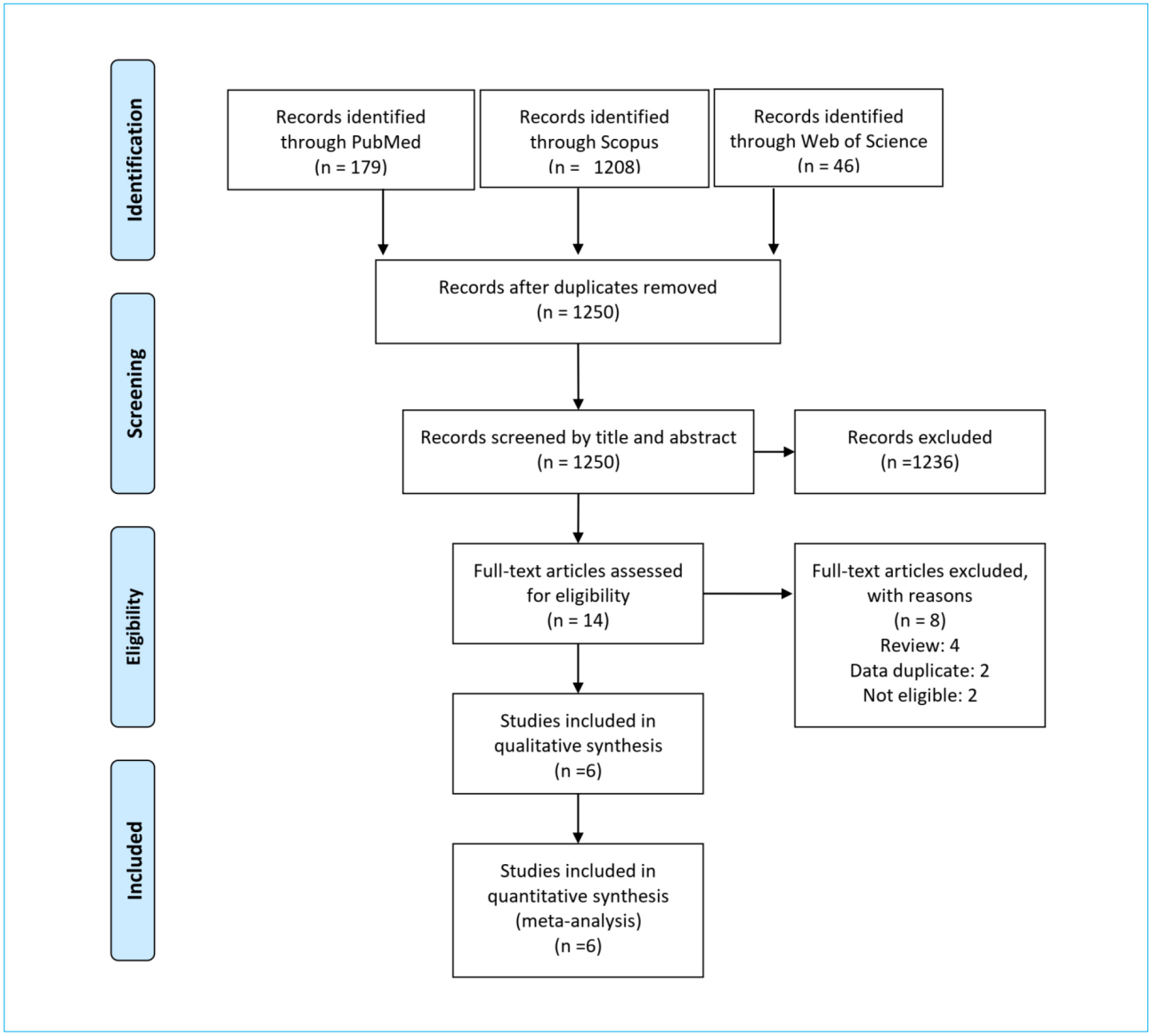

Figure 1. PRISMA flow chart of the study

Рисунок 1. Блок-схема исследования, разработанная согласно методическим рекомендациям PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis — Предпочтительные элементы отчетности для систематических обзоров и метаанализа)

allocates trials a score between zero ("very poor") and five ("rigorous").

Statistical analysis

Performing the meta-analysis (a random-effects model) and drawing the graphs was done using STATA software (StataCorp LLC, USA). The publication bias was not assessed as the included studies were less than 10 [18].

