



Journal of Nutrition and Food Security

Shahid Sadoughi University of Medical Sciences
School of Public Health
Department of Nutrition



Shahid Sadoughi
University of Medical Sciences
School of Public Health
Nutrition Department

eISSN: 2476-7425

pISSN: 2476-7417

JNFS 2024; 9(2): 361-371

Website: jnfs.ssu.ac.ir

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; MSc¹, Somayeh Saboori; PhD², Neda Mousavi; PhD³, Tooba Bahramfard; MSc⁴, Nicola Veronese; MD⁵, Mojtaba Yousefi; MSc¹ & Esmail 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 Zanzan Metabolic Diseases Research Center, Zanzan University of Medical Sciences, Zanzan, 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.

ARTICLE INFO

SYSTEMATIC REVIEW and META-ANALYSIS

Article history:

Received: 16 Jul 2022

Revised: 26 Sep 2022

Accepted: 26 Sep 2022

*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

This paper should be cited as: Hosseinikia M, Saboori S, Mousavi N, Bahramfard T, Veronese N, Yousefi M, et al. *The Association between Dietary Polyphenol and Non-Alcoholic Fatty Liver Disease Risk in Adults: A Systematic Review and Meta-Analysis of Observational Studies. Journal of Nutrition and Food Security (JNFS), 2024; 9(2): 361-371.*

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 (PPAR α) 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

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 $P\text{-value} < 0.05$ was considered statistically significant.

Quality assessment: The 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,

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**.

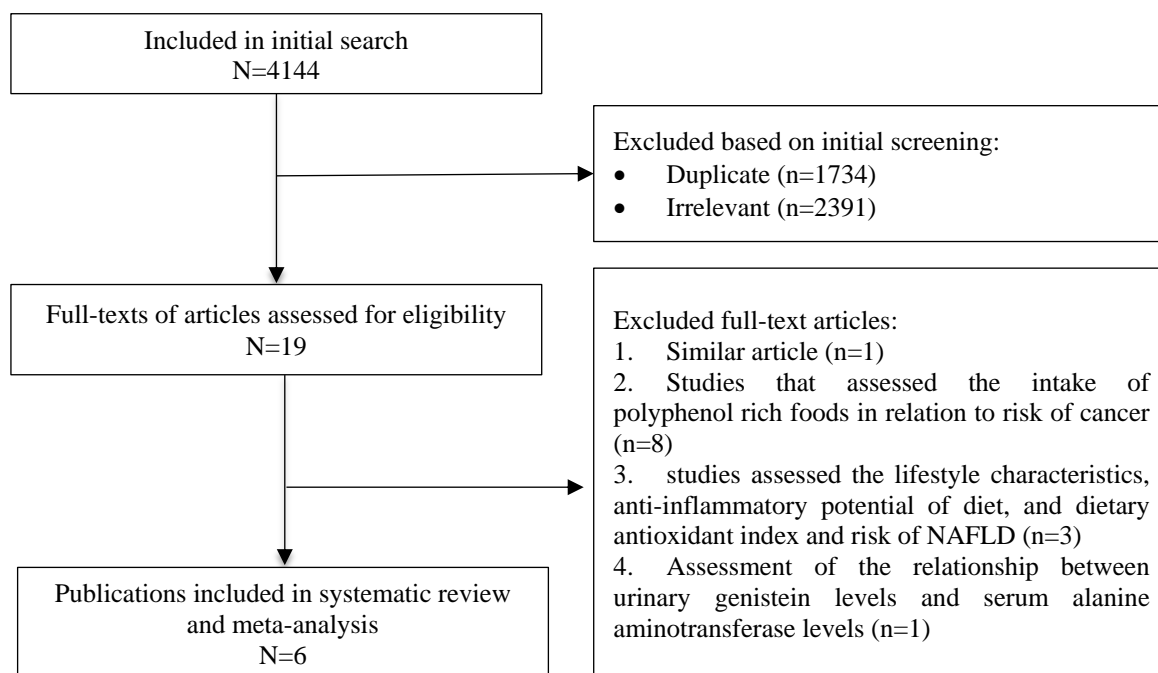


Figure 1. A flow diagram of selection of studies.

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).

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).

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 Phenolic acid | 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) 0.69 (0.49-0.98) | Age and sex. BMI, physical activity, smoking, SES, dietary intake of energy, and fat |
| Salomone, 2020 | Israel | Cross-sectional | Hydroxybenzoic acid Hydroxycinnamic acid | FFQ | Ultrasonography | 789 (305) | >221 vs. ≤221 | 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.

