PERSPECTIVE

Perspective: Flavan-3-ols and Cardiometabolic Health: First Ever Dietary Bioactive Guideline

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ABSTRACT

Guideline recommendation for a plant bioactive such as flavan-3-ols is a departure from previous recommendations because it is not based on deficiencies but rather improvement in health outcomes. Nevertheless, there is a rapidly growing body of clinical data reflecting benefits of flavan-3-ol intake that outweigh potential harms. Thus, the objective of the Expert Panel was to develop an intake recommendation for flavan-3-ols and cardiometabolic outcomes to inform multiple stakeholders including clinicians, policymakers, public health entities, and consumers. Guideline development followed the process set forth by the Academy of Nutrition and Dietetics, which includes use of the Evidence to Decision Framework. Studies informing this guideline (157 randomized controlled trials and 15 cohort studies) were previously reviewed in a recently published systematic review and meta-analysis. Quality and strength-of-evidence along with risk-of-bias in reporting was reviewed. In drafting the guideline, data assessments and opinions by authoritative scientific bodies providing guidance on the safety of flavan-3-ols were considered. Moderate evidence supporting cardiometabolic protection resulting from flavan-3-ol intake in the range of 400–600 mg/d was supported in the literature. Further, increasing consumption of dietary flavan-3-ols can help improve blood pressure, cholesterol concentrations, and blood sugar. Strength of evidence was strongest for some biomarkers (i.e., systolic blood pressure, total cholesterol, HDL cholesterol, and insulin/glucose dynamics). It should be noted that this is a food-based guideline and not a recommendation for flavan-3-ol supplements. This guideline was based on beneficial effects observed across a range of disease biomarkers and endpoints. Although a comprehensive assessment of available data has been reviewed, evidence gaps identified herein can inform scientists in guiding future randomized clinical trials. *Adv Nutr* 2022;13:2070–2083.

Statement of Significance: The Expert Panel found moderate evidence supporting cardiometabolic protection resulting from flavan-3-ol intake such that we are proposing the first dietary recommendation for a bioactive food compound.

Keywords: flavan-3-ols, cardiometabolic disease, guideline, bioactive compound, cardiovascular

Introduction

Cardiovascular diseases (CVDs) are the leading cause of death globally (1). Major risk factors for developing CVDs include age, biological sex (male), high blood pressure, smoking, dyslipidemia, and impaired fasting glucose among others (2). Because these risk factors cluster and interact multiplicatively, the term cardiometabolic disease is often used to describe a grouping of disorders including hypertension, dyslipidemia, impaired glucose and insulin dynamics, and abdominal adiposity that together increase the risk for CVDs as well as type 2 diabetes (3, 4). Acknowledging that diet quality plays a major role in cardiometabolic disease-free life expectancy (5), the American Heart Association published Strategic Impact Goals designed to improve cardiometabolic health and reduce related deaths through promotion of healthy behaviors including improvements in diet quality (6).

Whereas exclusive adherence to a healthy diet is ideal for optimizing disease risk and reducing disability-adjusted life years, the potential impact of migrating dietary patterns toward inclusion of key foods containing bioactive compounds should not be underestimated. A large and constantly evolving body of research suggests that dietary bioactives play a key role in human health maintenance as well as disease prevention and mitigation, particularly during the aging process. As such, the US NIH Office of Dietary Supplements has proposed the term bioactives or bioactive

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food compounds for use in referring to constituents in foods or dietary supplements other than those needed to meet basic human nutritional needs yet responsible for changes in health status. Among the more commonly studied bioactives is the family of secondary plant metabolites known as flavonoids. In recent years, the nutrition science community has provided evidence elucidating the effects of flavonoids on cardiometabolic health (7). Such research reports that the health-promoting properties of flavonoids are likely due to a synergistic combination of their antioxidant, anti-inflammatory, antimutagenic, and anticarcinogenic properties along with their modulating effects on cellular enzyme functionality (8). Although there are many subclasses of flavonoids grouped according to chemical structure, flavan-3-ols—abundantly present in tea, apples, pears, berries, and chocolate/cocoa products—are the most highly consumed flavonoid subclass according to data from the NHANES (9–12). As such, the objective of this Expert Panel was to review the available evidence assessing flavan-3-ol intake and cardiometabolic health for development of an intake guideline.

Methods

Guideline development process

Guideline development followed the process set forth by the Academy of Nutrition and Dietetics, which includes the use of the Evidence to Decision (EtD) framework (13). The steps followed to develop this guideline were:

1. Select the Expert Panel for working with the guideline development team.
2. Orient the Expert Panel to the process of guideline development.
3. Review the findings and evidence quality of the systematic review/meta-analysis and related evidence that will inform the guideline recommendation with the Expert Panel.
4. Orient and train the Expert Panel in the use of GRADE's EtD framework (14).
5. Develop a recommendation statement based on findings of the systematic review using the EtD framework in conjunction with review of toxicological and safety data as well as findings from other scientific organizations.
6. Assemble the draft guideline.
7. Conduct an external review of the guideline.
8. Respond to reviewer comments and update the guideline before manuscript submission.