We performed subgroup analyses based on the dose of intervention (< 600 and ≥ 600 mg/day) and intervention duration (< 12 and ≥ 12 weeks) when more than five trials were available. The statistical significance was defined as $p < 0.05$.

Results

From the three sources, 1433 articles were found in the initial search. After screening based on the title and abstract and carefully checking the full text of the remaining articles, six studies were identified that met all the study criteria (Fig. 1). A summary of the six included articles can be seen in Tables 1 and 2.

Table 1. Characteristics and findings of the included studies
Таблица 1. Характеристики и результаты включенных исследований

Authors *Авторы*	Country *Страна*	Date / *Дата*	Sample size *Размер выборки*		Total prescribed resveratrol (mg) *Всего назначено ресвератрола (мг)*	Duration of the study (weeks) *Продолжительность исследования (нед.)*	AST/*АСТ*				ALT/*АЛТ*			
			Treatment / *Препарат*	Placebo / *Плацебо*			Mean (intervention) *Среднее значение (препарат)*	SD (intervention) *Стандартное отклонение (препарат)*	Mean (placebo) *Среднее значение (плацебо)*	SD (placebo) *Стандартное отклонение (плацебо)*	Mean (intervention) *Среднее значение (препарат)*	SD (intervention) *Стандартное отклонение (препарат)*	Mean (placebo) *Среднее значение (плацебо)*	SD (placebo) *Стандартное отклонение (плацебо)*
Chachay et al.	Australia	2014	10	10	168.000	8	45	15	38	15	67.6	22.72	61.6	51.57
Faghihzadeh et al.	Iran	2014	25	25	42.000	12	22.62	6.41	21.04	5.53	36.67	15.56	33.92	16.43
Chen et al.	China	2015	30	30	54.600	13	23.5	10.51	27.51	11.64	33.86	18.69	34.93	24.68
Heebøll et al.	Denmark	2016	13	13	273.000	26	50.73	22.48	50.69	23.38	91.76	43.16	83.57	39.86
Asghari et al.	Iran	2018	25	26	50.400	12	32.52	11.19	34.27	21.06	46.2	25.19	40.94	28.81
Farzin et al.	Iran	2020	25	25	50.400	12	33.5	11.07	33.04	21.11	48.95	24.85	39.43	30.01

Table 2. Quality of the selected studies, based on the JADAD scale
Таблица 2. Качество выбранных исследований по шкале JADAD

Authors *Авторы*	Randomized *Рандомизировано*	Researcher blind *Ослепление исследователей*	Patient blind *Ослепление пациентов*	Account for all patients *Учет всех пациентов*	Total score *Всего баллов*
Chachay et al.	2	1	1	1	5
Faghihzadeh et al.	2	1	1	1	5
Chen et al.	2	1	1	0	4
Heebøll et al.	2	1	1	1	5
Asghari et al.	2	1	1	1	5
Farzin et al.	2	1	1	1	5

Eligible studies

In V.S. Chachay et al.'s study, 20 overweight or obese men diagnosed with NAFLD from 2011 to 2012 were selected from outpatient liver clinics in Brisbane, Australia. The primary inclusion criterion was hepatic steatosis in ultrasound. They were randomly divided into two groups of 10 people; one group received 3000 mg of resveratrol daily, and the other group received the same amount of placebo daily for eight weeks. The participants took three capsules containing 500 mg of resveratrol or placebo before breakfast and another three capsules before bed. The placebo was uniformly filled with microcellulose. Eight weeks of resveratrol administration did not reduce insulin resistance, steatosis, or abdominal fat distribution compared to baseline. No changes in plasma lipids or antioxidant activity were observed. ALT and AST levels increased in the intervention group, and none of the NAFLD features were improved compared to the placebo [17].

In the study of F. Faghihzadeh et al., 50 adults with NAFLD were randomly divided into two groups of 25 patients. One group received a daily capsule containing 500 mg of trans-resveratrol; the other group received the same medium-chain triglyceride as the placebo for 12 weeks. Serum levels of ALT and AST decreased significantly in both groups after 12 weeks. Patients who took resveratrol had a more significant decrease in ALT compared to the placebo group. Significant changes in inflammatory markers were observed in the resveratrol group, and inflammatory factors were lower compared to the baseline and placebo [2].