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 ($I^2 = 0.0\%$; $=0.972$).

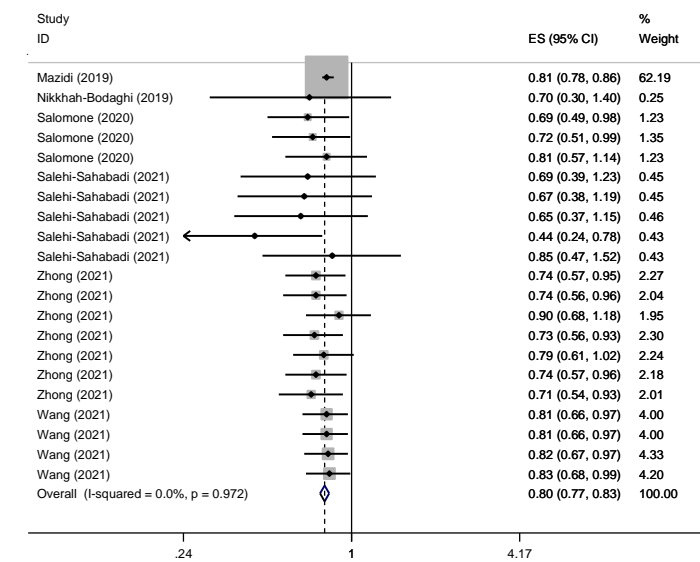


Figure 2. Forest plot for the association between polyphenol intake and risk of NAFLD.

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.

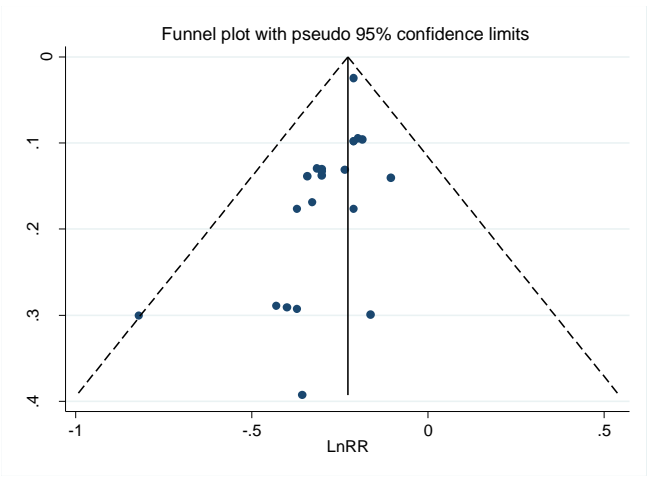


Figure 3. Funnel plots of polyphenol intake and risk of NAFLD.

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- κ B pathway and subsequently suppress inflammation, regulate PPAR α 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

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.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

- Asghari S, et al. 2018. 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. *Advanced pharmaceutical bulletin*. **8** (2): 307-317.
- Barsalani R, Riesco E, Lavoie J & Dionne I 2012. Effect of exercise training and isoflavones on hepatic steatosis in overweight postmenopausal women. *Climacteric*. **16** (1): 88-95.
- Brooke BS, Schwartz TA & Pawlik TM 2021. MOOSE reporting guidelines for meta-analyses of observational studies. *JAMA surgery*. **156** (8): 787-788.
- Chalasani N, et al. 2018. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. **67** (1): 328-357.
- Cooper H, Hedges LV & Valentine J 2009. Handbook of research synthesis and meta-analysis. Russell Sage Foundation.
- de Araújo FF, de Paulo Farias D, Neri-Numa IA & Pastore GM 2021. Polyphenols and their applications: An approach in food chemistry and innovation potential. *Food chemistry*. **338**: 127535.
- Duval S 2005. Publication bias in meta-analysis: Prevention, assessment and adjustments. Hoboken: John Wiley & Sons.
- European Association for the Study of The Liver & European Association for the Study of Diabetes 2016. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *Obesity facts*. **9** (2): 65-90.
- Greenland S 1987. Quantitative methods in the review of epidemiologic literature. *Epidemiologic reviews*. **9** (1): 1-30.
- Katsagoni CN, et al. 2017. Associations between lifestyle characteristics and the presence of nonalcoholic fatty liver disease: a case-control study. *Metabolic syndrome and related disorders*. **15** (2): 72-79.
- Kim S-A & Shin S 2020. Fruit and vegetable consumption and non-alcoholic fatty liver disease among Korean adults: a prospective cohort study. *Journal of epidemiology and community health*. **74** (12): 1035-1042.
- Koch W 2019. Dietary polyphenols—important non-nutrients in the prevention of chronic noncommunicable diseases. A systematic review. *Nutrients*. **11** (5): 1039.
- Li S, et al. 2018. The Potential and Action Mechanism of Polyphenols in the Treatment of Liver Diseases. *Oxidative medicine and cellular longevity*. **2018**: 8394818.
- Lo CK-L, Mertz D & Loeb M 2014. Newcastle-Ottawa Scale: comparing reviewers' to authors' assessments. *BMC medical research methodology*. **14** (1): 1-5.
- Loffredo L, et al. 2017. Effects of dark chocolate on endothelial function in patients with non-