Guideline team structure

The Academy of Nutrition and Dietetics (Academy), who were consulted to lead this project, led the process of Expert Panel recruitment. An independent Work Group Selection Subcommittee from the Council of Research led the selection process to ensure appropriate expertise and limit selection bias. An open recruitment message with a link to online application was circulated via stakeholders for experts in the topic area via the Academy and related scientific societies in the field of nutrition (e.g., the ASN). Interested candidates provided conflict-of-interest (COI) forms, curriculum vitae, and personal statements indicating interest and qualifications related to the topic. Each candidate was evaluated based on a set of standard predetermined criteria (experience in subject matter and COI), and candidates with the highest scores were selected for the Expert Panel, with the highest scoring candidate selected for the chair position. A total of 6 members were appointed to develop the guideline. The Expert Panel members were a mix of practitioners and researchers in the field of interest. The Expert Panel participated in all steps of the guideline development process, which included reviewing and evaluating the evidence, developing a recommendation statement based on the EtD framework, and writing a manuscript. The Expert Panel and members of the guideline development team met via web meetings for the duration of the project. In the interest of full disclosure, the Expert Panel was required to disclose potential conflicts of interest by completing the Academy of Nutrition and Dietetics Conflict of Interest Form. COIs were updated at the beginning of every meeting.

Target audience for guideline recommendation

The Expert Panel defined the scope of the guideline to focus on flavan-3-ol intake and risk of cardiometabolic disease in the general adult population. This recommendation is written from the perspective of individual decision-making rather than a public health perspective. As such, the target audience for this guideline was the general adult population including healthy individuals as well as those with overweight or obesity and those who are at risk of chronic disease.

Systematic review process

The systematic review/meta-analysis informing this guideline development was based on the published manuscript by Raman et al. (15). This review systematically examined available evidence from both randomized controlled trials and prospective cohort studies in adults (≥18 y old) to evaluate the potential effects of flavan-3-ol intake on cardiometabolic health. Included studies should have quantified the amount of flavan-3-ol consumed per day or per week, and comparators included studies with low flavan-3-ol content,

Author disclosures: The Academy of Nutrition and Dietetics was hired as a consultant for leading and guiding the process of developing a guideline on the topic. Every effort was made to avoid any actual or reasonably perceived conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the Expert Panel. All members on this project were required to complete, sign, and submit a disclosure and attestation form showing any relationships that might be perceived or actual conflicts of interest. Disclosures were updated throughout the guideline development process.
The guideline development was funded by the Academy of Nutrition and Dietetics Foundation through an Institute for the Advancement of Food and Nutrition Sciences (IAFNS) grant. (IAFNS evolved from ILSI North America.) The funders had no influence on any of the steps involved in developing the guidelines. IAFNS is a nonprofit science organization that pools funding from industry collaborators and advances science through in-kind and financial contributions from public- and private-sector participants.
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Abbreviations used: COI, conflict of interest; CVD, cardiovascular disease; EFSA, European Food Safety Authority; EGCG, epigallocatechin gallate; EtD, Evidence to Decision; FMD, flow-mediated dilation; HbA1c, glycated hemoglobin.

no flavan-3-ol intake, or placebo. The systematic review was conducted using GRADE methodology. From 1946 to March 2019, a systematic search of multiple databases was conducted (MEDLINE, the Cochrane Central databases, and Commonwealth Agricultural Bureau), and studies were screened for inclusion or exclusion [Figure 1 in Raman et al. (15)]. A total of 157 randomized controlled trials and 15 cohort studies met the eligibility criteria. All included studies were critically appraised for risk of bias, with relevant data extracted from included studies. Descriptive synthesis of evidence was conducted for all identified outcomes, and when possible, meta-analysis was conducted. For continuous data, results were summarized as mean difference between treatment groups with 95% CI, and dichotomous outcomes were reported as ORs or RRs with 95% CIs. The published systematic review/meta-analysis by Raman et al. (15) was reviewed in depth by the Expert Panel and vetted critically on the strength of systematic review methods employed, synthesis of evidence, and strength of evidence rating/quality or grading using the AMSTAR 2 tool (https://amstar.ca/Amstar_Checklist.php).

Evidence to recommendation

The Expert Panel and the guideline development team used GRADE's EtD framework to help translate available evidence into a recommendation statement. The purpose of the EtD framework is to use evidence in a structured and transparent manner to help develop recommendation statements. Along with the EtD framework, the framework for developing recommended intakes of bioactive dietary substances by Yates et al. (16) was also used to guide the development of this recommendation statement. The Expert Panel individually and blindly completed GRADE's EtD framework, used evidence summaries on effects of flavan-3-ol intakes on health outcomes, reviewed benefits and harms, certainty of evidence, outcome importance, resource use and equity, patient values, and acceptability and feasibility of a recommendation to increase flavan-3-ol intake. The results of the EtD survey and implications of those judgments for the recommendation were reviewed by the Expert Panel members. Each Expert Panel member completed the EtD framework to provide a justification for having a recommendation for this topic. There was a consensus to write a recommendation based on the results of the EtD framework. Multiple web calls were conducted to identify core concepts/ideas that needed to be included, with the wording of the recommendation discussed at length. After much discussion and multiple rounds of editing to reach consensus, a recommendation statement was developed and accepted unanimously by the Expert Panel.

The guidelines underwent an external peer review evaluation by recruited subject matter experts using the AGREE II tool (Appraisal of Guidelines for Research and Evaluation). Comments from external reviewers were collated by the guideline development team and sent to the Expert Panel for discussion and editorial consideration. The Expert Panel Chair coordinated the final revision of the guideline document based on review comments.

Results

Recommendation for flavan-3-ols and cardiometabolic health

Among the general adult population, we suggest increasing consumption of nutrient-dense foods rich in flavan-3-ols and low (or absent) in added sugars, including but not limited to tea, apples, berries, and cocoa. Based on moderate quality research, consumption of 400–600 mg/d flavan-3-ols can reduce risk associated with cardiovascular disease and diabetes. Increasing consumption of dietary flavan-3-ols may help improve blood pressure, cholesterol concentrations, and blood sugar. A continually growing body of research demonstrates higher consumption may reduce the risk of certain cardiometabolic disease and related mortality. This is a food-based guideline and not a recommendation for flavan-3-ol supplements because these may cause gastrointestinal irritation and/or liver injury, particularly when taken in excess or on an empty stomach.

