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Short-Communication

Flavonoid intake in relation to lipid profile and fasting blood glucose: A cross-sectional analysis of the MASHHAD PERSIAN cohort study

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Abstract

Objective: Flavonoids are plant compounds with health benefits, but studies on their link to fasting blood glucose (FBG) and lipid profile are inconsistent. This study aimed to investigate the relationship between flavonoid intake and these factors.

Materials and Methods: This cross-sectional study involved 3423 participants (56% women and 44% men) aged 35 to 70 years. Flavonoid intakes were calculated through a food frequency questionnaire (FFQ) by using the Phenol Explorer (PE) database. A multivariable analysis was performed to examine the association between flavonoid intake and health outcomes by comparing the highest and lowest intake levels, and results are presented as odds ratios (ORs) with 95% confidence intervals (95% CIs).

Results: This study has shown that the highest total flavonoid intakes were significantly associated with the lower odds of elevated levels of triglycerides (TG), total cholesterol (TC), and low-density lipoprotein-cholesterol (LDL-C). Also, the highest intakes of flavanone had a significant relationship with lower odds of elevated FBG levels. Moreover, flavanols and flavonols consumption were significantly related to both lower odds of elevated TC and TG levels. In addition, flavanols intakes were significantly associated with lower odds of elevated LDL-C levels. Furthermore, the highest Flavones intake was significantly related to the lower odds of reduced levels of high-density lipoprotein-cholesterol (HDL-C).

Conclusion: This cross-sectional study revealed that flavonoid intake and its subclasses could be related to healthier levels of lipid profile and FBG levels. However, conducting high-quality prospective studies to reach definite findings is necessary.

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Introduction

Cardiovascular diseases (CVDs) have been identified by the World Health Organization (WHO) as the leading cause of death, accounting for 33.0% (17.9 million) of all global deaths in 2019 (Di Cesare et al. 2024; Luo et al. 2024; Muharram et al. 2024). Also, 20.5 million deaths were related to CVDs in 2021, approximately one-third of all global deaths in that year (Di Cesare et al. 2024). In addition, by 2030, global deaths from CVDs are projected to exceed 23 million (Nawsherwan et al. 2022). Furthermore, from 2025 to 2050, the prevalence of CVDs is expected to rise by 90.0%, crude mortality by 73.4%, and crude disability-adjusted life years (DALYs) by 54.7% (Chong et al. 2024). Dyslipidemia, insulin resistance, smoking, hypertension, obesity, and type 2 diabetes mellitus are recognized as major risk factors for CVDs (Adeva-Andany et al. 2019; Teo and Rafiq 2021). Dyslipidemia could be defined as elevated levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), or triglycerides (TG), as well as reduced levels of high-density lipoprotein cholesterol (HDL-C) (Hedayatnia et al. 2020). Previous studies have reported the association between dyslipidemia and type II diabetes (Powell-Wiley et al. 2021), atherosclerosis (Garg et al. 2015), arterial diseases, including coronary and peripheral artery diseases (Mahalle et al. 2014; Tao et al. 2024), reduced quality of life (Lalonde et al. 2001), and increased mortality (Liu et al. 2021).

Dietary interventions are recognized as an effective and side-effect-free approach for preventing and managing hyperlipidemia (Giles 2024). In this regard, recent research has been conducted to explore the lipid-modifying effects of nutraceuticals found in natural foods (Cicero et al. 2017; Sahebkar et al. 2016). Flavonoids are substances with a polyphenolic structure containing two benzene rings connected by a heterocyclic pyran ring (Lee and Heffern 2022). Flavonoids are categorized into the following subclasses according to their degree of oxidation and chemical structure (Chen et al. 2023): anthocyanidins, isoflavonoids, flavanones, flavones, flavonols, and flavanols (Cahyana and Adiyanti 2021). Flavonoids are found in some natural foods, including nuts, seeds, vegetables, fruits, wine, tea, and coffee (Górecki and Hallmann 2020; Panche et al. 2016). Flavonoids, due to their antioxidant properties (Hassanpour and Doroudi 2023), may play a protective role against the pathogenesis of various diseases, including cancer (Mir et al. 2024), Alzheimer's disease (Minocha et al. 2022), and CVDs (Mansour et al. 2024). While some previous studies have explored the association between flavonoid intake and lipid profile or fasting blood glucose (FBG) levels (Al-Ishaq et al. 2019; de Farias et al. 2023; Esfandiar et al. 2024; Grosso et al. 2017; Penczynski et al. 2018; Wan et al. 2024), their finding were inconsistent. So, our study aimed to comprehensively assess the association of the total flavonoid intake and flavonoids' various subclasses with lipid profile and FBG levels in adults.

