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ORIGINAL ARTICLE

The Association between Polyphenols Intake and Odds of Non-Alcoholic Fatty Liver Disease (NAFLD) among Adult Population

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ABSTRACT

Background: Insulin resistance, diabetes, visceral fat mass, obesity, dyslipidemia and metabolic syndrome are the major risk factors in relation to non-alcoholic fatty liver disease (NAFLD). This aim of this study was to determine any relationship between risk of NAFLD and the dietary polyphenols.

Methods: In this case-control study, totally, 225 newly diagnosed NAFLD patients and 450 controls aged 20-60 years were enrolled. The matching food consumption data and the Food frequency questionnaire with the phenol-explorer database were used for dietary polyphenol intake. Logistic regression models were utilized to express confidence intervals (CIs) and odds ratios (ORs).

Results: NAFLD patients revealed a higher body mass index (BMI), were more smokers and with less physical activity compared to the control group. No significant difference was visible between the two groups in dietary intake of various polyphenol types. After adjustment for potentials confounders, participants who were in the highest tertile of total flavonoids (OR=0.65, 95%CI=0.44-0.98) and total phenolic acids (OR=0.63, 95% CI=0.42-0.94), no association was observed between lower risk of NAFLD and the lowest tertile. The risk of NAFLD was 66% lower (OR=0.44, CI=0.24-0.78, P=0.006) among participants who were in the highest tertile of lignans intake in comparison to the lowest tertile.

Conclusion: Our study showed that high intake of lignans lowered the odds of NAFLD. We strongly recommend that the concepts reported in this study are needed to be evaluated in future longitudinal researches.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) also presented as hepatic steatosis is a disorder in absence of alcohol abuse characterized by liver fat deposition (1). NAFLD covers a spectrum of liver diseases ranged from a simple hepatic steatosis to non-alcoholic steatohepatitis (NASH) defined by hepatocellular injuries and inflammation (2). In the last decades, NAFLD has increasingly attracted attention by *researchers*, clinicians and health policy-makers (3). The worldwide prevalence of NAFLD was estimated to range from 20% to 30% (4).

Insulin resistance, diabetes, visceral fat mass, dyslipidemia, obesity, and metabolic syndrome are the important risk factors in relation to NAFLD. The global opportunities for NAFLD diagnosis has resulted in a high prevalence of sedentary life style and with an excess of caloric consumption (4). So the common management of NAFLD is consisted of lifestyle counseling to reach a gradual weight decline by energy restriction and an increase in physical activity resulting in an improvement in serum liver enzymes (5).

In addition to total energy intake, the diet composition can also influence the metabolic functions (6). Some recent studies recommended the consumption of polyphenol-rich diets for prevention and treatment of chronic diseases such as cardiovascular diseases and NAFLD (7-9). Polyphenols have bioactive compounds consisted of several different antioxidants illustrated not to be necessary for human body, but they are considered as health promoting constituents. Fruits, vegetables, and beverages such as tea, coffee, red grape, fruit juices and dark chocolate were recognized as important sources for these hydrosoluble ingredients (7, 10).

Some of the more well-known activities include anti-inflammatory, antioxidant, anti-carcinogenic, anti-allergic, anti-viral and anti-microbial effects (11). Based on literature, only in one previous case-control study undertaken on Iranian adults, total polyphenol intake was evaluated with the odds of NAFLD that demonstrated no significant association (12). Also, limited experimental or epidemiologic studies have investigated the protective effect of polyphenols in NAFLD (13, 14). However, most of studies concentrated on some specific classes of flavonoids and polyphenols; while, assessing the intake of polyphenol subclasses was less investigated (14); and, there is limited data on other subclasses, even though they may be of equal importance. Regarding the limited available data on correlation between polyphenol intake, its subclasses and the NAFLD, this study determined any correlation between dietary intake of total polyphenol and it subclasses with the risk of NAFLD among adult population.