Evidence summary

In a recent systematic review/meta-analysis by Raman et al. (15) evaluating flavan-3-ols and cardiometabolic health, significant improvements in most vascular and metabolic outcomes were observed when comparing the effects of flavan-3-ol interventions with controls (**Tables 1** and **2**). For example, a reduction in systolic (−1.46 mmHg; 95% CI: −2.27, −0.65 mmHg) and diastolic blood pressure (−0.99 mmHg; 95% CI: −1.50, −0.45 mmHg) was observed with a concomitant increase in acute (1.70%; 95% CI: 1.31, 2.08%) and chronic flow-mediated dilation (FMD) (1.21%; 95% CI: 0.70, 1.73%). Further, significant improvements were observed in the following outcome measures: serum lipids (LDL cholesterol: −0.07 mmol/L; 95% CI: −0.13, 0.009 mmol/L; triglycerides: −0.03 mmol/L; 95% CI: −0.07, −0.003 mmol/L; HDL cholesterol: 0.03 mmol/L; 95% CI: 0.01, 0.04 mmol/L; total cholesterol:HDL cholesterol ratio: −0.14; 95% CI: −0.28, −0.003) and glucose metabolism measures [glycated hemoglobin (HbA1c): −0.05%; 95% CI: −0.09, −0.01%; and HOMA-IR: −0.15; 95% CI: −0.29, −0.01]. No significant changes were observed for inflammatory biomarkers, or for blood glucose and total cholesterol.

Of the 157 randomized controlled trials, only 48 were determined to be of good methodological quality. Accordingly, a GRADE assessment was provided for the good quality studies. A low quality of evidence was assigned to all vascular outcomes except systolic blood pressure, which was assigned moderate quality. A moderate to high quality of evidence was assigned to all metabolic outcomes (*Moderate:* HDL cholesterol, HbA1c, HOMA-IR along with *High:* LDL cholesterol, total cholesterol, triglycerides, fasting blood glucose). Quality assessment information was not provided for inflammatory biomarkers or lipid ratios.

TABLE 1 Total results and results by quartile of intake for flavan-3-ols and cardiometabolic outcomes from randomized controlled trials included in Raman et al. (15)[1]

Outcomes	Total flavan-3-ol analysis			Total flavan-3-ol dose quartile		
	Number of studies	Mean difference (summary estimate)[2]	Median daily intake, mg	Quartiles by intake	Intake range, mg	Mean difference (summary estimate)[2]
Blood pressure						
SBP, mmHg	91	− 1.46 (−2.27, −0.65)*	435.1	1	40.0–207.3	− 2.58 (−4.62, −0.54)*
				2	208.0–414.3	− 1.22 (−2.76, 0.34)
				3	456.0–793.0	− 1.25 (−2.20, −0.29)*
				4	800.0–2000.0	− 1.16 (−2.18, −0.14)*
DBP, mmHg	91	− 0.99 (−1.50, −0.45)*	499.3	1	40.0–208.0	− 1.87 (−2.97, −0.77)*
				2	234.0–472.3	− 0.86 (−2.19, 0.48)
				3	494.0–793.0	− 0.41 (−1.10, 0.28)
				4	800.0–2000.0	− 0.71 (−1.35, −0.07)*
Flow-mediated dilation						
Acute FMD, %	24	1.70 (1.31, 2.08)*	651	1	100.0–311.1	1.11 (0.51, 1.70)*
				2	311.1–497.8	1.70 (1.35, 2.05)*
				3	805.2–918.0	2.57 (1.10, 4.05)*
				4	963.0–2728.6	1.63 (1.04, 2.23)*
Chronic FMD, %	23	1.21 (0.70, 1.73)*	NR	1	34.0–189.0	1.59 (0.56, 2.62)*
				2	206.0–444.0	1.36 (-0.22, 2.94)
				3	572.0–887.0	1.15 (0.11, 2.19)*
				4	900.0–1152.0	1.02 (0.44, 1.61)*
Glucose metabolism						
Blood glucose, mmol/L	81	− 0.03 (−0.07, 0.02)	533	1	34.0–208.0	− 0.11 (−0.23, 0.01)
				2	221.8–518.8	0.02 (−0.05, 0.08)
				3	547.8–800.0	− 0.02 (−0.10, 0.06)
				4	805.0–1543.5	0.04 (−0.08, 0.15)
HOMA-IR	35	− 0.15 (−0.29, −0.01)*	662	1	<226.0	− 0.12 (−0.32, 0.08)
				2	227.0–582.0	− 0.20 (−0.43, 0.04)
				3	583.0–889.0	− 0.26 (−0.45, −0.08)*
				4	>889.0	− 0.03 (−0.65, 0.59)
HbA1c, %	27	− 0.05 (−0.09, −0.01)*	661	1	<401.0	− 0.003 (−0.08, 0.08)
				2	401.0–661.0	− 0.10 (−0.17, −0.04)*
				3	662.0–963.0	0.03 (−0.10, 0.15)
				4	>964.0	− 0.07 (−0.30, 0.16)
Serum lipids						
TC, mmol/L	91	− 0.07 (−0.14, 0.007)	548.5	1	38.5–257.1	0.05 (−0.07, 0.17)
				2	270.8–547.9	0.01 (−0.04, 0.06)
				3	549.2–850.0	− 0.15 (−0.26, −0.05)*
				4	870.0–1543.4	− 0.12 (−0.29, 0.06)

(*Continued*)

TABLE 1 (*Continued*)