- alcoholic steatohepatitis. *Nutrition, metabolism and cardiovascular diseases*. **28** (2): 143-149.
- Loffredo L, et al.** 2016. Effects of dark chocolate on NOX-2-generated oxidative stress in patients with non-alcoholic steatohepatitis. *Alimentary pharmacology & therapeutics*. **44** (3): 279-286.
- Mantel N & Haenszel W** 1959. Statistical aspects of the analysis of data from retrospective studies of disease. *Journal of the national cancer institute*. **22** (4): 719-748.
- Marcelo C, Warwick M, Marcelo C, Malik M & Qayyum R** 2018. The relationship between urinary genistein levels and serum alanine aminotransferase levels in adults in the USA: National Health and Nutrition Examination Survey 1999-2010. *European journal of gastroenterology & hepatology*. **30** (8): 904-909.
- Mazidi M, Katsiki N & Banach M** 2019. A higher flavonoid intake is associated with less likelihood of nonalcoholic fatty liver disease: results from a multiethnic study. *Journal of nutritional biochemistry*. **65**: 66-71.
- Ministrini S, Montecucco F, Sahebkar A & Carbone F** 2020. Macrophages in the pathophysiology of NAFLD: The role of sex differences. *European journal of clinical investigation*. **50** (6): e13236.
- Mohammadi F, et al.** 2014. Association of cardiometabolic risk factors and hepatic enzymes in a national sample of Iranian children and adolescents: the CASPIAN-III study. *Journal of pediatric gastroenterology and nutrition*. **58** (4): 463-468.
- Moore MP, Cunningham RP, Dashek RJ, Mucinski JM & Rector RS** 2020. A fad too far? dietary strategies for the prevention and treatment of NAFLD. *Obesity*. **28** (10): 1843-1852.
- Mozaffari-Khosravi H, Naghdipour-Biregani A, Zavar-Reza J & Poursoleiman F** 2016. The effects of dark chocolate consumption on oxidative stress and blood pressure in patients with metabolic syndrome: a randomized clinical trial. *Journal of nutrition and food security*. **1** (1): 1-8.
- Naeini F, Namkhah Z, Ostadrahimi A, Tutunchi H & Hosseinzadeh-Attar MJ** 2021. A Comprehensive Systematic Review of the Effects of Naringenin, a Citrus-Derived Flavonoid, on Risk Factors for Nonalcoholic Fatty Liver Disease. *Advances in nutrition*. **12** (2): 413-428.
- Nikkhah-Bodaghi M, Ghanavati M & Hekmatdoost A** 2019. Polyphenol intakes and risk of impaired lipid profile, elevated hepatic enzymes and nonalcoholic fatty liver disease. *Nutrition and food science*. **49** (5): 903-910.
- Perumal DK, Adhimoolam M, Ivan EA & Rajamohammed MA** 2019. Effects of soy isoflavone genistein on lipid profile and hepatic steatosis in high-fat-fed Wistar rats. *National journal of physiology, pharmacy and pharmacology*. **9** (9): 856-861.
- Rafiei H, Omidian K & Bandy B** 2017. Comparison of dietary polyphenols for protection against molecular mechanisms underlying nonalcoholic fatty liver disease in a cell model of steatosis. *Molecular nutrition & food research*. **61** (9): 1600781.
- Rodriguez-Ramiro I, Vauzour D & Miniñane A** 2016. Polyphenols and non-alcoholic fatty liver disease: impact and mechanisms. *Proceedings of the nutrition society*. **75** (1): 47-60.
- Saadati S, et al.** 2019. The effects of curcumin supplementation on liver enzymes, lipid profile, glucose homeostasis, and hepatic steatosis and fibrosis in patients with non-alcoholic fatty liver disease. *European journal of clinical nutrition*. **73** (3): 441-449.
- Sakata R, Nakamura T, Torimura T, Ueno T & Sata M** 2013. Green tea with high-density catechins improves liver function and fat infiltration in non-alcoholic fatty liver disease (NAFLD) patients: a double-blind placebo-controlled study. *International journal of molecular medicine*. **32** (5): 989-994.
- Salehi-Sahlabadi A, et al.** 2021. Dietary polyphenols and the odds of non-alcoholic fatty liver disease: A case-control study. *Clinical nutrition ESPEN*. **41**: 429-435.
- Salomone F, et al.** 2020. Higher phenolic acid intake independently associates with lower