Materials and Methods

This study was performed as a case-control study that was approved in institution ethics committee and human rights were respected based on Helsinki Declaration. A written consent letter was provided from each patient. Totally, 225 newly diagnosed NAFLD patients and 450 controls aged 20-60 years in Tehran, Iran were enrolled in this study. NAFLD diagnosis was based on absence of any alcohol intake, chronic elevation of liver enzymes, an ultrasonography liver scan confirming NAFLD (Grade II and III) and exclusion of hepatic diseases with other etiologies. The patients in the case group were new ones that did not receive any treatment before the study. Healthy individuals were considered as control group confirmed by laboratory test results and the liver sonography findings (denoting to the absence of any stages of hepatic steatosis).

Also, the control group was chosen from patients referring to other wards of the hospital such as otolaryngology, maxillofacial surgery, orthopedics and ophthalmology who were not confirmed for NAFLD using common diagnostic methods and also lack of history of alcohol intake less than 10 mg/day in women and less than 20 mg/day in men. Case and control patients were matched for gender and age. Information about enzymes levels and demographic variables were undertaken completing general information questionnaire.

Also, the liver enzymes were checked again following referring to the hospital. Then, to complete data on dietary intake and other information, the patients were invited to the research center on a scheduled date. Participants with a history of certain diseases (cardiovascular disease, myocardial infarction, stroke, diabetes, cancer, viral hepatitis, Wilson's disease and autoimmune disorders of the liver) were excluded from the study. Also, pregnant women and lactating mothers and subjects with an arbitrary special diet were excluded. In our study, the nutritionists interviewed and all questions were responded completely by the patients.

Validated 168-item semi-quantitative food frequency questionnaire (FFQ) was used to assess dietary intake (15). The FFQ compromised several Iranian foods with standard serving sizes. The frequency for consumption of each food was categorized to 9 divisions. Participants were requested to declare their average dietary intake during the previous year by selecting one of the following choices: never or less than once a month, 3-4 times per month, once a week, 2-4 times per week, 5-6 times per week, once daily, 2-3 times per day, 4-5 times per day, and 6 or more times a day. Portion size of each food was converted into grams by standard Iranian Household Measures (16). Daily nutrient intake for each participant was calculated using national nutrient databank of the United States Department of Agriculture's (USDA) (17). Finally, the frequency of each food consumed was converted into daily intake. The nutrient composition for all foods was determined applying modified nutritionist IV software.

Dietary intake of polyphenols were calculated using an updated version of phenol explorer database (www.phenol-explorer.eu) consisted of 501 polyphenols classified in 6 classes and 31 sub-classes and also data on the effect of food processing on the polyphenol content (18). We measured the data of total polyphenols and its main subgroups included phenolic acids, lignans, stilbenes polyphenols and flavonoids from 80 food items. The predominant subclasses of flavonoids including flavanols, flavones, flavanones, and anthocyanidins; and also phenolic acids including hydroxibenzoic acids, and hydroxicinamic acids were measured.

The total polyphenols mostly calculated using Folin assay and when not available, we summed up the polyphenol subclasses as total polyphenols. For flavonoids and phenolic acids, we calculated based on chromatography after hydrolysis if available, and for other flavonoids subclasses such as anthocyanins which were analyzed by pH differential method; we added their amount to other flavonoids. Stilbenes were computed using chromatography method and lignans were measured by chromatography after hydrolysis. For all calculations, we considered the processes of food preparation such as cooking, frying, and other methods and used the retention factor reported in the "phenol explorer database". By multiplying the daily consumption of each food by the polyphenol content, the polyphenols were determined.

A trained dietician evaluated anthropometric assessments. A standard digital scale (Seca, Germany), was used to determine the weight, while participants used minimum clothes in absence of any shoes and was recorded to the nearest 100 g. A mounted tape was used to assess the height in a standing relaxed shoulder position in absence of any shoes to the nearest 0.5 cm. Body mass index (BMI) was measured as weight (kg) divided by height in square meters (m^2).

The subjects were requested to respond demographic and socioeconomic questions including age, the status of their educational level, job, smoking, having home, home type, any foreign travel, the amount of income and their diseases history. Socioeconomic status (SES) was clarified using the three variables of education (academic and non-academic education), family size (≤4, >4 subjects), and acquisition (house ownership or not). To compute SES score, if subjects had family members of ≤4, owned a house or had academic education al level, they were given a score of 1. If participants had non-academic educational level, had family members of >4, or leasehold property, they were given a score of 0. Then, SES score was calculated by summing the assigned scores (maximum score of 3 to minimum SES score of 0). The score 3 was regarded as high SES and scores 0, 1, and 2 were considered as low and moderate SES (19).