In the study by S. Chen et al., adults aged 20 to 60 with NAFLD diagnosed by ultrasound at Chongqing Hospital in China were selected. They were divided into two groups: resveratrol and placebo. The placebo group received two placebo capsules containing only pullulan and maltodextrin. The resveratrol group received two 150 mg capsules of resveratrol (along with pullulan and maltodextrin) twice a day for three months. The intervention had no significant effect on anthropometric characteristics. The two groups had no significant difference in the intensity of fatty liver infiltration. Resveratrol consumption did not affect the number of red and white blood cells, platelets, or hemoglobin concentration. The two groups had no significant difference in blood urea nitrogen or creatinine levels. The levels of ALT and AST in the resveratrol group were significantly lower at the end of the study. A significant decrease in mean serum glucose was found in the resveratrol group. HOMA-IR (Homeostasis Model Assessment of Insulin Resistance) changes were significantly higher in the resveratrol group than in the placebo group. Changes in serum insulin and C-peptide levels were not significantly different between the two groups. Total cholesterol was significantly reduced in the resveratrol group compared to the placebo group [13].

In the study by S. Heebøll et al., 28 obese patients with hepatic steatosis and at least one of the criteria of metabolic syndrome were included at Aarhus Hospital in Denmark. One group of participants was given the placebo three times a day, and the other group was assigned 500 mg of resveratrol three times daily (1500 mg daily). After six months, participants were admitted for end-of-trial tests. In this study, a daily dose of 1.5 g of resveratrol for six months did not lead to significant clinical improvement in patients with NAFLD and nonalcoholic steatohepatitis. Compared to the placebo group, resveratrol had no significant effect on ALT levels [16].

In the study of S. Asghari et al., 90 patients with NAFLD (men and women aged 20 to 60 with a body mass index between 25 and 35 kg/m^2) were assigned to one of the following three groups for 12 weeks: caloric restriction low-calorie diet group (n = 30); resveratrol group (n = 30) who received 600 mg of pure trans-resveratrol daily (300 mg twice a day); and the placebo group (n = 30) who received two placebo capsules daily. ALT, AST, and lipid profiles in the resveratrol group did not change significantly compared to the placebo group. No significant changes were observed in the degree of hepatic steatosis, serum glycemic parameters, and high-density lipoprotein cholesterol and sirtuin-1 [15].

In the study of L. Farzin et al., 50 patients with NAFLD (35 men and 15 women) in the age range of 20 to 60 years and with a body mass index between 25 and 35 kg/m^2 at the Golgasht outpatient clinic in Tabriz (Iran) were randomly assigned to two groups for 12 weeks. The resveratrol group received two capsules per day, each containing 300 mg of resveratrol, and the placebo group received two placebo capsules containing corn starch daily. Resveratrol supplementation significantly reduced body weight, body mass index, and waist circumference. No significant changes were observed in the lipid profile, the serum's atherogenic index, and the level of liver enzymes [21].

Meta-analysis

Six studies with a total sample size of 128 patients in the treatment group and 128 patients in the placebo group had the necessary data to be included in the meta-analysis. The random effect model was used for meta-analysis. Figures 2 and 3 show that resveratrol did not significantly affect AST and ALT levels in NAFLD patients.

Subgroup analysis based on the intervention duration (less than or higher than 12 weeks) showed that resveratrol did not affect AST and ALT levels either less than or more than 12 weeks. (Figs. 4, 5).

Moreover, the intervention dose (less than or more than 600 mg/d) had no significant effect on the results. (Figs. 6, 7).