Materials and Methods

This is a cross-sectional study conducted on individuals who participated in the Persian cohort study in Mashhad, Iran. The study population consists of employees of Mashhad University of Medical Sciences who have been referred to the employee health monitoring center (Persian cohort) located at Emam Reza (AS) Hospital in Mashhad. The protocol of the conducted study was approved by the ethical committee of Mashhad University of Medical Sciences (Ethical approval ID: IR.MUMS.REC.1395.526). The consent form was read and signed by the included participants before enrolling in our study.

Eligibility criteria

Individuals who met the following criteria were eligible for inclusion in our

study: a) having Iranian citizenship, residency in Mashhad for at least one year, completion of the informed consent form, and age between 35 and 70 years.

The exclusion criteria of this study included:

Women who were pregnant or breastfeeding.Individuals who were taking supplements and medications that affected arterial stiffness, including dietary and antioxidant supplements, glucocorticoids, antihypertensive drugs, and statins.People with total calorie intakes of less than 800 kcal or more than 4200 kcal. Individuals with diabetes, cardiovascular diseases, chronic kidney disease, cancers, or autoimmune diseases. Participants whose data have been incompletely recorded.

Laboratory measurements

Participants were asked to have a 10-12 hr fasting period before blood sampling was performed. By using a centrifuge at 3000 rpm for 15 minutes, serum was extracted from whole blood. FBG, TC, TG, and LDL-C and HDL-C were measured using routine enzymatic colorimetric methods. The autoanalyzer device was used to measure the mentioned laboratory markers in our study.

Flavonoid intake assessment

In the present study, a food frequency questionnaire (FFQ) was used to perform dietary assessment. Due to the point that items examined in the FFQ have better coverage in the PhenolExplor (PE) database than in USDA databases, we used PE to evaluate the flavonoid content of each recorded food item. PE is available at http://phenol-explorer.eu. In the first step, the intakes of each food item were recorded using the FFQ. In the second step, the flavonoid profile of each record was obtained according to PE. Finally, total flavonoid consumption was calculated by summing the flavonoid subclasses. In the items of the FFQ that consist of different foods, we considered the mean flavonoid profile. However, in cases where a specific food was predominantly consumed within an FFQ item, the flavonoid profile of that food was considered, such as green olives (code F7-6), green bell peppers (code F5-14), and white onions (code F5-13).

Statistical analysis

All statistical analyses in this study were performed using SPSS (version 26), and a p-value <0.05 was deemed statistically significant. Also, each analysis was considered two-tailed. Quantitative data were checked for normality by performing the Kolmogorov-Smirnov test. Quantitative data with a normal distribution and without a normal distribution are presented as mean (±standard deviation) and median (quartile 1 and quartile 3), respectively. Also, qualitative data are presented as numbers (%). Measures of total flavonoid and each of the flavonoid subclass intake were divided into quintiles. Also, each outcome was divided into low-risk and high-risk groups according to certain cutoff points as follows: FBG >99 mg/dl, TC >200 mg/dl, TG > 150 mg/dl, LDL-C >120 mg/dl, and HDL-C <40 in men and HDL-C <50 mg/dl in women. Multivariable analyses were conducted to examine the associations between total and subclass-specific flavonoid intake and the odds of having high-risk levels of FBG and lipid profile markers, by comparing the highest intakes with the lowest (quintile 5 VS. quintile 1), by reporting odds ratio (OR) with 95% confidence interval (95% CI). In this analysis, the impacts of the cofounders, including body mass index (BMI), gender, age, physical activity level (PAL), and total energy intake, on the overall results were adjusted.

Results

Among the individuals participating in the Mashhad PERSIAN cohort study, 3423 people (1506 men and 1917 women) were eligible for inclusion in this research. The mean age and BMI were 43.79 ± 7.93 years and 26.39 ± 3.69 kg/m^2, respectively. The

characteristics of the participants in this study are summarized in Table 1. The total flavonoid intake in our population was 752.43 ± 343.53 mg/day. Flavanols and isoflavonoids had maximum and minimum intakes with median (q1, q3) of 550.10 (366.70, 750.36) mg/day, and 0.88 (0.10, 5.07) mg/day, respectively. Measures of the intakes of each flavonoid subclass and their main sources are presented in Table 2.