Statistical analysis was done by Statistical Package Software for Social Science (version 21, SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov's test and histogram chart were used to test the normality of the data. Dietary intake and baseline characteristics were presented as mean±SD or median (25-75 interquartile range) for quantitative variables, and number and percentages for qualitative parameters. Comparison of the data was performed between the two groups using Chi Square and independent sample t-test for categorical and continuous variables, respectively.

Dietary polyphenol subclasses were divided into tertiles according to their intakes in the control subjects. The association between the risk of NAFLD and dietary polyphenols and its subclasses was investigated using logistic regression. Analysis was adjusted for potential confounders including sex, age, physical activity, BMI, SES, smoking, and dietary intake of fat and energy. The odds ratio (OR) with 95% confidence interval (CI) of NAFLD across tertiles of polyphenols intake was presented. A P value ≤0.05 was considered statistically significant.

Results

General information and dietary intakes of all subjects were presented in Table 1. No significant difference was visible between the two study groups regarding sex, age and SES (P>0.05). However, NAFLD patients were more smokers, had a higher BMI, and had lower physical activity in comparison to the control group (P<0.05). Also, NAFLD patients had higher dietary intake of refined grains, high fat dairy products, calorie, and red and processed meat (P<0.05); whereas, the intake of vegetables was less than the controls (P<0.05). No significant difference was noted between the two groups regarding the dietary intake of carbohydrate, protein, fat, fiber, whole grains, fruits, nuts and legumes (P>0.05).

Table 2 shows dietary intake of polyphenols and its subclasses between all groups. No significant differences were seen between the two study groups in dietary intake of various polyphenol types (P>0.05). The correlation between the risk of NAFLD and dietary polyphenols was demonstrated in Table 3. Based on multivariate logistic regression analysis after adjustment for age and sex, it was demonstrated that participants who were in the highest tertile of total phenolic acids (OR=0.63, 95%CI=0.42-0.94) and total flavonoids (OR=0.65, 95%CI=0.44-0.98) had lower risk of NAFLD when compared with the lowest tertile. The association between the risk

Table 1: General characteristics and dietary intake among study groups.

Variables	Controls (n=450)	NAFLD (n=225)	P value*
Age (years)	37.8±8.9	38.6±8.7	0.293
Male, n (%)	233 (51.8)	125 (55.6)	0.354
BMI (Kg/m^2)	25.0±3.0	30.5±4.0	<0.001
Smoking, n (%)	12 (2.7)	16 (7.1)	0.006
Physical activity (MET/min/week)	1590±949	1119±616	<0.001
High SES, n (%)	86 (19.1)	56 (24.9)	0.102
Dietary intake			
Energy intake (Kcal/d)	2227±645	2369±621	0.006
Carbohydrate (% of energy)	57.3±6.9	57.2±7.6	0.874
Protein (% of energy)	13.6±2.2	13.5±2.5	0.799
Fat (% of energy)	31.6±6.6	31.4±7.5	0.830
Fiber (g/1000 Kcal)	15.8±6.4	16.7±8.3	0.154
Whole grains (g/day)	53.8 (25.1-112.8)	64.0 (30.7-115.3)	0.711
Refined grains (g/day)	311±149	375±196	<0.001
High fat dairy products (g/d)	82.6 (39.9-157.5)	238.1 (112.6-326.8)	<0.001
Fruits(g/day)	318±228	327±227	0.628
Vegetables(g/day)	302±148	262±138	0.001
Nuts and legume (g/d)	15.7 (9.1-26.7)	14.9 (8.9-28.5)	0.596
Red and process meat(g/day)	21.3±13.7	26.4±17.8	0.001

Data were presented as mean±SD or median (25-75 interquartile range) for continues variables, and number and percentages for categorical variables. *Independent sample t test and Chi Square were used for continuous and categorical variables, respectively. NAFLD: Non Alcoholic Fatty Liver Patients, SES: socioeconomic status, BMI: body mass index, MET: metabolic equivalent

Table 2: Dietary intake of polyphenols between study groups.