Outcomes	Total flavan-3-ol analysis			Total flavan-3-ol dose quartile		
	Number of studies	Mean difference (summary estimate)[2]	Median daily intake, mg	Quartiles by intake	Intake range, mg	Mean difference (summary estimate)[2]
LDL-C, mmol/L	87	− 0.07 (−0.13, −0.009)*	518.7	1	38.5–257.1	− 0.04 (−0.13, 0.06)
				2	270.8–536.0	− 0.01 (−0.06, 0.03)
				3	547.9–814.0	− 0.10 (−0.20, −0.004)*
				4	850.0–1543.4	− 0.12 (−0.26, 0.02)
HDL-C, mmol/L	92	0.03 (0.01, 0.04)*	508.9	1	38.5–230.7	0.05 (0.008, 0.090)*
				2	233.3–500.0	0.02 (−0.006, 0.042)
				3	517.7–812.2	0.04 (0.008, 0.071)*
				4	814.0–1543.4	− 0.02 (−0.04, 0.001)
TG, mmol/L	92	− 0.03 (−0.07, −0.003)*	533.3	1	38.5–241.7	− 0.05 (−0.11, 0.02)
				2	242.1–518.7	0.001 (−0.08, 0.08)
				3	547.9–805.0	− 0.02 (−0.06, 0.03)
				4	812.2–1543.4	− 0.05 (−0.13, 0.03)

[1] Data from Raman et al. (15) Supplementary Tables 3 and 7–17. DBP, diastolic blood pressure; FMD, flow-mediated dilation; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NR, not reported; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

[2] Mean difference between flavan-3-ol treatment group and control group. Summary estimate represents 95% CI. ∗Indicates significance of $P < 0.05$.

When the meta-analysis was limited to studies of good methodological quality, the following outcome measures were significant: systolic blood pressure (−1.29 mmHg; 95% CI: −2.45, −0.13 mmHg) and diastolic blood pressure (−1.24 mmHg; 95% CI: −2.13, −0.34 mmHg), acute FMD (1.15%; 95% CI: 0.71, 1.59%), chronic FMD (1.30%; 95% CI: 0.59, 2.00%), total cholesterol (−0.06 mmol/L; 95% CI: −0.11, −0.001 mmol/L), HDL cholesterol (0.02 mmol/L; 95% CI: 0.001, 0.05 mmol/L), and HOMA-IR (−0.29; 95% CI: −0.48, 1.0). Notable differences from the original analysis of all studies include nonsignificant findings for LDL cholesterol, triglycerides, and HbA1c. Results were not provided for inflammatory biomarkers or lipid ratios.

Rationale and supporting evidence for the recommendation

The Academy of Nutrition and Dietetics, National Academies of Science, Engineering, and Mathematics, and most experts agree that clinical practice guidelines should be based on high-quality systematic reviews of evidence (13, 17–21). Our recommendation reflects careful consideration of the systematic review/meta-analysis by Raman et al. along with other scientific evidence reporting on flavan-3-ols and cardiometabolic health outcomes with much supporting data reported herein (15). Not only was the strength of evidence considered, but the Expert Panel also considered the magnitude of benefits and harms, costs, barriers and facilitators, resource and feasibility issues, and implementation factors. Strength of recommendation was assigned based on the Expert Panel's evaluation of the totality of evidence, benefits and harms, consistency, clinical effect, and both generalizability and applicability.

The influence of flavan-3-ols on cardiometabolic risk factors served as the basis for the recommendation statement, although again, strength of evidence was stronger for some biomarkers (i.e., systolic blood pressure, total cholesterol, HDL cholesterol, and insulin/glucose dynamics). Dose consistency among various meta-analyses including data from randomized clinical trials and observational (cohort) studies supports the 400–600 mg/d recommendation for cardiometabolic health. The Expert Panel also considered the European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition, and Allergies' Scientific Opinions authorizing the health claim on consumption of cocoa flavanols and maintenance of normal endothelium-dependent vasodilation, and the specific proposed concentrations for proanthocyanidins and catechins by the Chinese Nutrition Society (22, 23). Although the small effects exerted by flavan-3-ols on individual biomarkers (e.g., a 1 mm Hg decrease in systolic and diastolic blood pressure) might seem clinically insignificant in isolation, it has been noted that each 2-mmHg increase in systolic blood pressure increases mortality due to ischemic heart disease and stroke by 7% and 10%, respectively (24). As another example, a 0.026-mmol/L increase in HDL cholesterol concentrations has been reported to reduce CVD risk by 2–3% (25). Similarly, a 1% reduction in CVD risk has been reported with either a 1% reduction in LDL cholesterol or 1% increment in HDL cholesterol concentrations (26). Taken collectively, the cumulative improvements, albeit modest, in multiple biomarkers shown across the current scientific literature could have substantial benefits to overall risk reduction at both the individual and public health level.

To better understand the protective effects of flavan-3-ols, it is important to first consider their bioaccessibility and bioavailability. Due to extensive metabolism by both human and microbial systems, metabolites (not native forms of flavan-3-ols) are the main forms present in circulation and available for tissue uptake, metabolism, and biological activity (27). During absorption in the small intestine, flavan-3-ols can be subjected to metabolic activities in enterocytes (28). Next, hepatic phase II conjugation with methyl, sulfate, and glucuronide conjugation alters their polarity, after which metabolites can be recycled back into the small intestine by biliary excretion (29). The human microbiota is capable of efficiently metabolizing flavan-3-ols and their conjugated metabolites into smaller molecular weight compounds that are efficiently absorbed into the bloodstream and detected in human urine. A variety of flavan-3-ol metabolites have been detected in human plasma postingestion, which can be freely circulating or bound to proteins in the bloodstream. It has been suggested that after entering the bloodstream, flavan-3-ols interact with a series of complex molecular mechanisms that mediate CVD (27–34). Furthermore, direct interactions between flavan-3-ols and the gut microbiome are likely to alter host immune and inflammatory status as well as microbiome diversity. For example, the activity of absorbed parent compounds and of microbial metabolites appears to involve action on key cell receptors or crosstalk between cell signaling pathways, ultimately differentially affecting various cells and tissues, depending on the cell phenotype and metabolic environment (35).

