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Review

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Citrus Flavanones: What Is Their Role in Cardiovascular Protection?

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ABSTRACT: Flavanones, including hesperidin and naringin, are polyphenolic compounds highly and almost exclusively present in citrus. Epidemiological studies reported an inverse relationship between their intake and the risk of cardiovascular diseases. Clinical and experimental data further showed their antihypertensive, lipid-lowering, insulin-sensitizing, antioxidative, and anti-inflammatory properties, which could explain their antiatherogenic action in animal models. Although flavanones may be promising compounds that are particularly active in cardiovascular disease prevention, clinical data are still scarce and most in vitro data have been obtained under nonphysiologically relevant conditions. Moreover, the mechanisms responsible for flavanone action are not fully elucidated. Therefore, further research is needed to better evaluate and understand the protective effects of flavanones in cardiovascular diseases.

KEYWORDS: *citrus flavanones, cardiovascular protection, vascular function, lipid profile, insulin resistance, inflammation, oxidative stress*

INTRODUCTION

Cardiovascular disease (CVD) represents one of the leading causes of death worldwide. Although epidemiological studies have revealed an inverse association between high consumption of fruits and vegetables and a reduced risk of CVD,[1−4] the role of the compounds providing these protective effects is still under investigation. Plant foods contain numerous bioactive molecules, among which are polyphenols. These molecules are the most abundant dietary antioxidants, and their effects on health have gained huge interest. Polyphenols are plant secondary metabolites characterized by a basic structure consisting of an aromatic ring with one or more hydroxyl groups. According to their chemical structures, polyphenols can be divided into four major classes: phenolic acids (C6−C1 and C6−C3), flavonoids (C6−C3−C6), stilbenes (C6−C2−C6), and lignans (C6−C3−C3−C6).[5] The main polyphenols found in the human diet are phenolic acids and flavonoids, which represent approximately two-thirds and one-third of the total daily intake of polyphenols, respectively.[6,7] Epidemiological studies have reported an inverse relationship between flavonoid-rich food consumption and cardiovascular events.[8,9] This observation is further supported by clinical and preclinical studies of either flavonoid-rich foods or isolated flavonoids demonstrating their beneficial effects on cardiovascular risk factors such as blood pressure, endothelial function, platelet function, and cholesterolemia.[10−19]

Dietary flavonoids are divided into six subclasses according to their structural features: flavonols, flavones, isoflavones, flavanones, anthocyanidins, and flavanols (catechins and proanthocyanidins). Some of these classes are present only in specific foods, whereas others are distributed in a wide range of foods. Considering the abundance of flavanones in citrus fruits and juices, both largely consumed in the world, these compounds contribute substantially to the total daily flavonoid intake. Evidence from epidemiological, clinical, and preclinical studies has shown that flavanones are biologically active compounds likely to contribute to cardiovascular prevention. The purpose of this review is to compile coherent data related to dietary flavanones and cardiovascular health.

DIETARY SOURCES AND FLAVANONE INTAKE

Flavanones represent a flavonoid subclass present in our diet almost exclusively in citrus fruits and, to a lesser extent, in tomatoes and some aromatic herbs (such as mint). In citrus fruits, flavanones account for approximately 95% of the total flavonoids.[20,21] The main aglycones are naringenin (5,7,4′-trihydroxyflavanone) in grapefruit, hesperetin (4′-methoxy-3′,5,7-trihydroxyflavanone) in orange and tangerine, and eriodictyol (5,7,3′,4′-tetrahydroxyflavanone) in lemon (see refs 20 and 21 for reviews) (Figure 1). In citrus fruits and citrus-derived products, flavanones are generally glycosylated by a disaccharide at position 7: either a neohesperidose, which imparts a bitter taste, such as naringin in grapefruit, or a flavorless rutinose, such as hesperidin in oranges.[22] In citrus fruits, the flavanone content also varies depending on the part of the fruit. The solid parts of the fruit, particularly the albedo (the white spongy portion) and the membranes separating the segments, are richest in flavanones compared to juice vesicles (pulp), which explains the higher content of flavanones in the whole fruit than in the juice.[23] In the edible part of oranges, the glycoside content (hesperidin and narirutin) ranges from 35 to 147 mg/100 g.[21,24] In grapefruit, naringenin glycoside (naringin and narirutin) content ranges from 44 to 106 mg/100 g in the edible fraction.[20,25] Citrus juices have lower flavanone concentrations because albedo and segments are discarded. After compilation of food composition data, Tomas-Barberan et