Polyphenols	Controls (n=450)	NAFLD (n=225)	*p* value*
Total polyphenols (mg/1000 kcal/day)	849±344	812±306	0.154
Lignans (mg/1000 kcal/day)	2.84±1.75	2.74±1.75	0.487
Stilbenes (mg/1000 kcal/day)	0.01 (0.00-0.04)	0.01 (0.00-0.04)	0.571
Total flavonoids (mg/1000 kcal/day)	301±195	282±193	0.236
Flavonoids subclasses			
Flavonols (mg/1000 kcal/day)	231±173	215±175	0.264
Flavanols (mg/1000 kcal/day)	37.2±21.3	35.2±19.3	0.227
Flavanones (mg/1000 kcal/day)	20.0±15.8	19.5±16.6	0.729
Flavones (mg/1000 kcal/day)	1.21±0.81	1.15±0.85	0.345
Anthocyanins (mg/1000 kcal/day)	6.4 (3.2-13.0)	6.1 (3.0-12.9)	0.530
Total phenolic acids (mg/1000 kcal/day)	95.0±50.0	90.8±50.9	0.308
Phenolic acids subclasses			
Hydroxibenzoic acids (mg/1000 kcal/day)	53.8±37.4	50.1±37.6	0.233
Hydroxicinamic acids (mg/1000 kcal/day)	40.9±26.1	40.5±30.2	0.841

*The differences between groups were checked using independent sample t-test. NAFLD: Non Alcoholic Fatty Liver Patients

of NAFLD and total flavonoids disappeared after additional adjustment for physical activity, SES, BMI, smoking, dietary fat and energy intake (OR=0.67, 95%CI=0.38-1.19). The risk of NAFLD was 66% less than participants (OR=0.44, 95%CI=0.24-0.78, P=0.006) who were in the highest tertile of lignans intake in comparison to the lowest tertile.

Discussion

The intake of total polyphenol and its subclasses (phenolic acid, flavonoid, lignan and stilbene intakes) showed relationship with the odds of NAFLD among Iranian adults assessed in the present case-control study. Although in age and sex adjusted model, higher dietary intake of total flavonoids and phenolic acids showed protective association with NAFLD; in the final adjusted model, only higher dietary lignans was related with lower odds of NAFLD. In our study, no significant association was seen between total polyphenols and

Table 3: Odds ratios (ORs) and 95% confidence intervals (CIs) for NAFLD based on tertiles dietary polyphenols.

Polyphenols classes	Tertiles of dietary intake			P for trend
	T1	T2	T3	
Total polyphenols				
NAFLD/Control	84/150	79/150	62/150	
Model 1*	1.00 (Ref)	0.90 (0.61-1.32)	0.69 (0.46-1.04)	0.074
Model 2†	1.00 (Ref)	0.99 (0.57-1.71)	0.69 (0.39-1.23)	0.194
Total flavonoids				
NAFLD/Control	90/150	72/150	63/150	
Model 1	1.00 (Ref)	0.79 (0.54-1.17)	0.65 (0.44-0.98)	0.043
Model 2	1.00 (Ref)	0.98 (0.57-1.69)	0.67 (0.38-1.19)	0.164
Total phenolic acids				
NAFLD/Control	90/150	75/150	60/150	
Model 1	1.00 (Ref)	0.81 (0.55-1.19)	0.63 (0.42-0.94)	0.026
Model 2	1.00 (Ref)	1.02 (0.59-1.75)	0.65 (0.37-1.15)	0.121
Lignans				
NAFLD/Control	89/149	68/150	68/151	
Model 1	1.00 (Ref)	0.75 (0.51-1.11)	0.75 (0.50-1.11)	0.171
Model 2	1.00 (Ref)	0.65 (0.38-1.11)	0.44 (0.24-0.78)	0.006
Stilbenes				
NAFLD/Control	73/143	77/156	75/151	
Model 1	1.00 (Ref)	0.95 (0.64-1.41)	0.95 (0.64-1.42)	0.868
Model 2	1.00 (Ref)	0.80 (0.46-1.39)	0.85 (0.47-1.52)	0.727

*Model 1: adjusted for age and sex. †Model 2: Additionally adjusted for BMI, physical activity, smoking, SES, dietary intake of energy, and fat. NAFLD: Non Alcoholic Fatty Liver Patients, T: Tertile

other subclasses with the odds of NAFLD.