The most documented cardiovascular activity of flavan-3-ols is their positive effects on vasculature. For example, biomarker-estimated flavan-3-ol intake was inversely associated with reduced systolic and diastolic blood pressure in the EPIC Norfolk study (36). Additionally, flavan-3-ols have also been shown to reduce arterial stiffness (37, 38). The exact mechanisms behind these improvements likely include the enhanced bioavailability of endothelial-derived nitric oxide, decreasing superoxide-mediated nitric oxide breakdown, and improvement in serum lipids. To put this in perspective, just a 1% increase in FMD has been shown to reduce CVD risk by 8% and 13% in asymptomatic and diseased populations, respectively (39). Lastly, animal and in vitro studies provide emerging evidence that flavan-3-ols improve inflammatory status via the interference of pro-oxidant enzyme-signaling cascades and adhesion molecule expression (40); however, fluctuations in background cytokine production contribute to difficulty in detecting subtle changes in inflammatory status. More recent evidence supporting the cardiovascular benefits derived from flavan-3-ols

TABLE 2 Results by CVD status and by duration for flavan-3-ol intake and cardiometabolic outcomes from randomized controlled trials included in Raman et al. (15)[1]

Outcomes	CVD status			Intake duration		
	Y/N[2]	Number of studies	Mean difference (summary estimate)[3]	Length of intervention, mo	Number of studies	Mean difference (summary estimate)[3]
Blood pressure						
SBP, mmHg	N	82	−1.40 (−2.23, −0.56)*	<3	61	−1.24 (−2.13, −0.35)*
				3–6	23	−1.70 (−3.26, −0.13)*
	Y	4	−3.45 (−5.21, −1.69)*	>6	2	−4.35 (−7.39, −1.31)*
DBP, mmHg	N	84	−1.01 (−1.53, −0.50)*	<3	64	−1.01 (−1.64, −0.38)*
				3–6	25	−0.98 (−1.90, −0.07)*
	Y	2	0.04 (−2.25, 2.32)	>6	2	−0.65 (−2.61, 1.31)
Flow-mediated dilation						
Acute FMD, %	N	18	1.64 (1.23, 2.06)*	<3	NR	NR
				3–6	NR	NR
	Y	?	NR	>6	NR	NR
Chronic FMD, %	N	17	1.05 (0.48, 1.62)	<3	22	1.22 (0.69, 1.75)*
				3–6	1	1.08 (−0.10, 2.26)
	Y	6	1.88 (0.30, 3.46)	>6	0	N/A
Glucose metabolism						
Blood glucose, mmol/L	N	80	−0.02 (−0.07, 0.02)	<3	48	−0.01 (−0.04, 0.05)
				3–6	27	−0.08 (−0.19, 0.03)
	Y	3	−0.22 (−0.76, 0.32)	>6	4	−0.12 (−0.67, 0.44)
HOMA-IR	N	30	−0.15 (−0.29, −0.01)*	<3	20	−0.10 (−0.27, 0.08)
				3–6	12	−0.30 (−0.50, −0.10)*
	Y	1	−0.30 (−2.04, 1.44)	>6	3	−0.18 (−1.01, 0.65)
HbA1c, %	N	24	−0.05 (−0.09, −0.004)*	<3	12	−0.002 (−0.07, 0.07)
				3–6	13	−0.08 (−0.14, −0.02)*
	Y	1	−0.20 (−0.53, 0.13)	>6	2	−0.14 (−0.37, 0.10)
Serum lipids						
TC, mmol/L	N	87	−0.06 (−0.14, 0.01)	<3	60	−0.05 (−0.14, 0.04)
				3–6	29	−0.09 (−0.21, 0.04)
	Y	4	−0.12 (−0.30, 0.07)	>6	2	−0.09 (−0.31, 0.13)
LDL-C, mmol/L	N	77	−0.07 (−0.13, −0.007)*	<3	55	−0.06 (−0.13, 0.02)
				3–6	26	−0.08 (−0.17, 0.02)
	Y	4	−0.07 (−0.38, 0.24)	>6	6	−0.11 (−0.26, 0.03)
HDL-C, mmol/L	N	84	0.03 (0.01, 0.05)*	<3	58	0.01 (−0.01, 0.02)
				3–6	31	0.05 (0.01, 0.09)*
	Y	4	0.02 (−0.05, 0.08)	>6	3	0.07 (0.01, 0.13)*
TG, mmol/L	N	85	−0.03 (−0.06, 0.01)	<3	59	−0.01 (−0.05, 0.04)
				3–6	30	−0.10 (−0.16, −0.04)*
	Y	4	−0.10 (−0.24, 0.03)	>6	3	−0.02 (−0.19, 0.15)

[1] Data pulled from Raman et al. (15) Supplementary Tables 3 and 7–17. CVD, cardiovascular disease; DBP, diastolic blood pressure; FMD, flow-mediated dilation; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NR, not reported; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

[2] Y/N = yes or no; Yes = CVD diagnosis, No = no CVD diagnosis.

