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The Association between Dietary Polyphenol and Non-Alcoholic Fatty Liver Disease Risk in Adults: A Systematic Review and Meta-Analysis of Observational Studies

Mahboobe Hosseinikia; MSc[1], Somayeh Saboori; PhD[2], Neda Mousavi; PhD[3], Tooba Bahramfard; MSc[4], Nicola Veronese; MD[5], Mojtaba Yousefi; MSc[1] & Esmaeil Yousefi Rad; PhD[*2]

[1] Department of Nutrition and Food Sciences, Yasuj University of Medical Sciences, Yasuj, Iran; [2] Nutritional Health Research Centre, Department of Nutrition, Lorestan University of Medical Sciences, Khorram-abad, Iran; [3] Zanjan Metabolic Diseases Research Center, Zanjan University of Medical Sciences, Zanjan, Iran; [4] Student Research Committee, Lorestan University of Medical Sciences, Khorram-abad, Iran; [5] Department of Internal Medicine and Geriatrics, Geriatrics Section, University of Palermo, Palermo, Italy.

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SYSTEMATIC REVIEW and META-ANALYSIS

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Corresponding author
esyussefirad2@yahoo.com
Nutritional Health Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran.

Postal code: 6446-14155
Tel: +98 66 33120149

ABSTRACT

Background: Non-alcoholic fatty liver disease **(**NAFLD) is regarded as a global health issue with increasing prevalence worldwide. Polyphenols play a pivotal role in alleviating inflammatory and oxidative stress pathways associated with the pathogenesis of NAFLD, however the literature are still scarce. **Methods:** This systematic review and meta-analysis was designed to investigate the association between dietary polyphenols and the risk of NAFLD with a meta-analysis approach. All observational studies in the online databases of PubMed, Scopus, Web of Science, Embase and Google Scholar up to June 2021 were searched, determining appropriate keywords, to identify relevant articles. Data were summarized using risk ratios (RRs) with 95% confidence intervals (CIs). **Results:** Of the total number of 4144 articles identified in the first phase of the literature search, 6 studies covering 21 arms on polyphenol intake and NAFLD risk containing 9436 participants in the case groups and 19996 participants in the control groups were included in study. The summary effect size (ES) for the risk of NAFLD, comparing the highest with lowest intakes of polyphenol, was 0.80 (95% CI: 0.77-0.83, P<0.0001, I^2 = 0.0%;), indicating a significant inverse association. **Conclusions:** Our results proved that higher dietary intake of polyphenols can reduce the risk of NAFLD. However, due to small number of determined studies, these findings require further investigations to confirm recommendations for intensifying polyphenol intake in the general population.

Keywords: *Polyphenols; Flavonoids; NAFLD; Non-alcoholic fatty liver disease; Meta-analysis*

Introduction

Globally, switching to a diet high in simple carbohydrates and fats combined with low physical activity leads to ectopic fat accumulation in the liver, known as non-alcoholic fatty liver disease (NAFLD) (Chalasani *et al.*, 2018, European Association for the Study of The Liver and

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European Association for the Study of Diabetes, 2016) with a broad spectrum ranging from simple steatosis to hepatocellular carcinoma (Westerouen Van Meeteren *et al.*, 2020). The prevalence of NAFLD is 46% and 17% in the USA and India (Vernon *et al.*, 2011), respectively while it is relatively low in Africa (13%) with a prevalence rate of 31% in the Middle East countries and 32% in South America (Younossi *et al.*, 2016). Insulin resistance, inflammation and oxidative stress are the main underlying involved mechanisms in the disease pathogenesis (Ministrini *et al.*, 2020, Moore *et al.*, 2020). Despite the high prevalence and incidence of NAFLD, currently there is no obvious therapy (Moore *et al.*, 2020) and studies are concentrated on weight loss, physical activity, dietary polyphenols and antioxidants (Mohammadi *et al.*, 2014, Naeini *et al.*, 2021, Shidfar *et al.*, 2019).