Polyphenols are remarkably recognized as hydrosoluble antioxidant compounds found in fruits, vegetables, beverages and dark chocolates (20). Although dietary polyphenols were investigated for several chronic diseases such as diabetes, metabolic syndrome (MetS) and cardiovascular diseases (CVD), there were few studies in relation to the NAFLD patients (10, 20-24). To our knowledge, only in one previous case-control study among Iranian adults, total polyphenol intake was assessed regarding the odds of NAFLD and was in line with our study showing no significant association (12).

Findings about the association between polyphenols and it subclasses with chronic diseases such as diabetes, CVDs, and MetS are controversial. In two previous cohort studies in patients with MetS, no significant relationship was observed between intake of flavonoids and total polyphenols with MetS components (23, 24). Also in cohort studies, same results were observed in diabetic and CVD patients (10, 20, 25). However, results from the Health Professionals' Follow-up Study, the US cohorts of Nurses' Health Study and the European Prospective Investigation into Cancer and Nutrition (EPIC) denoted to a reduced risk of diabetes for higher dietary intakes of flavonoids (26, 27).

However, the beneficial effects of polyphenols on liver steatosis and its pathogenesis and clinical symptoms were presented in several *in vitro* evidences, and clinical trials (9, 28, 29). also, In the *in vivo* and *in vitro* models of NAFLD, the beneficial effects of flavonoids and its component were indicated via regulation of several genes which contributed to lipid accumulation, inflammation, fibrosis, insulin resistance or oxidative stress (30). Nevertheless, in this study, the protective correlation between total flavonoids and phenolic acids which observed in age and sex adjusted models, was not confirmed after adjusting the main risk factors of NAFLD including physical activity, SES, BMI, smoking, and energy and fat intakes (31).

Also, no significant association was found regarding risk of NAFLD with hydroxybenzoic acids and hydroxycinnamic acids among flavones, flavanols, flavanones, phenolic acids, and anthocyanins. It was shown that hydroxycinnmic acids found in coffee, had beneficial effects against cardiovascular and metabolic diseases (31). It may be justified by some reasons such as big difference of body mass and lifestyle factors between case and controls, besides of no differences in dietary polyphenols between the two groups. To our knowledge, stilbenes were not previously investigated for NAFLD and showed poor intake in the present study that was not expected to be an effective nutrient to be associated with NAFLD; however, resveratrol as a component of stilbenes revealed beneficial effects for NAFLD in clinical trials (32).

Our results demonsrated that dietary lignans

had protective correlation with the odds of NAFLD. Based on data in literature, no published study has investigated the associations between the risk of NAFLD and lignans. Consistent with our findings, two cohort studies in Iranian and Polish adults found an inverse association between waist circumference and dietary lignans (23, 24). However, in other previous studies, lignan intake illustrated no association between other diseases and metabolic factors (10, 20, 22).

The main dietary sources of lignin intake among our participants were breads based on wheat flour, legumes and almonds, olive oil, vegetables including cucumber, cabbages, pumpkin and garlic and also fruits consisted of orang family, apricot and dried peach and figs (22). These foods formed major part of a healthy dietary pattern and are related with lower risk of NAFLD (10, 22). The invers association between the risk of NAFLD and garlic has been identified in a recent study too (33).

Also, sesame, a food source of lignin showed lipid lowering and fatty acid oxidation inducer effects in experimental and trial studies (34). One of the richest sources of lignans is flaxseed showing that its supplementation could significantly reduce the liver enzymes, insulin resistance and hepatic fibrosis and steatosis in NAFLD (35, 36). However, such controversies in the findings can be explained by differences in probable problems in measurements and the methods for measuring polyphenols (37).