[3] Mean difference between flavan-3-ol treatment group and control group. Summary estimate represents 95% CI. *Indicates significance of $P < 0.05$.

was published from the COSMOS randomized clinical trial evaluating a cocoa extract supplement (500 mg flavanols/d) in ~21,000 older adults (41). Following a median treatment and follow-up period of 3.6 y, a significant 27% reduction in CVD deaths was observed as well as a significant 16% reduction in major cardiovascular events (i.e., myocardial infarction, stroke, CVD death). Although it is critical to extend mortality follow-up, current results support long-term cardiovascular benefits through the provision of a flavan-3-ol–rich intervention. Additionally, a recent meta-analysis of cohort studies investigating the relation between flavonoid consumption and cardiovascular outcomes (42) builds upon findings from Raman et al. (15). Individuals with the highest intake of flavan-3-ols, catechins, and proanthocyanidins had a 15%, 25%, and 17% significantly lower RR, respectively, of CVD compared with individuals with the lowest intake (42).

Although Raman et al. found moderate evidence in prospective cohort studies that flavan-3-ol intake was associated with a reduced risk of CVD mortality, CHD, stroke, and type 2 diabetes mellitus, no association was shown for incidence of hypertension (15). However, a notable limitation in evaluation of these prospective cohort studies is the tool for assessing risk-of-bias. This tool did not include an "ascertainment of exposure" question, which is one of the unique challenges that should be considered in nutrition-related systematic reviews (43). Additionally, the majority of included prospective cohort studies within Raman et al. included only a single dietary assessment and, therefore, the data did not likely constitute moderate level evidence (15). Several other challenges/limitations arise regarding intake of flavan-3-ols using data from prospective cohort studies. First, if a substantial portion of the diet is replaced by a food (or foods) high in flavan-3-ols, then total energy intake and other nutrients associated with plant food intake (e.g., dietary fiber) likely also improve. This can lead to the conclusion that a wide variety of flavan-3-ol sources and amounts can provide a detectable health benefit. It remains unclear, however, how much of that benefit is directly attributable to the effects of flavan-3-ols compared with elimination of less healthy components from the diet, a reduced caloric intake, or increased consumption of other healthy dietary constituents. Additionally, it should be noted that confounding factors including potential effect modifiers and multicollinearity along with lack of adjustment for covariates might affect any observed association. These phenomena can also occur to a lesser extent in clinical trials of flavan-3-ol–rich foods. Despite challenges that arise from use of data from prospective cohort studies, the consistency among these investigations considered for this guideline support the Expert Panel recommendation of 400–600 mg/d flavan-3-ol intake for cardiometabolic health.

Future prospective cohort studies would benefit from using omics technologies to identify and validate novel biomarkers of exposure to assist researchers in overcoming measurement error from assessing flavan-3-ol intake via FFQs. Additionally, although genetic instrumental variable analysis, commonly known as Mendelian randomization, cannot establish causality, it does have the potential to eliminate reverse-causation that is prevalent in traditional nutrition epidemiology. Of interest, a genetically predicted extra daily cup of tea consumption was associated with a decrease in small vessel stroke (OR: 0.79; 95% CI: 0.69, 0.91; $P = 0.001$) in a recent Mendelian randomization analysis of UK Biobank participants (44).

Potential risks or adverse events associated with flavan-3-ol intake

The potential risks of increasing flavan-3-ol intake through supplementation are of concern and warrant elaboration. Concentrated green tea extracts and purified catechins, including the well-known epigallocatechin gallate (EGCG), have been implicated in both benefits and harms from green tea. Liver injury and gastrointestinal distress are the most widely reported adverse effects associated with flavan-3-ol consumption, mainly arising from supplementation with concentrated green tea extracts in a fasted state. Because intake recommendations should draw heavily upon toxicology tenets, the Expert Panel considered evidence from 3 high-quality systematic reviews and risk assessments when developing the guideline (**Table 3**) (45–47). The systematic reviews highlight numerous reports of potential green tea extract–mediated hepatotoxicity that suggest liver damage can occur after ingestion of bolus doses in high quantities (>800 mg) for extended periods of time. Liver injury due to green tea supplements typically manifests within 3 mo of chronic ingestion; however, the latency to onset of symptoms can range from 10 d to 7 mo (48, 49). Most cases present symptoms of acute hepatitis accompanied by marked hepatocellular enzyme elevations. Under specific conditions such as fasting, higher doses and repeated administration of green tea extract result in systemic plasma catechin concentrations that are substantially higher than when ingested under fed conditions and/or low single doses. Damage to the liver can occur through the first- and second-phase metabolism of catechins when saturation of drug metabolizing enzymes occurs. In several animal toxicity studies, EGCG has been shown to accumulate in the liver causing dose-dependent liver necrosis resulting in the primary cause-of-death in test animals (50–53). Toxicity worsened when EGCG was administered as a high-dose supplement to animals under fasting conditions. Other reported adverse effects of flavan-3-ol preparations include gastrointestinal distress (i.e., nausea, vomiting, and stool abnormalities), dizziness, and muscle fatigue (47, 54, 55). In animal models, absorbed EGCG damaged the gastrointestinal tract in a dose-dependent manner (56).

The Expert Panel also considered several assessments and opinions by authoritative scientific bodies that provided guidance around the safety of green tea extracts or EGCG including the US Pharmacopeia (47), Health Canada (57), EFSA (55), and Norwegian Institute of Public Health (58). Each has provided cautionary guidance around the use of

TABLE 3 Systematic reviews of risk assessment associated with flavan-3-ol intake[1]