Table 1. Characteristics of the participants included in the study

Variables	Measures*
Age (years)	43.79 ± 7.93
Gender (female, %)	56
Smoking (yes, %)	6.8
BMI (kg/m^2)	26.39 ± 3.69
Energy intake (kcal/day)	2763.2 ± 671.61
PAL (MET.h/day)	38.79 ± 5.33
FBG (mg/dl)	94.75 ± 21.32
TG (mg/dl)	117.91 ± 69.3
TC (mg/dl)	180.37 ± 35.78
LDL-C (mg/dl)	100.11 ± 29.91
HDL-C (mg/dl)	56.67 ± 13.45

Abbreviations: BMI, body mass index; PAL, physical activity levels; FBG, fasting blood glucose; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol. *) Data are presented as mean ± SD or N (%)

Table 2. Intake of flavonoid subtypes and their dietary sources in participants included in the study

Flavonoid Subclass	Intake Amount (mg/day) [a]	Food Sources
Flavanols	550.10 (366.70, 750.36)	Major sources: Tea (91%), Apple (5%), Peach/Nectarine (1%), Plum (0.1%) Minor sources [b]: Chocolate, Broad beans, Barley, Natural fruit juices, Flavored milks, Grapes, apricots, cherries/Sour cherries, Beans, Lentil/Mung beans, bananas, Nuts, Green beans, Pumpkin, Berry, pomegranate, persimmon, strawberries, Kiwi, Fig, Green peas, Jam
Flavonols	104.90 (77.89, 134.07)	Main sources: Tea (62%), onions (19%), beans (6%), fresh and cooked vegetables (4%), apples (3%), walnuts (2%), cucumbers (1%), and beans (1%). Other sources: Lettuce, tomatoes, bell peppers, pumpkin, berries, plums, agar, chocolate, lentils/mung beans, various types of cabbage, celery/artichoke, beets/turnips, potatoes, carrots, apricots, peaches/plums, strawberries, pears, citrus fruits, natural fruit juices, dried fruits, raisins/currants, and nuts.
Flavanones	29.82 (15.95, 46.81)	Main sources: Citrus fruits (96%) and tomatoes (4%). Other sources: Natural fruit juices and nuts.
Flavones	14.52 (8.94, 22.30)	Main sources: fresh and cooked vegetables (83%), celery/artichoke (7%), watermelon (5%), melon (2%), lentils/mung bean (1%), and bell peppers (1%). Other sources: Natural fruit juices, various types of cabbage, lettuce, carrots, olives, green peppers, beets/turnips, olive oil, beans, cucumbers, potatoes, and nuts.
Anthocyanins	10.31 (6.32, 16.40)	Main sources: cherries (36%), grapes (17%), beans (17%), plums (16%), berries (12%), strawberries (9%), Minor sources: natural fruit juices (4%), apples (3%), jams (1%), and peaches/nectarines (1%)
Isoflavones	0.88 (0.10, 5.07)	Main sources: soy (97%), beans (3%) Other sources: peanuts and seed kernels

a) Data are presented as median (q1, q3). b) Less than 1%

Association of flavonoid intakes and FBG

As mentioned in Table 3, the highest quintile (quintile 5) of total flavonoid intakes had no significant relationship with elevated FBG compared to the lowest intake (quintile 1) total flavonoid intakes (p>0.05). Among the flavonoid subclasses,

the highest flavanone intake had a significant association with 31% lower odds of elevated FBG compared to the first quintile (OR: 0.69, 95% CI: 0.53 to 0.90, p=0.006). However, no significant association was detected between higher intakes of other flavonoid subclasses and FBG levels (p>0.05).