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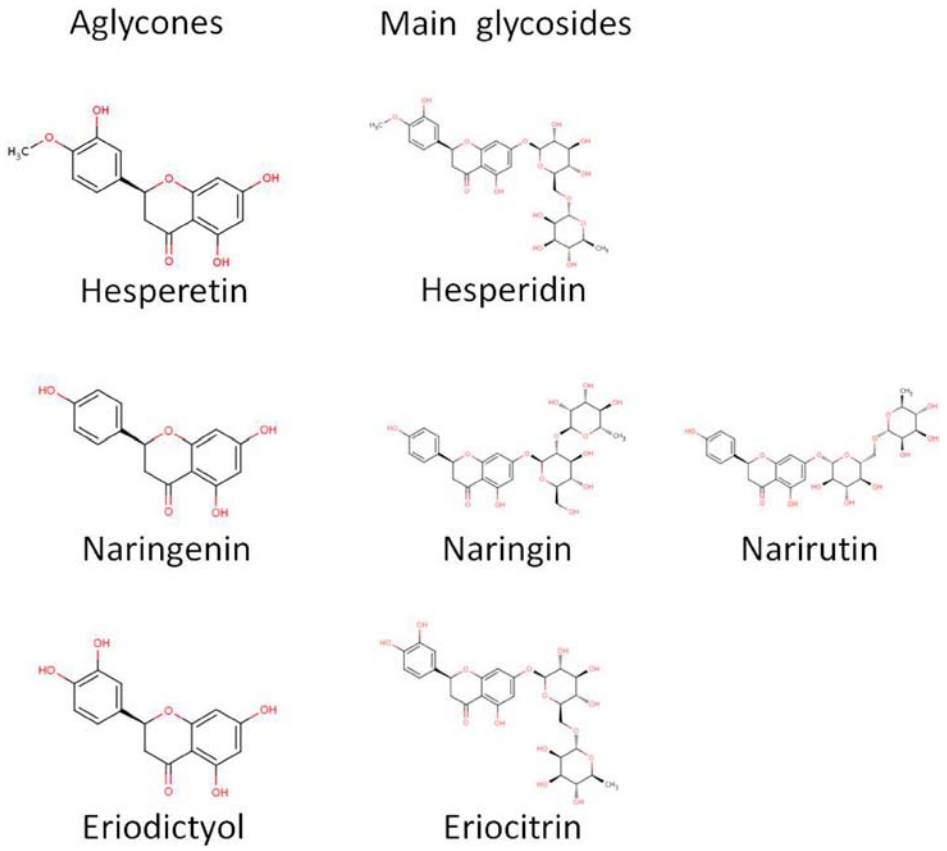

Figure 1. Citrus flavanones.

al. have estimated the mean flavanone content in orange juice (hesperidin plus narirutin) to range from 14 to 77 mg/100 mL.[23] In another study, the content of naringenin glycosides in various brands of grapefruit juices was estimated to vary between 17 and 76 mg/100 mL.[26]

Because food composition databases lacked information on polyphenols for a long time, flavanone intake has not been estimated in many epidemiological studies. The daily intake of flavanones in adults from different countries was estimated to range from 2.7 to 78 mg of aglycone equiv.[7,27] The flavanone intake seems particularly high in southern Europe, where it has regularly been classified as the first-[28] or second-most[29−32] consumed flavonoid group. Oranges (as whole fruits and juices) appear to be the main contributor to flavanone intake.[32]

FLAVANONE BIOAVAILABILITY

Prior to absorption, glycosylated forms of flavanones must be hydrolyzed by the glycosidase activities of the colonic microflora.[5,33] The free aglycones released are then taken up and conjugated by phase II enzymes in both the intestine and the liver. As a result, flavanones exist in the plasma mainly as sulfated and glucuronidated metabolites.[34] However, glycosides have also been detected in urine.[35] Because flavanones must reach the colon to be absorbed, their plasma concentrations are maximal around 6 h after ingestion.[5]