Polyphenols are natural components widely distributed in fruits, vegetables, several beverages and cereals and represents the most plentiful antioxidants in the human diet (de Araújo *et al.*, 2021). Anti-obesogenic, anti-diabetic, anti-oxidative, anti-inflammatory, anti-tumorigenic and anti-neurodegenerative roles made therapeutic properties in these compounds (Koch, 2019). It is suggested that polyphenols down regulate the sterol regulatory element-binding protein 1c (SREBP-1c) and de novo lipogenesis, up regulate the peroxisome proliferator activator receptor alpha (PPARα) and fatty acid oxidation, strengthen the antioxidant defense system and neutralize the inflammatory cascades, at the molecular levels (Rodriguez-Ramiro *et al.*, 2016). Observational studies disclosed a reduced risk of NAFLD in participants at the highest ranges of dietary polyphenol intake compared with the lowest levels (Zhong *et al.*, 2021). However, there is no meta-analysis study for assessing the association between different dietary polyphenol intakes and the risk of NAFLD incidence. Therefore, the present systematic review and meta-analysis have been carried out to investigate the relationship between polyphenol consumption and risk of NAFLD based on the existing observational studies.

Materials and Methods

Search strategy and study selection: The present study was accomplished according to MOOSE Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (Brooke *et al.*, 2021) and followed a pre-planned, but unpublished protocol that can be requested by contacting the corresponding author. A comprehensive literature search was performed by two independent qualified investigators, under supervision of experienced health information specialists, in the online databases of PubMed, Scopus, Web of Sciences, Embase and Google Scholar from 1986 up to June 2021. The following keywords in titles, abstracts as well as keywords were applied in the search strategy: ("NAFLD" OR "Non-alcoholic fatty liver disease" OR "fatty liver" OR "liver fat" OR "liver steatosis") AND ("flavonoids" OR "flavonols" OR "flavones" OR "anthocyanidins" OR "flavanones" OR "flavan-3-ols" OR "proanthocyanidins" OR "quercetin" OR "catechin" OR "isoflavones" OR "anthocyanins" OR "resveratrol" OR "polyphenol" OR "apigenin" OR "luteolin" OR "hesperetin" OR "hesperidin" OR "naringenin" OR "kaempferol" OR "tamarixetin" OR "matairesinol" OR "epicatechin" OR "epicatechin gallate" OR "coumestrol" OR "tannin" OR "lignans" OR "phenolic acid"), without any restriction in the time of publications and languages. In addition, the reference lists of the relevant articles were checked to prevent missing any publications. All administered studies were entered into the Endnote software for analysis. Duplicate citations were removed, the titles and abstracts were screened, and eligible studies were reviewed in full by two reviewers.

Inclusion and exclusion criteria: The observational studies with cohort, case-control, and cross-sectional design on adults (≥18 y); determining the intake of total polyphenols and different subclasses as the exposure, and odds of NAFLD, as the outcome variables were included in this meta-analysis. The letters to editor, commentaries, short communications, reviews, ecological, and animal studies, as well as research on children and unpublished papers were excluded.

Data extraction: Data required for each eligible

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study were extracted by two independent investigators (Hosseinikia *M* & Bahramfard *T*), and any disagreements were reconciled by discussion or referral to third reviewer (Saboori S). Any reported ORs or HRs or RRs and corresponding 95% CIs for the association between polyphenol consumption and the risk of NAFLD were extracted from each study. In addition to effect sizes (ESs), the following information were extracted: the first author's name, year of publication, country of origin, demographic characteristics of participants (age range and gender), number of participants, duration of follow-up for prospective studies, methods used for exposure and outcome assessment, and confounding variables adjusted in the statistical analysis. All extracted data were included in a standardized Microsoft Excel.