Association of flavonoid intake and lipid profile

Flavonoid intakes and TG levels

By comparing quintile five of the total flavonoids consumption by quintile 1, a significant association was detected between the highest total flavonoid intake and 32% lower odds of elevated TG levels (OR: 0.68, 95% CI: 0.52 to 0.89, p=0.006), Also the highest flavanols and flavonols intakes were significantly related to 39% and 30% lower odds of increased TG levels in comparison to the lowest intakes, respectively (OR: 0.61, 95% CI: 0.46 to 0.80, p<0.001, OR: 0.70, 95% CI: 0.53 to 0.92, p=0.01, respectively). However, higher intakes of other flavonoid subclasses were not associated with TG levels (p>0.05) (Table 3).

Table 3. Association of the highest quintile of flavonoid subclasses and total flavonoid intake with fasting blood glucose and lipid profile, versus the lowest, using multivariable regression analysis.

Flavonoid Group	Fasting Blood Glucose OR (95% CI) / p-value	Triglyceride OR (95% CI) / p-value	Total Cholesterol OR (95% CI) / p-value	LDL-C OR (95% CI) / p-value	HDL-C OR (95% CI) / p-value
Flavanols	1.08 (0.83–1.40) / 0.56	0.61 (0.46–0.80) / <0.001	0.70 (0.54–0.90) / 0.006	0.70 (0.51–0.96) / 0.03	0.88 (0.59–1.29) / 0.52
Flavonols	0.95 (0.73–1.23) / 0.95	0.70 (0.53–0.92) / 0.001	0.76 (0.59–0.98) / 0.04	0.75 (0.54–1.02) / 0.07	0.83 (0.56–1.22) / 0.83
Flavones	0.79 (0.61–1.02) / 0.07	1.06 (0.80–1.39) / 0.66	0.93 (0.72–1.19) / 0.58	0.91 (0.66–1.25) / 0.56	0.53 (0.34–0.82) / 0.005
Flavanones	0.69 (0.53–0.90) / 0.006	0.90 (0.69–1.19) / 0.49	0.91 (0.70–1.18) / 0.50	1.19 (0.76–1.65) / 0.28	0.83 (0.55–1.27) / 0.40
Anthocyanins	0.77 (0.58–1.00) / 0.05	1.09 (0.83–1.45) / 0.51	0.79 (0.61–1.02) / 0.07	0.76 (0.55–1.06) / 0.10	0.73 (0.46–1.11) / 0.14
Isoflavonoids	0.88 (0.68–1.14) / 0.35	0.91 (0.69–1.19) / 0.49	0.78 (0.61–1.00) / 0.05	0.86 (0.63–1.16) / 0.33	0.96 (0.63–1.45) / 0.85
Total Flavonoids	1.06 (0.81–1.37) / 0.65	0.68 (0.52–0.89) / 0.006	0.71 (0.55–0.91) / 0.008	0.69 (0.50–0.94) / 0.02	0.91 (0.62–1.33) / 0.63

Multivariable models were adjusted for smoking status, BMI, and total energy intake. Abbreviations**:** LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; OR, odds ratio; 95% CI, 95% confidence interval.

Flavonoid intakes and TC levels

Multivariable analysis showed that the highest total flavonoid intake was significantly associated with 29% lower odds of elevated TC levels in comparison to the lowest intake (OR: 0.71, 95% CI: 0.55 to 0.91, p=0.008). In addition, the highest intakes of flavanols and flavonols were significantly related to 30% and 24% lower odds of increased TC levels, respectively (OR: 0.70, 95% CI: 0.54 to 0.90, p = 0.006, OR: 0.76, 95% CI: 0.59 to 0.98, p = 0.04, respectively). However, no significant relationship exists between the consumption of other flavonoid subclasses and TC levels (p>0.05) (Table 3).

Flavonoid intakes and LDL-C levels

In this study, the highest intakes of total flavonoids had a significant relationship with 31% lower odds of elevated LDL-C levels compared to the lowest intakes (OR: 0.69, 95% CI: 0.50 to 0.94, p=0.02). Furthermore, among the flavonoid subclasses, the highest intakes of flavanols were significantly associated with 30% lower odds of elevated LDL-C levels (OR: 0.70, 95% CI: 0.51 to 0.96, p=0.03), compared to the lowest. However, TC levels were not related to the consumption of other flavonoid subclasses (p>0.05) (Table 3).

Flavonoid intakes and HDL-C levels

Total flavonoid intake had no significant association with HDL-C levels (OR: 0.91, 95% CI: 0.62 to 1.33, p=0.63). Meanwhile, the highest flavones consumption was significantly related to 47% lower odds of decreased HDL-C levels compared to the lowest intake (OR: 0.53, 95% CI: 0.34 to 0.82, p=0.003). However, HDL-C levels were not associated with other flavonoid subclass intakes (p>0.05) (Table 3).