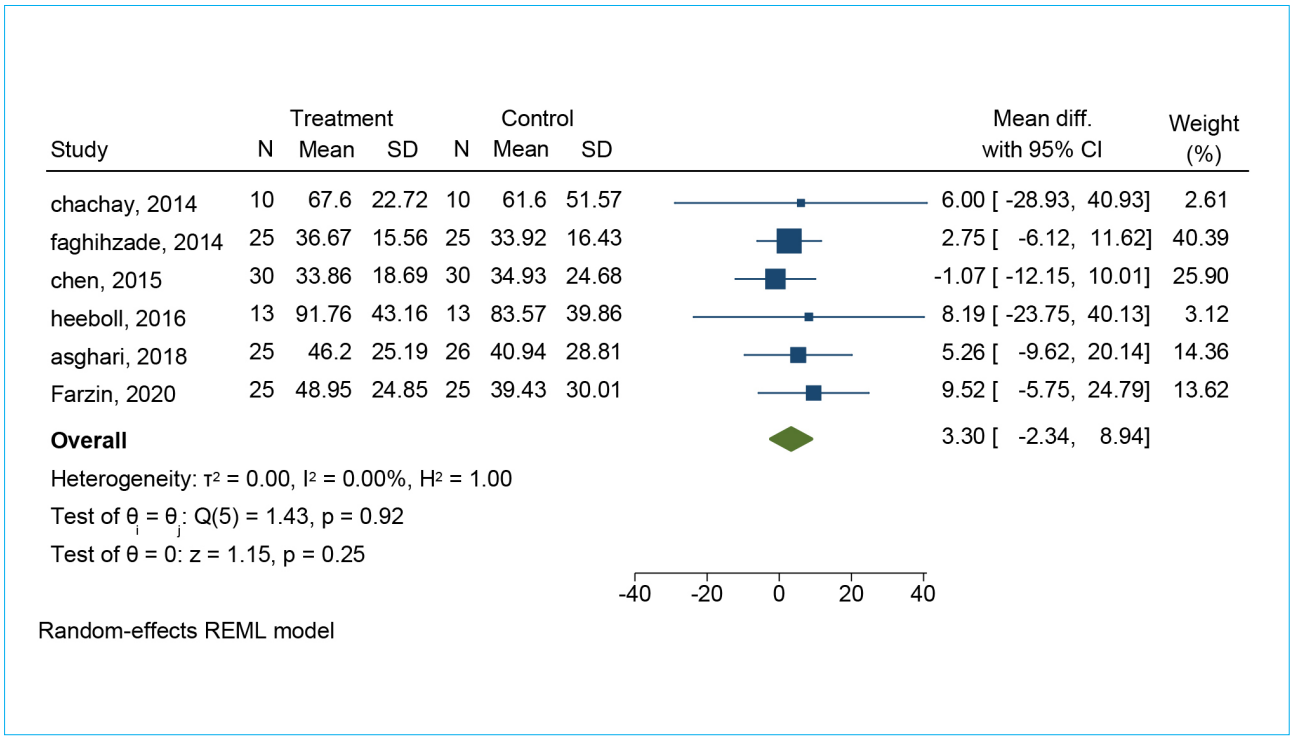

Figure 2. Forest plot for the impact of resveratrol on the serum ALT

Рисунок 2. Форест-диаграмма влияния ресвератрола на уровень АЛТ в сыворотке

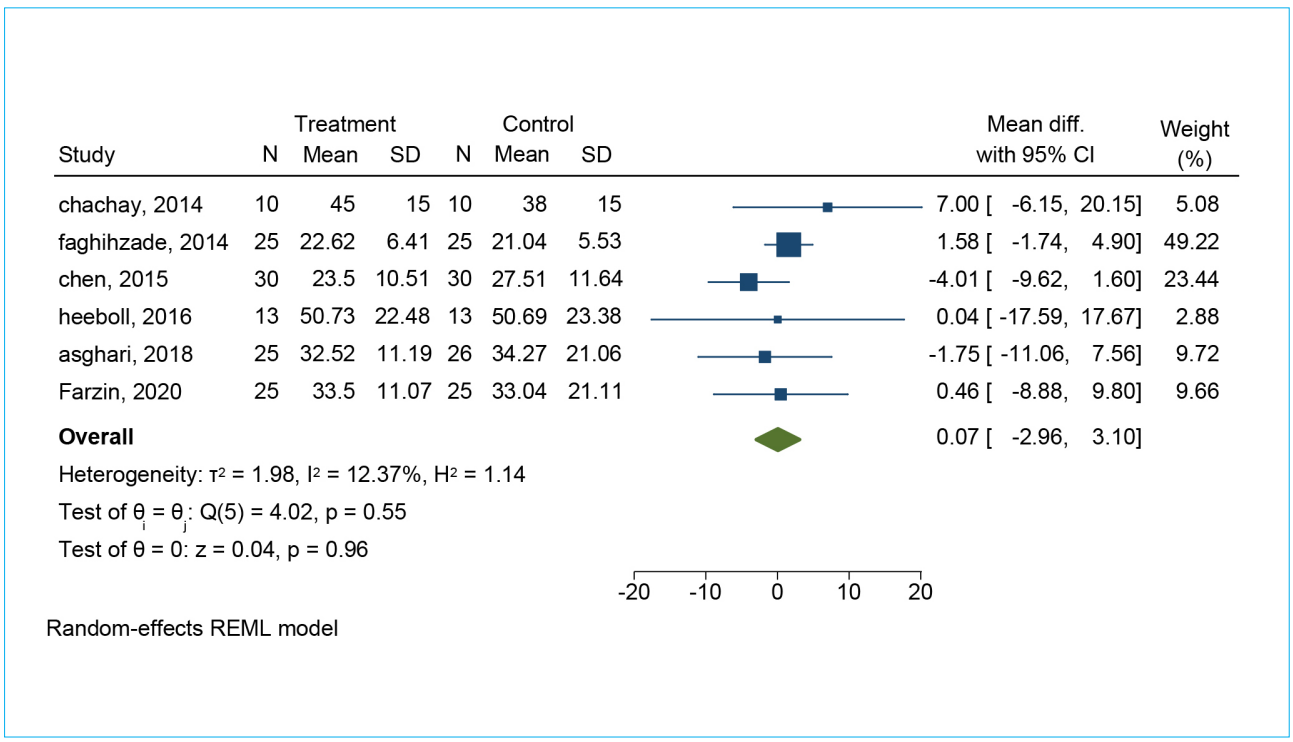

Figure 3. Forest plot for the impact of resveratrol on the serum AST