Also, the variations in polyphenol contents in relation to processing including cooking, freezing, storing, and canning could be other reasons (38). Furthermore, the differences in the absorption of polyphenols subgroups can describe the various bioactivities and contrasting results among several studies (39). On the other hand, the kind, the source and the amount might be different in many regions (40). Moreover, dietary intake of polyphenols of individuals in various regions was dependent on consumption of certain foods rich in polyphenols, such as nuts and olive oil (21).

These differences noted for food sources and polyphenol bioavailability could partially describe the variation in risk of chronic diseases among various countries. The present study had some strengths; using a valid nutrition questionnaire and having all our data filled out by a trained expert. Furthermore, the statistical analysis was controlled for many potential confounding factors. The first limitation of our study was based on the case-control design of the study that could not explain the causal relationships. NAFLD diagnosis was based on ultrasonography, whereas the gold standard was liver biopsy. In addition, we did not divide NAFLD into simple fatty liver and NASH. Threfore, we recommended more clinical trials and cohort studies to be conducted to confirm a causal relationship between the risk of NAFLD and dietary polyphenols.

Conclusion

In conclusion, our study revealed that high intake of lignans lowered the odds of NAFLD. We strongly recommend that the concepts reported in this study must be tested in future longitudinal researches in order to determine any correlation between total and subgroup of polyphenol intake and various stages of fatty liver disease.

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Conflict of Interest

None declared.

References

1 Rostamizadeh P, Mazloom Z. The effect of licorice and probiotics on nonalcoholic fatty liver disease (NAFLD): A systematic review. *Int J Nutr Sci.* 2019;4:163-9. DOI:10.30476/ijns.2019.84178.1042.

2 Ranjbar T, Masoumi SJ. The effect of stevia rebaudiana on nonalcoholic fatty liver disease (NAFLD): A review. *Int J Nutr Sci.* 2018;3:2-6.

3 Sherafatmanesh S, Ekramzadeh M, Moosavi L. The role of carbohydrate related factors in pathogenesis of nonalcoholic fatty liver disease: A review. *Int J Nutr Sci.* 2017;2:52-7.

4 Basirat R, Yosaee S, Azadbakht L, et al. Predictive power of visceral adiposity index and model of adipose distribution in patients with non-alcoholic fatty liver disease (NAFLD). *Int J Nutr Sci.* 2017;2:97-102.

5 Zelber-Sagi S, Ratziu V, Oren R. Nutrition and physical activity in NAFLD: an overview of the epidemiological evidence. *World J Gastroenterol.* 2011;17:3377. DOI:10.3748/wjg.v17.i29.3377. PMID:21876630.

6 Mascitelli L, Goldstein MR. Might some of the beneficial effects of the Mediterranean diet on non-alcoholic fatty liver disease be mediated by reduced iron stores? *J Hepatol.* 2013;59:639. DOI:10.1016/j.jhep.2013.03.041. PMID:23707366.

7 Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. *Oxid Med Cell Longev.* 2009;2:270-8. DOI:10.4161/oxim.2.5.9498. PMID:20716914.

8 Rodriguez-Mateos A, Vauzour D, Krueger CG, et al. Bioavailability, bioactivity and

impact on health of dietary flavonoids and related compounds: an update. *Arch Toxicol*. 2014;88:1803-53. DOI:10.1007/s00204-014-1330-7. PMID:25182418.

9 Rodriguez-Ramiro I, Vauzour D, Minihane A. Polyphenols and non-alcoholic fatty liver disease: impact and mechanisms. *Proc Nutr Soc*. 2016;75:47-60. DOI:10.1017/S0029665115004218. PMID:26592314.

10 Mehrabani D, Mehrvarz S, Rabiee M. The effect of aqueous and hydroalcoholic extracts of the mango fruit on development of embryonic tissues during pregnancy. *Int J Nutr Sci.* 2019;4:202-5. DOI:10.30476/ijns.2019.83956.1040.

11 Mehrabani D, Vahedi M, Eftekhari MH, et al. Food avoidance in patients with ulcerative colitis: A review. *Int J Nutr Sci.* 2017;2:189-95.