Discussion

This study revealed that total flavonoid and flavanols intake was significantly associated with lower odds of elevated TG, TC, and LDL-C levels. In addition, flavonols consumption was significantly related to the lower odds of increased TG and TC levels. Also, flavone intake was significantly related to lower odds of reduced HDL-C levels. Furthermore, flavanone intake had a significant association with lower levels of FBG. However, the consumption of anthocyanins and isoflavonoids was not related to the odds of reduced HDL-C levels and elevated FBG, TG, TC, and LDL-C.

A meta-analysis of a prospective cohort study conducted by Liu et al. showed highest intake of total flavonoid was significantly associated with a 9% reduction in the risk of type 2 diabetes (T2DM), in comparison to the lowest intake group (RR: 0.91, 95%CI: 0.87 to 0.96) (Liu et al. 2014). Also, this study reported that a 500 mg/day increase in total flavonoid intake is significantly associated with a 5% lower risk of T2DM (Liu et al. 2014). However, in our study, no significant association was detected between the highest intakes of total flavonoids and elevated FBG levels compared to the lowest. Also, the present study reports a significant inverse association between the highest quintile intakes of flavanones and odds of elevated FBG levels, in comparison to the first quintile. In this regard, a study conducted by Zhou et al. showed a significant inverse association between the highest total flavonoid intake (fourth quartile: >140.145 mg/day) and elevated FBG levels in comparison to the first (first quartile: ≤20.645 mg/day) based on the fully adjusted model. However, according to this model, no significant relationship was observed between intake of total flavan 3-ols, subtotal catechins, total isoflavones, Total Anthocyanidins, total flavanones, Total Flavones, and Total Flavonols, and elevated FBG levels compared to the lowest intake (Zhou et al. 2023).

Also, Yeon et al. reported that flavanone intakes that were adjusted based on the received energy, were significantly

lower in men with impaired fasting glucose (IFG) compared to men with normal fasting glucose (Yeon et al. 2015). However, a randomized control trial (RCT) showed no significant influence of hesperidin, as one of the main types of flavonol, on blood glucose (Shams-Rad et al. 2020). In the meta-analysis conducted by Guo et al., a significant negative association was identified between the risk of T2DM and intakes of flavan-3-ols, flavanols, flavonols, and isoflavones [Guo, 2019 #1348]. Although this research, similar to ours, found that the highest intakes of flavonols were significantly related to lower odds of elevated FBG levels, in the present study, consumption of isoflavones, flavan-3-ols, and flavanols was not significantly associated with changes in the odds of elevated FBG levels. Inhibition of α-glucosidase activity was the main mechanism for the possible hypoglycemic effect of flavonoids that were mentioned in the previous studies (Matsui et al. 2002).

In the present study, the highest total flavonoid intake was significantly related to lower odds of elevated TG, TC, and LDL-C levels in comparison to the lowest. However, total flavonoid intake had no significant association with the odds of reducing levels of HDL-C. Similar to our findings, Li et al. reported that in female individuals, higher total flavonoid intakes (that were derived from nuts, vegetables, and fruits) had no significant relationship with HDL-C, while higher intakes of flavonol and total flavonoid intakes were significantly associated with lower TG levels. However, in this study, a significant relationship showed that the higher anthocyanin intake from nuts, vegetables, and fruit sources was significantly associated with increased levels of HDL-C levels (Li et al. 2013). However, these associations were not detected in males. In the most adjusted model of another study, it was shown that the intake in the highest quartile of total flavonols (≥22.74 mg/day) was significantly associated with a reduction in hyperlipidemia risk compared to the intake in the first quartile (≤7.17 mg/day). In addition, in this model, the highest intake of anthocyanin (fourth quartile: ≥11.20 mg/day) was significantly associated with reduced risk of hyperlipidemia in comparison to the lowest intake (first quartile: ≤0.14 mg/day). However, no significant association was detected between the highest intake of total flavonoids, subtotal catechins, total isoflavones, total Flavan-3-ols total flavonones, total flavones, and risk of hyperlipidemia compared to the lowest intake based on this model (Wan et al. 2024),