Data synthesis and statistical analysis: For comparison between the highest *and the* lowest ranges of polyphenol intake, ORs and RRs (with 95% CIs) were used to calculate weighted ORs and RRs. At the first, random effects models were utilized to estimate the pooled effect sizes. Existence of heterogeneity was checked by the Cochran's Q-test and I^2 test. The significant values were considered at I^2 >50% (Mantel and Haenszel, 1959). The fixed-effects model was applied, as there was a low heterogeneity between the assessed studies (Greenland, 1987). Publication bias was investigated using the funnel plot, Egger's, and Begg's regression asymmetry tests (van Enst *et al.*, 2014). A trim-and-fill method was used to detect the effect of probable missing studies on the overall effect (Duval, 2005). Further, we performed a sensitivity analysis using a fixed sample of each excluded study to assess the impact of that study on the overall estimate. (Cooper *et al.*, 2009). The statistical analyzes were performed using STATA version 14.0 (Stata Corporation, College Station, TX, USA). All p-values were for a two-sided test and P-value<0.05 was considered statistically significant.

Quality assessment: **T**he quality of the studies in the current meta-analysis was assessed by two independent authors using the Newcastle Ottawa Scale (NOS), designed for nonrandomized studies (Stang, 2010, Wells *et al.*, 2011). According to this criterion, a maximum of nine points would be considered for each study according to the following parameters: four points for participant's selection, two points for comparison, and three points for the assessment of outcomes. Studies are scored between 7-9 as high quality, 4-6 as high risk, and 0-3 as high risk of bias. (Lo *et al.*, 2014).

Results

Search results and study selection: In our initial search, 4144 articles were identified. After exclusion of duplicate papers and those failed to meet the inclusion criteria, we considered 19 English full-text potentially relevant studies. After full-text review, we excluded 8 additional studies because they regarded intakes of polyphenol rich foods (fruits, vegetables, soy foods, honey, dark chocolate, coffee, mushroom and raw orange) and not polyphenols or flavonoids in specific, as the exposure variable (Kim and Shin, 2020, Loffredo *et al.*, 2017, Loffredo *et al.*, 2016, Mozaffari-Khosravi *et al.*, 2016, Veronese *et al.*, 2018, Xia *et al.*, 2019, Zhang *et al.*, 2020a, Zhang *et al.*, 2020b, Zhang *et al.*, 2021). Three studies assessed the lifestyle characteristics, anti-inflammatory potential of diet, and dietary antioxidant index and risk of NAFLD, and were ultimately excluded (Katsagoni *et al.*, 2017, Tyrovolas *et al.*, 2019, Vahid *et al.*, 2020). Additionally, we excluded the study of Marcelo (Marcelo *et al.*, 2018) in which the relationship between urinary genistein levels and serum alanine aminotransferase levels were investigated. Moreover two identical papers were observed (Salehi-Sahlabadi *et al.*, 2021, Sohouli and Lari, 2020), therefore Salehi-Sahlabadi et al. (Salehi-Sahlabadi *et al.*, 2021) study ,which seems to be more credible, were included. After the above-mentioned exclusions, 6 papers consisting of one paper from cohort study (Zhong *et al.*, 2021), two case-control studies (Nikkhah-Bodaghi *et al.*, 2019, Salehi-Sahlabadi *et al.*, 2021) and three cross-sectional articles (Mazidi *et al.*, 2019, Salomone *et al.*, 2020, Wang *et al.*, 2021) were enrolled for the current meta-analysis. Dietary intake of total polyphenols (n=2) (Nikkhah-Bodaghi *et al.*, 2019,

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Salehi-Sahlabadi *et al.*, 2021), total flavonoids (n=3) (Mazidi *et al.*, 2019, Salehi-Sahlabadi *et al.*, 2021, Zhong *et al.*, 2021), total phenolic acid (n=2) (Salehi-Sahlabadi *et al.*, 2021, Salomone *et al.*, 2020), lignans, stilbenes, hydroxybenzoic acid, hydroxycinnamic acid, flavanones, flavan-3-ols, flavonols, flavones, isoflavones and anthocyanins (n=1) (Zhong *et al.*, 2021), total isoflavones, daidzein, genistein, glycitein (n=1) (Wang *et al.*, 2021) were assessed among included publications. A flow diagram of the study selection is illustrated in **Figure 1**.