Рисунок 3. Форест-диаграмма влияния ресвератрола на уровень АСТ в сыворотке

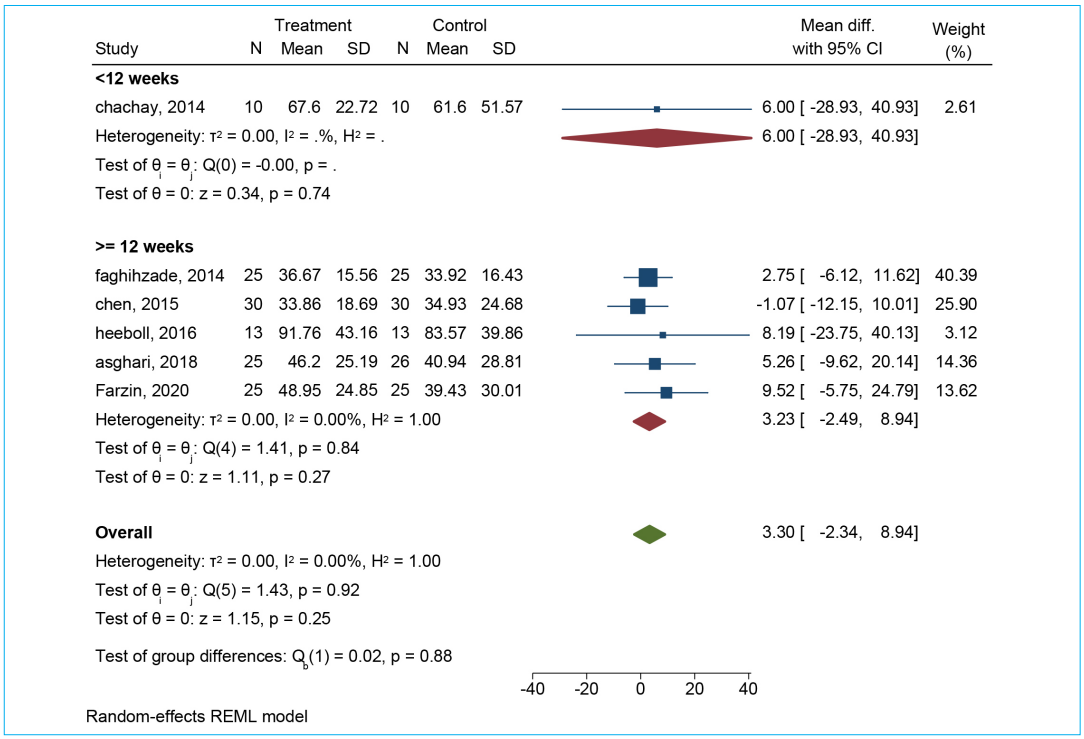

Figure 4. Forest plot for subgroup analysis based on the intervention duration for the impact of resveratrol on the serum ALT