In contrast to our result, a significant association was reported by Kim et al. between increased HDL-C and higher total flavonoid intakes (Kim et al. 2016). Also, unlike our research, this study found a significant negative relationship between higher anthocyanin intakes and increased LDL-C levels. In the present study, a significant association of flavanols intake and TG, TC, and LDL-C levels was found. Regarding that 91% of flavanols consumption in our study was obtained from tea sources, reviewing previous research on tea intake and lipid profile could be helpful. The study by Cornelis et al. showed that higher tea consumption was significantly associated with lower TC and LDL-C levels and higher HDL-C levels (Cornelis and van Dam 2020). However, in a meta-analysis that used 6 effect sizes from randomized control trials, it was demonstrated that black tea had no significant impact on lipid profile, including TG, TC, LDL-C, and HDL-C levels compared to the placebo groups in individuals with hypercholesterolemia (Araya-Quintanilla et al. 2019). In the study by Li et al., a significant association was detected between the higher intakes of flavonols and lower TG levels (Li et al. 2013), which aligns with our finding. Also, the meta-analysis on RCTs conducted by Sahebkar revealed that quercetin supplementation (as one of the flavonols) had no significant impact on lipid profile.

However, in the subgroup analysis, it was mentioned that quercetin supplementation with a dosage of ≥ 500 mg/day led to a significant decrease in TG levels (WMD: -24.54 mg/dL, 95% CI: -33.09 to -15.99, $p < 0.00001$), while TC, LDL-C, and HDL-C were not significantly changed (Sahebkar 2017). In the present study, the highest quintile of the flavones intakes had a significant negative association with odds of reduced HDL-C levels, while having no association with odds of elevated levels of TC, TG, and LDL-C, in comparison to the lowest quintile. These findings were in contrast with the results of research conducted by Oh et al., which reported a significant negative association between Flavone intakes and TG levels in Korean women aged 30 years or older. However, in this study, the association between the flavones intake and other lipid profiles, including TC, LDL-C, and HDL-C levels, was not significant (Oh et al. 2017). Furthermore, in our study, isoflavonoid consumption was not associated with odds of adverse levels of lipid profile; this is while in the meta-analysis on RCTs, it was reported that intakes of soy as a rich source of isoflavonoids led to a significant decrease in TC, TG, LDL-C, and HDL-C in postmenopausal women (Moradi et al. 2020). The possible anti-lipidemic effects of flavonoids could be attributed to certain mechanisms. For example, these compounds can play an important role in improving the lipid profile by reducing the digestion and absorption of fats, inhibiting the enzymes of the lipid biosynthesis pathway, and modulating the metabolism of blood lipids and lipoproteins (Assini et al. 2013). Also, flavanols in apples could be related to the inhibition of the pancreatic lipase enzyme and prevent the absorption of triglycerides (Sugiyama et al. 2007). Evidence has shown that tea catechins, especially epigallocatechin gallate (EGCG), effectively reduce intestinal cholesterol absorption by altering proteins involved in cholesterol transport from the intestinal brush border, including the ATP-Binding Cassette Proteins, B-type 1-scavenger receptor, P-glycoprotein 1, multidrug resistance protein 1, and Niemann-Pick C1-Like 1 (NPC1L1) protein (Bahadoran et al. 2013; Jodoin et al. 2002; Sugiyama et al. 2007; Susanti et al. 2019). In addition, these catechins inhibit the pancreatic phospholipase-2A enzyme and intestinal phosphatidylcholine hydrolysis and subsequently reduce lipid absorption from the gastrointestinal tract (Asgary et al. 2014). Furthermore, the possible hypolipidemic effects of quercetin, as one of the most well-studied flavonols, may be related to the ability of this flavonoid to activate the AMP-activated protein kinase (AMPK) signaling pathway, which leads to a decrease in expression of sterol regulatory element-binding protein 1 (SREBP1c) and peroxisome proliferator-activated receptor-γ (PPAR-γ) in the liver, increases the expression of the peroxisome proliferator-activated receptor-α (PPAR-α), and inhibit de novo fatty acid synthesis (Jiang et al. 2025; Markowska et al. 2024; Nasser et al. 2021; Saleh Al-maamari et al. 2021; Wang et al. 2016; Wang et al. 2021). Moreover, isoflavonoids, by reducing the 3-methyl-3-hydroxymethylglutaryl CoA reductase (HMG-CoA reductase) activity, may lead to reduced cholesterol levels in the body (Baskaran et al. 2015; Sung et al. 2004). In addition, in study conducted by Fotouhi et al, reported that naringin (as a flavanone found in citrus fruits) increased the enzyme carnitine palmitoyl transferase (CPT) in the liver, and subsequent β-oxidation (Fotouhi et al. 2025; Longo et al. 2016). The summary of mechanisms for the association of flavonoid intakes with lipid profile is presented in Table 4.