- prevalence of insulin resistance and non-alcoholic fatty liver disease. *JHEP reports*. **2** (2): 100069.
- Shidfar F, et al.** 2019. Reduction of some atherogenic indices in patients with non-alcoholic fatty liver by vitamin D and calcium co-supplementation: a double blind randomized controlled clinical trial. *Iranian journal of pharmaceutical research*. **18** (1): 496.
- Sohouli MH & Lari A** 2020. The Association between Polyphenols Intake and Odds of Non-Alcoholic Fatty Liver Disease (NAFLD) among Adult Population. *International journal of nutrition sciences*. **5** (3): 122-129.
- Stang A** 2010. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European journal of epidemiology*. **25** (9): 603-605.
- Sun J, et al.** 2016. Flaxseed lignans alleviate high fat diet-induced hepatic steatosis and insulin resistance in mice: Potential involvement of AMP-activated protein kinase. *Journal of functional foods*. **24**: 482-491.
- Timmers S, et al.** 2011. Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. *Cell metabolism*. **14** (5): 612-622.
- Tyrovoulas S, et al.** 2019. The anti-inflammatory potential of diet and nonalcoholic fatty liver disease: the ATTICA study. *Therapeutic advances in gastroenterology*. **12**.
- Vahid F, Rahmani D & Hekmatdoost A** 2020. The association between dietary antioxidant index (DAI) and nonalcoholic fatty liver disease (NAFLD) onset; new findings from an incident case-control study. *Clinical nutrition ESPEN*. **41**: 360-364.
- van Enst WA, Ochodo E, Scholten RJ, Hooft L & Leeftang MM** 2014. Investigation of publication bias in meta-analyses of diagnostic test accuracy: a meta-epidemiological study. *BMC medical research methodology*. **14** (1): 1-11.
- Vernon G, Baranova A & Younossi ZM** 2011. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Alimentary pharmacology & therapeutics*. **34** (3): 274-285.
- Veronese N, et al.** 2018. Coffee Intake and Liver Steatosis: A Population Study in a Mediterranean Area. *Nutrients*. **10** (1): 89.
- Wang X, et al.** 2021. Dietary isoflavones intake is inversely associated with non-alcoholic fatty liver disease, hyperlipidaemia and hypertension. *International journal of food sciences and nutrition*. **73** (1): 60-70.
- Wells G, et al.** 2011. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
- Westerouen Van Meeteren MJ, Drenth JP & Tjwa ET** 2020. Elafibranor: a potential drug for the treatment of nonalcoholic steatohepatitis (NASH). *Expert opinion on investigational drugs*. **29** (2): 117-123.
- Xia Y, et al.** 2019. Raw orange intake is associated with higher prevalence of non-alcoholic fatty liver disease in an adult population. *Nutrition (Burbank, Los Angeles County, Calif.)*. **60**: 252-260.
- Yang H, et al.** 2019. Quercetin improves nonalcoholic fatty liver by ameliorating inflammation, oxidative stress, and lipid metabolism in db/db mice. *Phytotherapy research*. **33** (12): 3140-3152.
- Younossi ZM, et al.** 2016. Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*. **64** (1): 73-84.
- Zhang S, et al.** 2020a. Association between edible mushroom intake and the prevalence of newly diagnosed non-alcoholic fatty liver disease: results from the Tianjin Chronic Low-Grade Systemic Inflammation and Health Cohort Study in China. *British journal of nutrition*. **123** (1): 104-112.
- Zhang S, et al.** 2020b. Soy Food Intake Is Inversely Associated with Newly Diagnosed Nonalcoholic Fatty Liver Disease in the TCLSIH

Cohort Study. *Journal of nutrition*. **150** (12): 3280-3287.

Zhang S, et al. 2021. Association between consumption frequency of honey and non-alcoholic fatty liver disease: results from a cross-sectional analysis based on the Tianjin Chronic Low-grade Systemic Inflammation and Health

(TCLSIH) Cohort Study. *British journal of nutrition*. **125** (6): 712-720.

Zhong QW, et al. 2021. Higher flavonoid intake is associated with a lower progression risk of non-alcoholic fatty liver disease in adults: a prospective study. *British journal of nutrition*. **125** (4): 460-470.