Рисунок 4. Форест-диаграмма для анализа подгрупп на основе продолжительности вмешательства по влиянию ресвератрола на уровень АЛТ в сыворотке

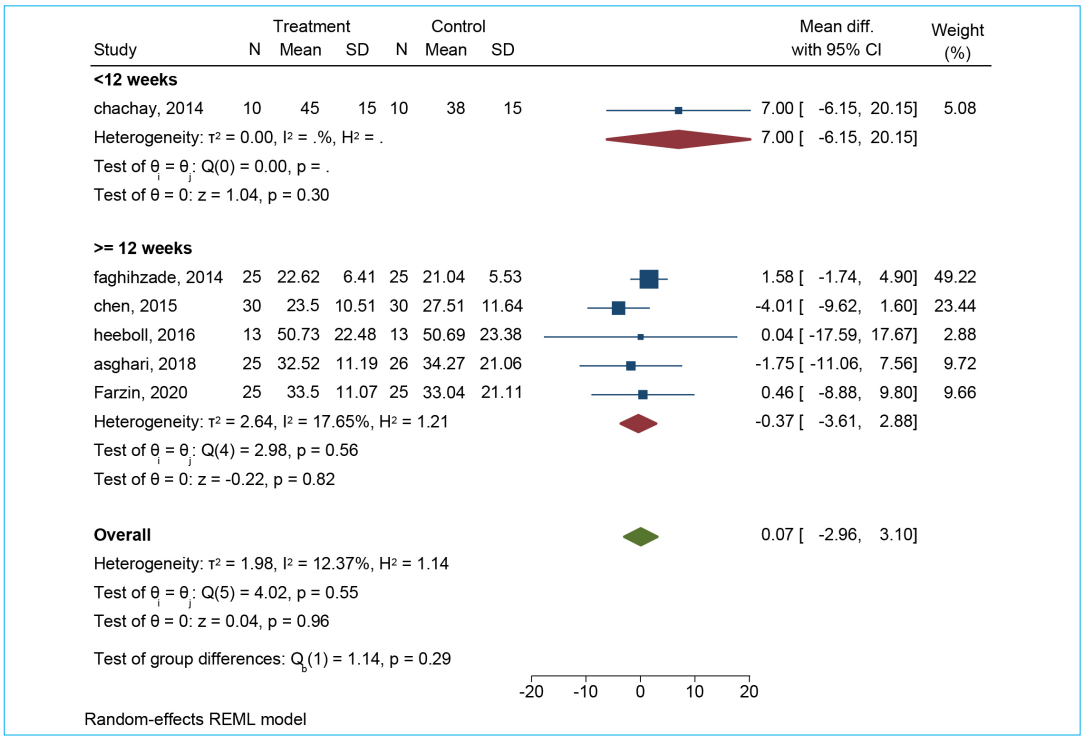

Figure 5. Forest plot for subgroup analysis based on the intervention duration for the impact of resveratrol on the serum AST

Рисунок 5. Форест-диаграмма для анализа подгрупп на основе продолжительности вмешательства по влиянию ресвератрола на уровень АСТ в сыворотке