12 Nikkhah-Bodaghi M, Ghanavati M, Hekmatdoost A. Polyphenol intakes and risk of impaired lipid profile, elevated hepatic enzymes and nonalcoholic fatty liver disease. *Nutr Food Sci.* 2019. DOI:10.1108/nfs-12-2018-0338.

13 Mazidi M, Katsiki N, Banach MJTJonb. A higher flavonoid intake is associated with less likelihood of nonalcoholic fatty liver disease: results from a multiethnic study. *J Nutr Biochem*. 2019;65:66-71. DOI:10.1016/j.jnutbio.2018.10.001. PMID:30623852.

14 Zhao L, Zhang N, Yang D, et al. Protective Effects of Five Structurally Diverse Flavonoid Subgroups against Chronic Alcohol-Induced Hepatic Damage in a Mouse Model. *Nutrients.* 2018;10:1754. DOI:10.3390/nu10111754. PMID:30441755.

15 Esmaillzadeh A, Kimiagar M, Mehrabi Y, et al. Dietary patterns, insulin resistance, and prevalence of the metabolic syndrome in women. *Am J Clin Nutr.* 2007;85:910-8. DOI:10.1093/ajcn/85.3.910. PMID:17344515.

16 Ghaffarpour M, Houshiar-Rad A, Kianfar H, et al. The manual for household measures, cooking yields factors and edible portion of foods. *Sci Open.* 1999;7:213.

17 Bowman SA, Friday JE, Moshfegh AJ. MyPyramid Equivalents Database, 2.0 for USDA survey foods, 2003–2004: documentation and user guide. US Department of Agriculture. 2008 Sep.

18 Rothwell JA, Perez-Jimenez J, Neveu V, et al. Phenol-Explorer 3.0: a major update of the Phenol-Explorer database to incorporate data on the effects of food processing on polyphenol content. *Database (Oxford).* 2013;2013:bat070. DOI:10.1093/database/bat070. PMID:24103452.

19 Valipour G, Esmaillzadeh A, Azadbakht L, et al. Adherence to the DASH diet in relation to psychological profile of Iranian adults. *Eur J Nutr.* 2017;56:309-20. DOI:10.1007/s00394-015-1081-0. PMID:26520851.

20 Vitale M, Masulli M, Rivellese A, et al. Dietary intake and major food sources of polyphenols in people with type 2 diabetes: The TOSCA. IT Study. *Eur J Nutr* 2018;57:679-88. DOI:10.1007/s00394-016-1355-1. PMID:28004268.

21 Tresserra-Rimbau A, Medina-Remón A, Pérez-Jiménez J, et al. Dietary intake and major food sources of polyphenols in a Spanish population at high cardiovascular risk: the PREDIMED study. *Nutr Metab Cardiovasc Dis.* 2013;23:953-9. DOI:10.1016/j.numecd.2012.10.008. PMID:23332727.

22 Zamora-Ros R, Forouhi NG, Sharp SJ, et al. The association between dietary flavonoid and lignan intakes and incident type 2 diabetes in European populations: the EPIC-InterAct study. *Diabetes Care.* 2013;36: 3961-70. DOI:10.2337/dc13-0877. PMID:24130345.

23 Sohrab G, Hosseinpour-Niazi S, Hejazi J, et al. Dietary polyphenols and metabolic syndrome among Iranian adults. *Int J Food Sci Nutr.* 2013;64:661-7. DOI:10.3109/09637486.2013.787397. PMID:23607642.

24 Grosso G, Stepaniak U, Micek A, et al. Dietary polyphenols are inversely associated with metabolic syndrome in Polish adults of the HAPIEE study. *Eur J Nutr.* 2017;56:1409-20. DOI:10.1007/s00394-016-1187-z. PMID:26913852.

25 Jacques PF, Cassidy A, Rogers G, et al. Higher dietary flavonol intake is associated with lower incidence of type 2 diabetes. *J Nutr.* 2013;143:1474-80. DOI:10.3945/jn.113.177212. PMID:23902957.

26 Nimptsch K, Zhang X, Cassidy A, et al. Habitual intake of flavonoid subclasses and risk of colorectal cancer in 2 large prospective cohorts. *Am J Clin Nutr.* 2016;103:184-91. DOI:10.3945/ajcn.115.117507. PMID:26537935.