Table 3. Possible mechanism for the association of flavonoid intakes with lipid profile.

Flavonoid (Source)	Proposed Mechanism	Target / Pathway	References
Flavonoids (General)	Reduce fat digestion and absorption Inhibit enzymes in the lipid biosynthesis pathway Modulate lipid and lipoprotein metabolism	Lipid biosynthesis enzymes, lipid metabolic pathways	(Assini et al. 2013)
Flavanols (Apple)	Inhibit pancreatic lipase enzyme	Prevention of triglyceride absorption	(Sugiyama et al. 2007)
Catechins – EGCG (Tea)	Reduce intestinal cholesterol absorption Modulate cholesterol transport proteins (ABC proteins, SR-B1, P-gp1, MRP1, NPC1L1) Inhibit pancreatic phospholipase-2A Inhibit intestinal phosphatidylcholine hydrolysis	Cholesterol transport proteins, lipid digestion enzymes	(Asgary et al. 2014; Bahadoran et al. 2013; Jodoin et al. 2002; Sugiyama et al. 2007; Susanti et al. 2019)
Quercetin (Onion, Apple, Berries)	Activate the AMPK signaling pathway Downregulate SREBP1c and PPAR-γ Upregulate PPAR-α Inhibit de novo fatty acid synthesis in the liver	AMPK pathway, SREBP1c, PPAR-γ, PPAR-α, fatty acid synthesis enzymes	Jiang et al. 2025; Markowska et al. 2024; Nasser et al. 2021; Saleh Al-maamari et al. 2021; Wang et al. 2016; Wang et al. 2021
Isoflavonoids	Reduce the activity of HMG-CoA reductase in the liver May decrease cholesterol levels in the body	Inhibition of lipid synthesis, cholesterol synthesis	(Baskaran et al. 2015; Sung et al. 2004).
Flavanones (Naringenin)	Increase the activity of CPT in the liver Promote β-oxidation of fatty acids	Lipid oxidation, CPT pathway	(Fotouhi et al. 2025; Longo et al. 2016).

To the best of our knowledge, our study was the first large-scale research to comprehensively examine the associations of the total and subclass-specific flavonoid intake with lipid profile and FBG levels. A large sample size, the use of PE databases encompassing most FFQ items, and performing multivariable analysis were the strengths of this study. However, the impossibility of determining the cause-and-effect relationship between the flavonoid intakes and lipid profile and FBG levels was the main limitation of this study. In addition, another limitation of this study was that, since the investigation focused on dietary flavonoid intake rather than pure flavonoid consumption, such as supplements, the features of other bioactive components in flavonoid dietary sources were not accounted. So, attributing all observed associations solely to flavonoids should be interpreted with caution.

This study revealed that the consumption of total flavonoids, flavanols, and flavones was significantly associated with lower odds of adverse lipid profile levels. Also, higher flavanone intake was associated with lower odds of at-risk levels of FBG. However, other flavonoid subclasses intakes had no significant association with the at-risk level of the mentioned outcomes. It seems that to determine the exact influence of total flavonoids and their subclasses intakes on glycemic control and lipid profile, more high-quality RCTs are required.

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Conflicts of interest

The authors declare that they have no known competing interests

Data availability

Data will be made available on request from the corresponding author.

Authors' contributions

S.G. was involved in the study's conception and data collection, S.E.H. contributed to the methodology. M.K.R. carried out the formal analysis. M.S.J., S.M.A., M.H.A., and S.M.T.J. participated in drafting the manuscript, and M.S.J. assisted with editing. A.N. supervised the study. All authors reviewed and approved the final version of the manuscript.

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Ethical approval

The proposal of this study was approved by the Ethical Committee of Mashhad University of Medical Sciences (Ethical approval ID: IR.MUMS.REC.1395.526).

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