Author (year)	Study characteristics	Dose range	Key findings
Hu et al. (2018) (45)	Systematic review of human intervention studies of green tea and green tea extract preparations	Green tea: 96.3 to 1343 mg/d	Catechin-rich green tea preparations resulted in hepatic adverse events in a dose-dependent manner when ingested in large bolus doses, but not when consumed as brewed green tea or extracts in beverages or as part of food
	104 studies monitored and reported adverse events	Green tea extracts and purified EGCG: 29.5 to 4000 mg/d	Suggested safe intake level of 338 mg EGCG/d for green tea preparations ingested as a bolus dose
	53 studies examined brewed green tea or green tea extract delivered in beverage form. Remaining studies examined green tea preparations administered as a solid dosage via capsules		An Observed Safe Level (OSL) of 704 mg EGCG/d for preparations in beverage form
Yates et al. (2017) (46)	Risk assessment using basic principles to establish an EGCG upper limit as described in the FAO/WHO Technical Report	Human intervention studies: 100 to 1600 mg/d EGCG	None of the studies in healthy or diseased patients reported adverse liver effects of EGCG at doses <600 mg/d
	There were 10 animal studies, 27 human interventions, and 22 case reports		Higher doses (>600 mg/d) were associated with an elevation in liver enzyme activity within the normal range, whereas levels >800 mg/d were associated with liver enzyme activity above the normal range
			An overall average incidence of liver injury from consuming EGCG over ∼10 y is 0.0036 in 10,000 persons from case studies, where no dose–response information was derived
Oketch-Rabah et al. (2020) (47)	US Pharmacopeia systematic review of 204 human clinical research studies and 127 animal studies of green tea extracts	Human cases reviewed involved use of green tea extracts from 500 to 3000 mg/d (∼250 to 1800 mg/d EGCG)	Green tea extracts can contain hepatotoxic solvent residues, pesticide residues, pyrrolizidine alkaloids, and elemental impurities, but no evidence of their involvement in green tea extract–induced liver injury was found
	51 published case report articles reporting 75 individual cases associated with green tea extract intake		Animal and human data indicate repeated oral consumption of bolus doses during fasting significantly increases bioavailability of catechins (specifically EGCG)
			Published adverse event case reports associate hepatotoxicity with EGCG intake amounts from 140 to 1000 mg/d with substantial interindividual variability
			Statement: US Pharmacopeia recommended a cautionary label requirement in its Powdered Decaffeinated Green Tea Extract monograph that reads as follows: *Do not take on an empty stomach. Do not use if you have a liver problem and discontinue use and consult a healthcare practitioner if you develop symptoms of liver trouble, such as abdominal pain, dark urine, or jaundice (yellowing of the skin or eyes)*

[1] EGCG, epigallocatechin gallate.

high-dose supplemental green tea extracts or EGCG. For example, the recent scientific opinion from EFSA regarding the safety of green tea catechins concluded that there is evidence from clinical trials that intake of doses ≥800 mg EGCG/d taken in supplemental form can increase serum transaminases. Similarly, the Chinese Nutrition Society has proposed a 800 mg/d tolerable upper intake level for proanthocyanidins (23). As such, foods including tea, cocoa,

cinnamon, apples, and berries should be prioritized over supplementation when seeking potential cardiometabolic benefits from flavan-3-ols.

Considerations for equity, barriers, and facilitators

In order to assess the health equity of the guideline, it must be acknowledged that mean dietary intake of flavan-3-ols varies greatly among the general adult population. For example, in the United States, the mean intake is 223 mg/d compared with 793 mg/d in Ireland (59). Across the globe, the greatest food sources of flavan-3-ols include tea, apples, pears, berries, and chocolate/cocoa products (16, 59, 60). Despite the variety of flavan-3-ol sources, intake analysis from the NHANES 2007–2016 shows tea accounting for 35–94% of dietary flavan-3-ol intake in the United States (60). Among tea consumers, consumption was highest in older adults, non-Hispanic Whites, Asians, and individuals with higher education and socioeconomic status (61). Thus, these results suggest that the equity of health benefits derived from flavan-3-ols might not be achieved equally across all populations.

Regarding acceptability and feasibility, the key question is how stakeholders accept or agree with the conferred effects including benefits or harms as well as cost associated with adopting the guideline. First, given the pervasiveness of cardiometabolic diseases in the general adult population, individual awareness of these diseases has increased, especially among women (62). Thus, practical approaches to reduce risk are warranted. Acknowledging the high benefit-to-risk ratio when flavan-3-ols are consumed in the recommended range of 400–600 mg/d, it is advantageous that foods rich in flavan-3-ols are among the most highly consumed flavonoids by the general population (9–12). Further, the fact that each can be consumed in many forms at a variety of cost points (fresh, dried, beverage, fruit, etc.) extends the feasibility of the guideline. To highlight feasibility, estimated flavan-3-ol contents of primary food sources are provided in **Table 4** along with standard serving sizes (63, 64). Practically speaking, a combination of foods listed allows for intake in the range of the guideline recommendation for cardiometabolic health benefits. Finally, it should be noted that foods in this list with greatest alignment to the Dietary Guidelines for Americans 2020–2025 should comprise the majority of sources for bolstering flavan-3-ol intake (65).

Summary of considerations for special populations

The health efficacy of this bioactive guideline recommendation is dependent upon the bioactivity of flavan-3-ols. Thus, special populations such as those with autoimmune, cancer, and kidney or liver diseases can have altered absorption, distribution, metabolism, and excretion, thus affecting the bioavailability and subsequent effectiveness of phenolic compounds in food (66, 67). Similarly, specific life stages, such as pregnancy, can also affect the bioactivity of phenolic compounds. For example, some clinical trials evaluating flavan-3-ol intake from berries and cocoa/chocolate products on health outcomes in pregnancy showed improvement in maternal weight gain, glycemic control, inflammation, and placental function (68–70).