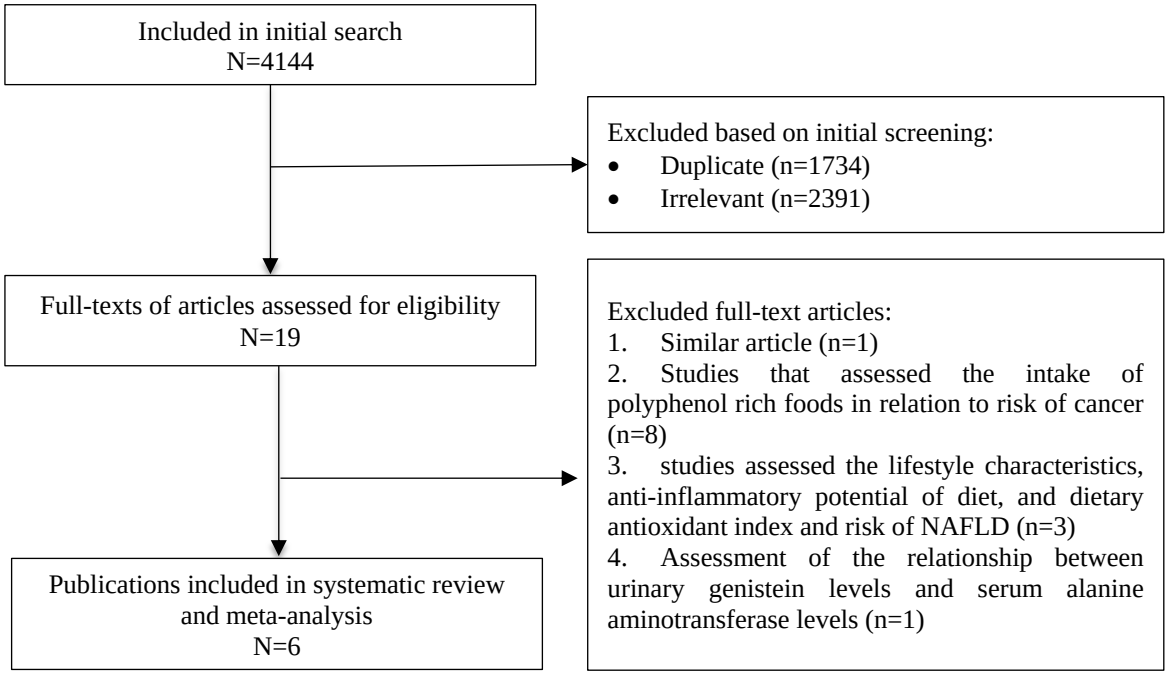

Figure 1. A flow diagram of selection of studies.

Study characteristics and quality assessment: **Table 1** presents the features of the included studies. The total number of participants in these studies ranged from 675 to 17,685, with the age range from 18 to 80 years. In total, 29,432 participants (prospective study=17,685, case-control and cross-sectional studies=11,747) were enrolled in the six publications. All of them included both genders, however one study reported ESs separately for males and females (Nikkhah-Bodaghi *et al.*, 2019). Out of six articles, one paper were from the United States, two papers from Iran, one study in Israel, and two studies were performed in China. Dietary intake of polyphenols were assessed using food frequency questionnaires (FFQs) in five papers (Nikkhah-Bodaghi *et al.*, 2019, Salehi-Sahlabadi *et al.*, 2021, Salomone *et al.*, 2020, Wang *et al.*, 2021, Zhong *et al.*, 2021), and an in-home administered questionnaire in one article (Mazidi *et al.*, 2019). In the case of outcome exposure, three papers assessed NAFLD by ultrasonography (Salehi-Sahlabadi *et al.*, 2021, Salomone *et al.*, 2020, Zhong *et al.*, 2021), one article by self-reporting (Wang *et al.*, 2021), one article by fatty liver index (FLI) (Mazidi *et al.*, 2019) and, one paper by fibro scan (Nikkhah-Bodaghi *et al.*, 2019). All of the included papers were adjusted for a wide range of potential confounders, including gender, age, body mass index, energy intake, smoking, alcohol consumption, and physical activity. In the quality assessment section, the comparability of cases and controls was evaluated and scored (Supplementary file).