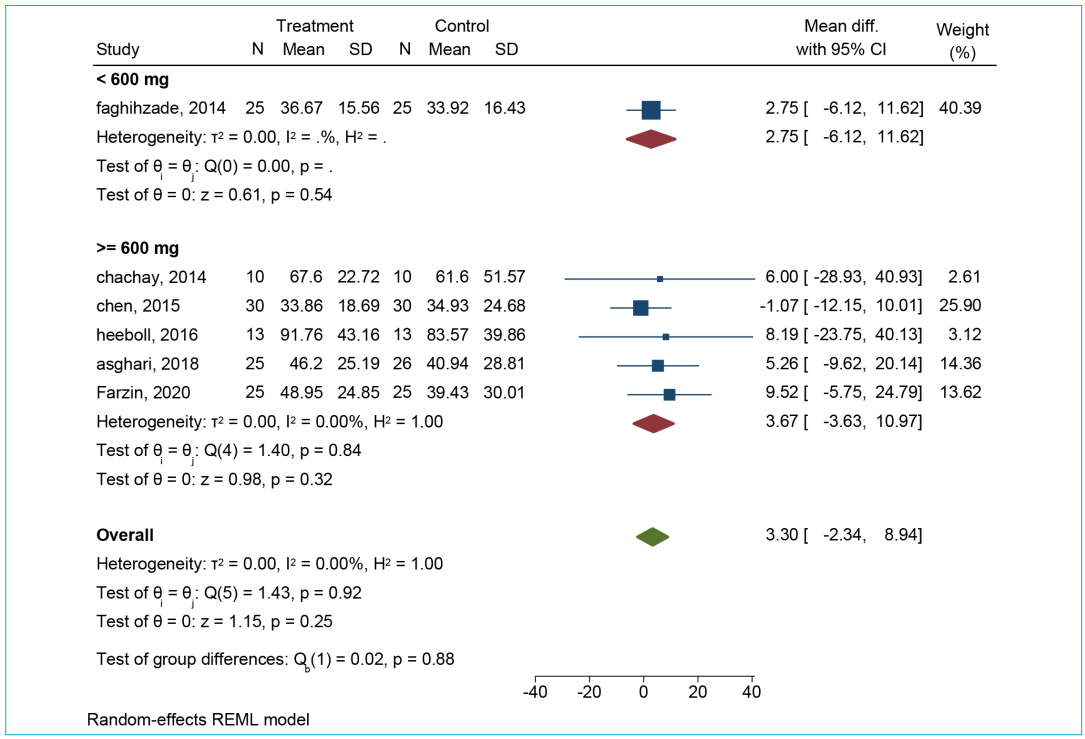

Figure 6. Forest plot for subgroup analysis based on the resveratrol dose for the impact of resveratrol on the serum ALT

Рисунок 6. Форест-диаграмма для анализа подгрупп на основе дозы препарата по влиянию ресвератрола на уровень АЛТ в сыворотке

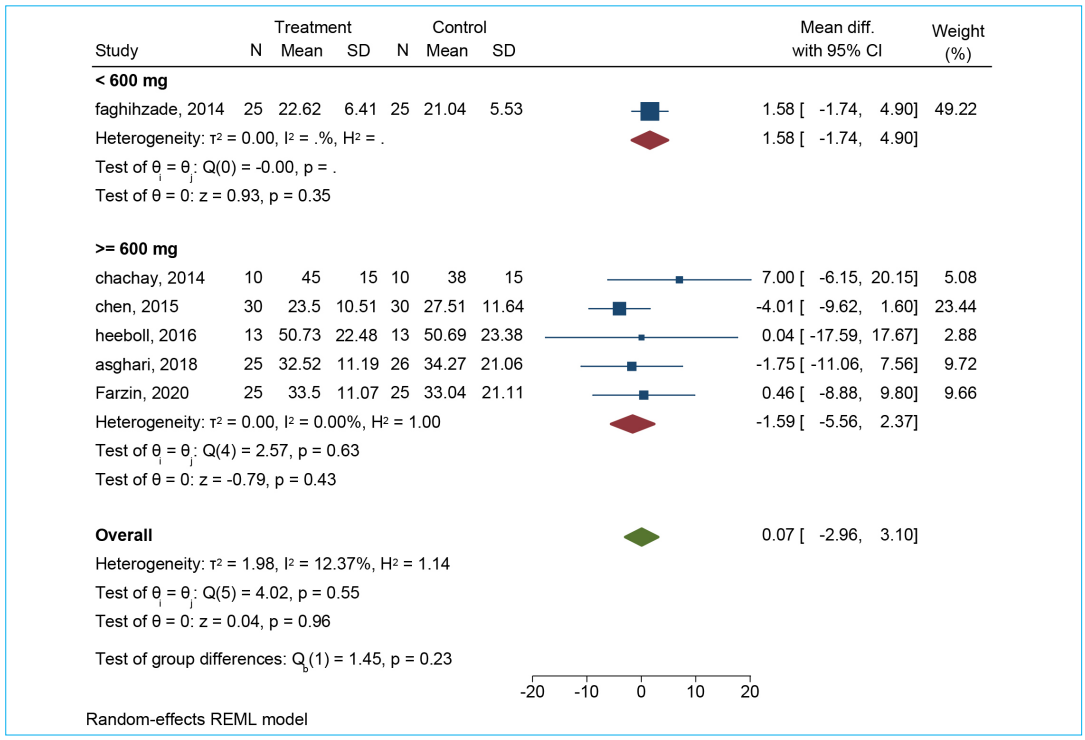

Figure 7. Forest plot for subgroup analysis based on the resveratrol dose for the impact of resveratrol on the serum AST

Рисунок 7. Форест-диаграмма для анализа подгрупп на основе дозы препарата по влиянию ресвератрола на уровень АСТ в сыворотке

Discussion

In this study, the effect of resveratrol on ALT and AST levels was investigated in NAFLD patients. In NAFLD, the level of these two liver enzymes increases due to the dysfunction of hepatocytes and, following the reduction of liver fat density (after therapeutic interventions), the decline of these enzymes is widely considered a sign of the beneficial effect of treatments. This meta-analysis included only RCTs, and there was no time limit for the literature search.