Evidence for intake of flavan-3-ol supplements

Although this bioactive can be consumed in supplement form, it should be noted that a supplement is intended to complement or enhance the diet. By the very definition, a supplement is defined as a dietary substance to supplement the diet by increasing the total dietary intake (71). Because toxicity is more commonly associated with high-dose single-nutrient supplementation than with foods (72), a food-first approach to flavan-3-ol intake could capitalize on the potential synergy of this bioactive with other nutrients in the food matrix while also minimizing risks associated with intake of supraphysiological doses of individual compounds from extracts or supplements. Furthermore, this guideline is a food-based guideline and not a recommendation for flavan-3-ol supplements. Lastly, as foods provide an assortment of nutrients and bioactive compounds with benefits for health, the Dietary Guidelines for Americans 2020–2025 and Canada's Dietary Guidelines recognize that nutrition requirements should be met primarily through foods (65, 73).

Discussion

A guideline recommendation for a plant bioactive such as flavan-3-ols is a departure from previous recommendations as it is not based on deficiencies but rather improvement in health outcomes. The Expert Panel found moderate evidence supporting cardiometabolic protection resulting from flavan-3-ol intake such that we are proposing the first dietary recommendation for a bioactive compound. The recommendation of 400–600 mg/d for flavan-3-ols to improve cardiometabolic health is based on beneficial effects observed across a range of disease biomarkers and endpoints. This recommendation is higher than the recent health claim of 200 mg/d for cocoa-flavanols by EFSA (22). The main reason for this discrepancy is that the EFSA health claim is only based on vasodilation as an endpoint and no other cardiometabolic disease markers. Regarding upper intake limits for flavan-3-ols, risk assessments of green tea catechins by EFSA concluded that no adverse effects are expected for intakes <800 mg/d (55).

It must be acknowledged that challenges were encountered in establishing this guideline, such as limitations from lack of homogeneity in protocols. For example, studies included in the Raman et al. systematic review/meta-analysis reported large discrepancies in quality as well as lack of consensus in population description, duration of supplementation, form of bioactive/food/extract, and statistical methods (15). Implementing methodological consensus in executing and describing randomized clinical trials would allow for more rigorous assessment of study findings for comparison and pooling of data. Other limitations include the following: inclusion of more men than women in randomized clinical trials, different biomarkers used to assess prevention and development of cardiometabolic disease, and

TABLE 4 Food sources rich in flavan-3-ols

Food[1]	Amount	Flavan-3-ol content,[2] mg
Tea, green, brewed (92303010)	8 ounces (240 g)[3]	318.74
Tea, black, brewed (92302000)	8 ounces (240 g)[3]	277.32
Blackberries, raw (63201010)	1 cup (150 g)	63.76
Craisins (62109100)	$\frac{1}{2}$ cup (80 g)	33.78
Dark chocolate, 70–85% cacao solids (91705030)	3 squares (18 g)	19.49
Red wine (93401010)	5 ounces (150 g)	16.62
Apple (63101000)	1 small (165 g)	15.33
Cocoa powder (118301150)	1 tablespoon (5 g)	13.06
Blueberries, raw (63203010)	1 cup (150 g)	10.04
Raspberries, raw (63219000)	1 cup (150 g)	8.74
Strawberries, raw (63223020)	1 cup (150 g)	6.90
Grapes, red or green, raw (63123000)	1 cup (150 g)	5.82

[1] Code in the Food Nutrition Database for Dietary Studies (FNDDS).
[2] Flavan-3-ol content using the What's in the Foods You Eat Search Tool (63) and the USDA Database for the Flavonoid Content of Selected Foods, Release 3.3 (64).
[3] Amount in grams specific to tea leaves by dry weight.

heterogeneity in dosages examined along with metabolism and assessment of circulating concentrations, which was not routinely evaluated. Additionally, it should be noted that cohort studies often relied on self-reported dietary intake, often at one time point, to assess benefit, which could contribute to information bias compromising internal validity; furthermore, the estimates of flavan-3-ol exposure were calculated from different food composition databases, which could preclude precise comparability. Although FFQ data can clearly differentiate between extremes of intake, this assessment method does not account for the extensive interindividual metabolism that these compounds undergo after ingestion, which could impact effectiveness. As such, future studies should integrate biomarker, genetic, and dietary assessment methods to assess the effect of flavan-3-ols and their metabolites on cardiometabolic health.

Considering a lack of homogeneity among studies, several research considerations would improve the generalizability (external validity) of results from randomized clinical trials. For example, dose-dependent trials are warranted to assess minimal and maximal dose effects along with identifying potential negative effects from higher doses. Additional repository databases should be developed not only to report studies, but also to archive raw data and results to allow future ancillary analyses. This would allow for comparison and merging of results, thus increasing the total sample size,13 thereby increasing statistical power. Further, standardization in biomarkers of intake and exposure to flavan-3-ols is warranted. For example, γ-valerolactones, a flavan-3-ol metabolite formed by the colonic microbiome, can be used as markers of chronic flavan-3-ol intake (74). Future research should also include more diverse populations to assess interindividual variability for optimizing dietary recommendations and food product development, especially for specific population subgroups. Further, although this guideline was developed from research on the general adult population, additional research evaluating flavan-3-ol intake earlier in the lifespan is warranted because dietary habits adopted earlier in life can contribute to the magnitude of effect of flavan-3-ols on cardiometabolic health.

In conclusion, when quality evidence is available to make an evidence-based intake guideline, such a recommendation can inform multiple stakeholders including clinicians, policymakers, public health entities, and consumers. Evidence gaps identified in the review process can inform scientists, thereby guiding future randomized clinical trials. In summary, upon review of data from human studies reporting effects of foods rich in flavon-3-ols, the Expert Panel found moderate evidence supporting cardiometabolic protection resulting from flavan-3-ol intake in the range of 400–600 mg/d. It should be noted that the beneficial effects were observed across a range of disease biomarkers and endpoints; furthermore, this is a food-based guideline and not a recommendation for flavan-3-ol supplements.

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had primary responsibility for the final manuscript; and all authors: read and approved the final manuscript.

Data Availability

There are no data specific to this manuscript.

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