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Table 1. Characteristics of the included studies of dietary polyphenol intake and odds of non-alcoholic fatty liver disease (NAFLD).

Author, Year	Country	Study design	Total/ subclasses of polyphenols	Exposure Assessment	Outcome Assessment	Participants (Cases)	Comparison	RR or OR (95% CI)	Adjustments/ match
Zhong, 2021	China	Cohort	Flavanones Flavan-3-ols Flavanols Flavones Isoflavones Anthocyanins Total flavonoids	FFQ	Ultrasonography	2694 (507)	Q5 vs Q1	0.74 (0.57-0.95) 0.74 (0.56-0.96) 0.90 (0.68-1.18) 0.73 (0.56-0.93) 0.79 (0.61-1.02) 0.74 (0.57-0.96) 0.71 (0.54-0.93)	sex, age, body mass index, household income, alcohol drinking status, smoking status, tea drinking status, physical activities, history of using statins, dietary glycemic index, dietary intakes of energy, carbohydrate, protein, fat, fiber, vitamin C, saturated fatty acid, polyunsaturated fatty acids
Nikkhah-Bodaghi, 2019	Iran	Case-control	Polyphenol	FFQ	Fibroscan	803 (196)	Q4 vs. Q1	0.7 (0.3-1.4)	energy (kcal), BMI (kg/m2), age (year), smoking/ age, sex
Salehi-Sahabadi, 2021	Iran	Case-control	Total polyphenols Total flavonoids Total phenolic acids Lignans Stilbenes	FFQ	Ultrasonography	675 (225)	T3 vs. T1	0.69 (0.39-1.23) 0.67 (0.38-1.19) 0.65 (0.37-1.19) 0.44 (0.24-0.78) 0.85 (0.47-1.52)	Age and sex. BMI, physical activity, smoking, SES, dietary intake of energy, and fat
Salomone, 2020	Israel	Cross-sectional	Phenolic acid Hydroxybenzoic acid Hydroxycinnamic acid	FFQ	Ultrasonography	789 (305)	>221 vs.≤221	0.69 (0.49-0.98) 0.72 (0.51-0.99) 0.81 (0.57-1.14)	age, gender, energy intake and BMI, pack-years (calculated among ever smokers, never smokers were considered as zero), SFA intake (% total Kcal), carbohydrate intake (% total Kcal) and sugared sweetened beverages consumption
Mazidi, 2019	US	Cross-sectional	Flavonoid	in-home administered questionnaires	FLI	17685(8029)	T3 vs. T1	0.81 (0.78,0.86)	age, gender, race, alcohol intake, energy intake, dietary intakes of protein, saturated fat, polyunsaturated fat, fiber and carbohydrates, smoking, physical activity, triglyceride, HTN and DM
Wang, 2021	China	Cross-sectional	Total isoflavones Daidzein Genistein Glycitein	FFQ	Self-report	6786 (174)		0.81 (0.66-0.97) 0.81 (0.66-0.97) 0.82 (0.67-0.97) 0.83 (0.68-0.99)	age, gender, drinking, smoking, physical activities level, education status, income and BMI

FFQ; food frequency questionnaire, BMI; body mass index , SES; socioeconomic status, SFA; saturated fatty acids, FLI; fatty liver index, HTN; hypertension, DM; diabetes.