This systematic review and meta-analysis showed that resveratrol supplementation does not affect serum ALT and AST levels in NAFLD patients.

Similarly, no significant effect was observed in the meta-analysis study by M. Darand et al., which investigated the effect of resveratrol on liver enzymes in older adults. However, the subgroup analysis found that the findings might have been influenced by resveratrol dose, study duration, and population health status [1]. On the other hand, we found that neither resveratrol dose nor intervention duration had any significant effect on the serum liver enzymes.

A significant effect was observed in the meta-analysis study by S. Soltani et al. However, the reviewed studies were not limited to NAFLD patients [22]. A systematic review and meta-analysis by S. Wei et al., including five randomized controlled trials, also showed that resveratrol did not affect liver enzymes in NAFLD patients [6].

The meta-analysis study by M. Akbari et al. showed that resveratrol does not significantly affect the level of liver enzymes in patients with metabolic syndrome [23].

M. Darand et al.'s study showed that the effect of resveratrol on liver health might be affected by the age of the participants [1]. Because of limitations in the available data, we could not run a subgroup analysis based on the age range of the patients. Therefore, the effect of age is still in question.

One of the possible reasons for the lack of effect of resveratrol on liver enzymes is the length of the period of taking the supplement. In this study, the subgroup analysis showed that taking resveratrol supplements even in more extended periods doesn't improve the liver enzymes. However, considering the small number of studies in the subgroup analysis, its interpretation should be done cautiously, and more studies with extended periods are needed.

There are still some limitations regarding the interpretation of the results. Most included studies had few participants, and the treatment duration was almost short. More RCTs with more participants and more extended follow-up are needed. Moreover, it should be considered that liver function tests are not the only clinical outcomes of liver health, not the best.

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Information about the authors

Pardis Ebrahimpour — Department of Nutrition and Food Hygiene, Student Research Committee, Hamadan University of Medical Sciences.
Contact information: Pardisebrpour@gmail.com;
6517838636, Hamadan, Shaheed Fahmideh Ave.
ORCID: https://orcid.org/0009-0007-5437-4402

Mohammad Karamian — Department of Nutrition and Food Hygiene, Student Research Committee, Hamadan University of Medical Sciences.
Contact information: mohamedkaramyan2000@gmail.com;
6517838636, Hamadan, Shaheed Fahmideh Ave.
ORCID: https://orcid.org/0009-0005-8298-7121

Amrollah Sharifi* — Department of Nutrition and Food Hygiene, Nutrition Health Research Center, Hamadan University of Medical Sciences.
Contact information: a.sharifi1983@gmail.com;
6517838636, Hamadan, Shaheed Fahmideh Ave.
ORCID: https://orcid.org/0000-0002-3164-0479

Сведения об авторах

Эбрахимпур Пардис — кафедра питания и пищевой гигиены Студенческого исследовательского комитета Хамаданского университета медицинских наук.
Контактная информация: Pardisebrpour@gmail.com;
6517838636, Хамадан, просп. Шахида Фахмиде.
ORCID: https://orcid.org/0009-0007-5437-4402

Карамян Мохаммад — кафедра питания и пищевой гигиены Студенческого исследовательского комитета Хамаданского университета медицинских наук.
Контактная информация: mohamedkaramyan2000@gmail.com;
6517838636, Хамадан, проспект Шахида Фахмиде.
ORCID: https://orcid.org/0009-0005-8298-7121

Шарифи Амролла* — кафедра питания и пищевой гигиены Студенческого исследовательского комитета Хамаданского университета медицинских наук.
Контактная информация: a.sharifi1983@gmail.com;
6517838636, Хамадан, проспект Шахида Фахмиде.
ORCID: https://orcid.org/0000-0002-3164-0479

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* Corresponding author / Автор, ответственный за переписку