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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

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#### ARTICLE INFO

## SYSTEMATIC REVIEW and META-ANALYSIS

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#### **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., Anti-obesogenic, anti-diabetic, 2021). 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 (PPARa) 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 determining the intake of total polyphenols and different subclasses as the exposure, and odds of NAFLD, as the outcome variables were included in meta-analysis. The letters to 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

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 followup 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<sup>2</sup> test. The significant values were considered at I<sup>2</sup> >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: 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 abovementioned 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 crosssectional 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**.

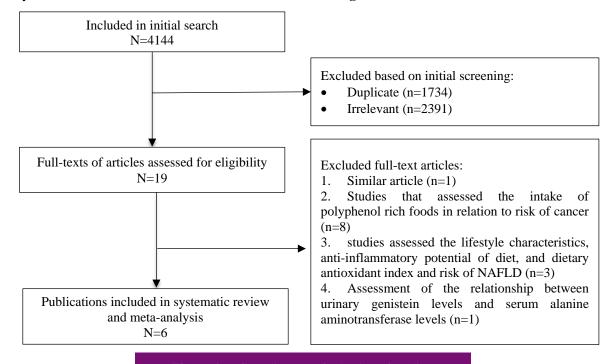


Figure 1. A flow diagram of selection of studies.

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).

**Table 1.** Characteristics of the included studies of dietary polyphenol intake and odds of non-alcoholic fatty liver disease (NAFLD). Adjustments/ match Participants (Cases) Exposure Assessment Outcome Assessment Comparison Total/ subclasses of polyphenols C G Country Study design ة % Flavanones 0.74 (0.57-0.95) sex, age, body mass index, household income, Flavan-3-ols 0.74 (0.56-0.96) alcohol drinking status, smoking status, tea drinking Flavanols 0.90 (0.68-1.18) status, physical activities, history of using statins, Zhong, 2021 China Cohort Flavones **FFQ** Ultrasonography 2694 (507) Q5 vs Q1 0.73 (0.56-0.93) dietary glycemic index, dietary intakes of energy, 0.79 (0.61-1.02) carbohydrate, protein, fat, fiber, vitamin C, saturated Isoflavones 0.74 (0.57-0.96) Anthocyanins fatty acid, polyunsaturated fatty acids Total flavonoids 0.71 (0.54-0.93) Nikkhahenergy (kcal), BMI (kg/m2), age (year), smoking/ Case-**FFO** Bodaghi, Iran Polyphenol Fibroscan 803 (196) O4 vs. O1 0.7(0.3-1.4)age, sex control 2019 Total polyphenols 0.69 (0.39-1.23) Age and sex. BMI, physical activity, smoking, SES, Total flavonoids 0.67 (0.38-1.19) dietary intake of energy, and fat Salehi-Case-T3 vs. T1 Sahabadi, Iran Total phenolic acids FFO Ultrasonography 675 (225) 0.65 (0.37-1.19) control 2021 Lignans 0.44 (0.24-0.78) Stilbenes 0.85 (0.47-1.52) 0.69 (0.49-0.98) Phenolic acid age, gender, energy intake and BMI, pack-years (calculated among ever smokers, never smokers 0.72 (0.51-0.99) Hydroxybenzoic acid Salomone, Crosswere considered as Israel FFQ Ultrasonography 789 (305) >221 vs. \( \le 221 2020 sectional zero), SFA intake (% total Kcal), carbohydrate Hydroxycinnamic acid 0.81 (0.57-1.14) intake (% total Kcal) and sugared sweetened beverages consumption age, gender, race, alcohol intake, in-home energy intake, dietary intakes of administere protein, saturated fat, Cross-Mazidi, 2019 US Flavonoid d FLI 17685(8029) T3 vs. T1 0.81 (0.78, 0.86) polyunsaturated fat, fiber and sectional questionnai carbohydrates, smoking, physical res activity, triglyceride, HTN and DM Total isoflavones 0.81 (0.66-0.97) age, gender, drinking, smoking, physical activities Cross-Daidzein 0.81 (0.66-0.97) level, education status, income and BMI China Wang, 2021 FFQ Self-report 6786 (174) sectional Genistein 0.82 (0.67-0.97)

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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0.83 (0.68-0.99)

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).

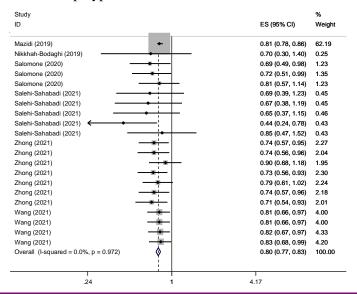


Figure 2. Forest plot for the association between polyphenol intake and risk of NAFLD.

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**.

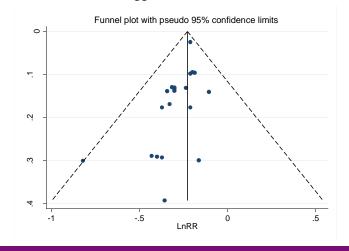


Figure 3. Funnel plots of polyphenol intake and risk of NAFLD.

#### **Discussion**

The present meta-analysis disclosed that the risk of NAFLD, 20% decreased in participants higher dietary polyphenols receiving 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 concluded trial 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, 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 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).

meta-analysis present The has advantages. First, this study is the first metaanalysis 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 metaanalysis, 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 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.

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