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Meta-Analysis of polyphenol Intake and NAFLD Risk: Six studies with a total of 29,432 participants and 9,436 NAFLD cases were included in this association. The calculated pooled RRs of NAFLD risk for the highest in comparison with the lowest categories of total polyphenols and polyphenol´s subclasses was 0.80 (95% CI: 0.77-0.83, P<0.0001), indicating a significant inverse association (Figure 2). Furthermore, no significant heterogeneity was observed between studies (I^2 = 0.0%; =0.972).

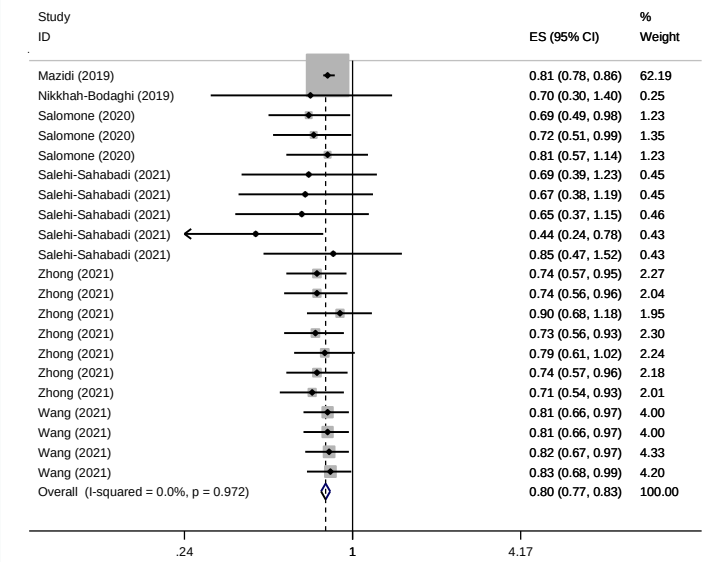

Figure 2. Forest plot for the association between polyphenol intake and risk of NAFLD.

Sensitivity analyses and publication bias: Sensitivity analysis revealed that the overall effect size regarding the association between polyphenol intake and NAFLD was independent from a single study, which indicated that our results were statistically robust. The funnel plot depicted for visually test of publication bias, and the Begg (P=0.043) and Egger's regression tests (P=0.005), exhibited a significant publication bias. However, the application of the trim-and-fill method failed to alter the pooled effect size, demonstrating the results were not affected by the publication bias. Funnel plots are provided in **Figure 3**.

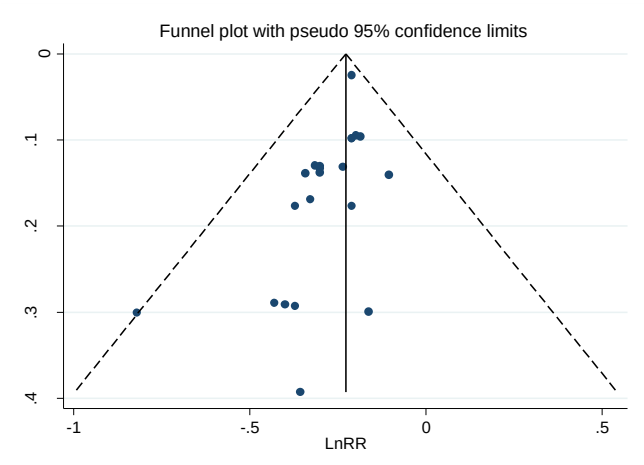

Figure 3. Funnel plots of polyphenol intake and risk of NAFLD.

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Discussion

The present meta-analysis disclosed that the risk of NAFLD, 20% decreased in participants receiving higher dietary polyphenols in comparison with the lower levels. The present systematic review focused on the observational studies assessing polyphenol intake and risk of NAFLD. Particularly, the included investigations measured total polyphenols, total flavonoids, flavanones, flavan-3-ols, flavanols, flavones, total isoflavones, anthocyanins, daidzein, genistein, glycitein, total phenolic acids, lignans and, stilbenes. Four of the six studies had high quality and the results were not affected by the publication bias.