27 Zamora-Ros R, Barupal DK, Rothwell JA, et al. Dietary flavonoid intake and colorectal cancer risk in the European prospective investigation into cancer and nutrition (EPIC) cohort. *Int J Cancer.* 2017;140:1836-44. DOI:10.1002/ijc.30582. PMID:28006847.

28 Salomone F, Godos J, Zelber-Sagi S. Natural antioxidants for non-alcoholic fatty liver disease: molecular targets and clinical perspectives. *Liver Int.* 2016;36:5-20. DOI:10.1111/liv.12975. PMID:26436447.

29 Van De Wier B, Koek GH, Bast A, et al. The

potential of flavonoids in the treatment of non-alcoholic fatty liver disease. *Crit Rev Food Sci Nutr*. 2017;57:834-55. DOI:10.1080/10408398.2014.952399. PMID:25897647.

30 Pisonero-Vaquero S, González-Gallego J, Sánchez-Campos S, et al. Flavonoids and related compounds in non-alcoholic fatty liver disease therapy. *Curr Med Chem*. 2015;22:2991-3012. DOI:10.2174/0929867322666150805094940. PMID:26242257.

31 Buscemi S, Marventano S, Antoci M, et al. Coffee and metabolic impairment: An updated review of epidemiological studies. *NFS J.* 2016;3:1-7. DOI:10.1016/j.nfs.2016.02.001.

32 Elgebaly A, Radwan IA, AboElnas MM, et al. Resveratrol Supplementation in Patients with Non-Alcoholic Fatty Liver Disease: Systematic Review and Meta-analysis. *J Gastrointestin Liver Dis*. 2017;26:59-67. DOI:10.15403/jgld.2014.1121.261.ely. PMID:28338115.

33 Zhang S, Gu Y, Wang L, et al. Association between dietary raw garlic intake and newly diagnosed nonalcoholic fatty liver disease: A population-based study. *Eur J Endocrinol*. 2019;181:591-602. DOI:10.1530/EJE-19-0179. PMID:31557727.

34 Ashakumary L, Rouyer I, Takahashi Y, et al. Sesamin, a sesame lignan, is a potent inducer of hepatic fatty acid oxidation in the rat. *Metabolism*. 1999;48:1303-13. DOI:10.1016/s0026-0495(99)90272-x. PMID:10535395.

35 Kristensen M, Savorani F, Christensen S, et al. Flaxseed dietary fibers suppress postprandial lipemia and appetite sensation in young men. *Nutr Metab Cardiovasc Dis*. 2013;23:136-43. DOI:10.1016/j.numecd.2011.03.004. PMID:21802266.

36 Leyva DR, Zahradka P, Ramjiawan B, et al. The effect of dietary flaxseed on improving symptoms of cardiovascular disease in patients with peripheral artery disease: rationale and design of the FLAX-PAD randomized controlled trial. *Contemp Clin Trials*. 2011;32:724-30. DOI:10.1016/j.cct.2011.05.005. PMID:21616170.

37 Zamora-Ros R, Touillaud M, Rothwell JA, et al. Measuring exposure to the polyphenol metabolome in observational epidemiologic studies: current tools and applications and their limits. *Am J Clin Nutr.* 2014;100:11-26. DOI:10.3945/ajcn.113.077743. PMID:24787490.

38 Rickman JC, Bruhn CM, Barrett DM. Nutritional comparison of fresh, frozen, and canned fruits and vegetables II. Vitamin A and carotenoids, vitamin E, minerals and fiber. *J Sci Food Agric*. 2007;87:1185-96. DOI:10.1002/jsfa.2824.

39 Manach C, Donovan JL. Pharmacokinetics and metabolism of dietary flavonoids in humans. *Free Radic Res.* 2004;38:771-85. DOI:10.1080/10715760410001727858. PMID:15493450.

40 Ozasa K, Nakao M, Watanabe Y, et al. Serum phytoestrogens and prostate cancer risk in a nested case-control study among Japanese men. *Cancer Sci*. 2004;95:65-71. DOI:10.1111/j.1349-7006.2004.tb03172.x. PMID:14720329.