An adverse association was detected between consumption of total polyphenol and polyphenol subgroups with NAFLD risk in this study. Our results are confirmed by previous *in vivo* and *in vitro* studies (Perumal *et al.*, 2019, Sakata *et al.*, 2013, Sun *et al.*, 2016). Clinical trials on the effects of polyphenol supplementation on NAFLD prepared inconclusive results. One randomized clinical trial concluded that resveratrol supplementation (150 mg/day) improve the intrahepatic lipid content in healthy obese volunteers (Timmers *et al.*, 2011). In another study, isoflavone supplementation (280 mg/day) significantly improved the results of FLI in the postmenopausal women (Barsalani *et al.*, 2012). In contrast to these findings, regarding a randomized clinical trial carried out on NAFLD patients, administration of 600 mg resveratrol for 12 weeks did not significantly improved serum antioxidant markers and liver fat content (Asghari *et al.*, 2018). Comparably, in another investigation supplementation with 1500 mg curcumin for 12 weeks did not affect lipid profile, insulin resistance and hepatic steatosis in NAFLD patients (Saadati *et al.*, 2019). These contradictory results could be due to the various designs of the studies, different administered dosages, measurement methods, study duration and sample sizes, baseline stage of the disease and characteristics of patients therefore, studies with normal baseline values failed to report significant results (Asghari *et al.*, 2018). The consequences of animal studies on the effect of quercetin and curcumin, as the dietary polyphenols, on liver enzymes and lipid accumulation are identical (Yang *et al.*, 2019). The underlying mechanisms of the protective effects of polyphenols on NAFLD include alleviating insulin resistance, inflammation and oxidative stress, regulating the intestinal microbiota and mediating microRNAs. Polyphenols inhibit the NF-κB pathway and subsequently suppress inflammation, regulate PPARα and enhance β-oxidation of fatty acids, activate AMPK, reduce SREBP-1c, and thereby inhibiting lipogenesis (Li *et al.*, 2018). Additionally, polyphenols and flavonoids have ROS-reducing effects through the-regulation of manganese superoxide dismutase (MnSOD) and uncoupling protein-2 (UCP2) in hepatocytes (Rafiei *et al.*, 2017).

The present meta-analysis has several advantages. First, this study is the first meta-analysis evaluating the potential association between dietary polyphenol intake and risk of NAFLD. Second, all of the included articles were adjusted for a wide range of potential confounders, including gender, age, body mass index, energy intake, smoking, alcohol consumption, and physical activity. Third, most of the papers gained the high-quality score, and eventually sensitivity analysis indicated that the overall effect size respecting the association between polyphenol intake and NAFLD was independent from a single study. Further, potential limitations should be taken into consideration as interpreting the findings. The numbers of studies entered in the current meta-analysis were limited. Therefore, we forced to pool the results of cross-sectional analysis on cohort and case-control studies. Due to the small number of included studies in this meta-analysis, it appeared improbable to perform a subgroup analysis to explore the potential effect of each polyphenol subgroup intake on NAFLD risk. Therefore, these findings require future investigations to support recommendations to enhance polyphenol intake in general population.

In conclusion, a substantial inverse association between polyphenol intake and risk of NAFLD

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was observed in this meta-analysis, providing further evidence in this regard. However, because of small number of the included studies in this meta-analysis, these findings require future investigations to support recommendations to increase polyphenol intake.

Conflict of interest

None declared

Author Contributions

Somayeh S and Hosseinikia M designed and searched systematically for the study. Hosseinikia H and Yousefi M reviewed and selected the articles and extracted data from articles under the supervision of Yousefi Rad E. Yousefi Rad E performed quality assessment of the studies. Somayeh S performed data analysis and interpretation. Bahramfard T, Mousavi N and Somayeh S drafted the manuscript. Yousefi Rad E and Veronese N revised the article for important intellectual content.

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