After consumption of orange juice, the metabolites identified in the plasma were hesperetin-7-glucuronide, hesperetin-3′-glucuronide, hesperetin-3′-sulfate, naringenin-4′-glucuronide, and naringenin-7-glucuronide.[36,37] The mean peak plasma concentrations of flavanones vary between 0.1 and 1 μM for intakes ranging from a 150 g orange to 500 mL of orange juice (Table 1).[36−43] After ingestion of grapefruit juice (8 mL/kg body wt), the flavanone mean peak plasma concentration was reported to reach 6 μM.[44] In our group, peak plasma concentrations of 0.64 and 0.42 μM were measured after the consumption of a 180 g grapefruit or 500 mL of grapefruit juice (both providing 115 mg aglycone equiv), respectively (unpublished data). Likewise, peak plasma concentrations of 0.47 and 0.6 μM were measured after the intake of 230 g of orange fruit or 550 mL of orange juice (also both providing 115 mg of aglycones), respectively. The similarity between the plasma concentrations of flavanones, observed after administration of whole citrus fruits or juices, suggests that the food matrix did not significantly affect the bioavailability of these flavonoids.

Urinary excretion of flavanones mainly occurs during the 24 h following ingestion, peaking between 6 and 12 h. The rate of urinary excretion, expressed as a percentage of the total intake, indicates that flavanones are among the most bioavailable dietary polyphenols.[45] Thus, after consumption of an orange (as juice or whole fruit), the relative urinary excretion of hesperetin varies between 1.7 and 6.4%.[37,41,42] Naringenin excretion after orange juice consumption was recorded to range from 1.1 to 17.7% of its intake.[42,44] From grapefruit juice, the mean urinary excretion of naringenin ranged from 14 to 30.2% of the ingested doses.[44,46] In these studies, the individual urinary excretion values ranged from not detected to 59% of the intake, illustrating the high interindividual variability of flavanone bioavailability.

Table 1. Overview of Flavanone Bioavailability in Human Intervention Studies

no. of subjects	source	portion	dose[a] (mg equiv)	t_{max} (h)	plasma t_{max} concn[a] (μM)	urinary excretion[a] (% intake)	ref
10	orange juice 1	400 mL	Nar: 9.6	4.7	Nar: 0.04	Nar: 2.60	37
			Hesp: 33.6	4.6	Hesp: 0.32	Hesp: 5.40	
	orange juice 2	400 mL	Nar: 12.4	5.7	Nar: 0.44	Nar: 0.70	
			Hesp: 76	6.4	Hesp: 0.37	Hesp: 1.70	
16	orange juice	–	Nar: 0.42 mg/kg bw	5.1	Nar: 0.12	Nar: 7.00	38
20	orange	150 g	Nar: 11.8	5.9	Nar: 0.08[b]	Nar: 12.50	36
			Hesp: 79.7	7.0	Hesp: 0.10[b]	Hesp: 4.53	
	orange juice	300 g	Nar: 9.4	4.5	Nar: 0.05[b]	Nar: 10.20	
			Hesp: 71.8	6.2	Hesp: 0.10[b]	Hesp: 4.63	
109	orange juice	300 g	Nar: 9.4	–	–	Nar: 14.50	36
			Hesp: 71.8	–	–	Hesp: 3.90	
8	orange juice	250 mL	Nar: 3.5		–	Nar: 17.70	42
			Hesp: 51	–	Hesp: 0.92	Hesp: 6.30	
7	blood orange juice	150 mL	Nar: 6	5.0	Nar: 0.06[b]	–	40
			Hesp: 51	5.3	Hesp: 0.14[b]	–	
		300 mL	Nar: 12	5.0	Nar: 0.13[b]	–	
			Hesp: 102	5.1	Hesp: 0.26[b]	–	
16	orange juice	5 mL/kg bw	Hesp: 1 mg/kg bw	7.0	Hesp: 0.48	Hesp: 4.06	43
5	orange juice	0.5 L	Nar: 24	4.6	Nar: 0.06	Nar: 7.11	41
			Hesp: 111	5.4	Hesp: 0.46	Hesp: 4.13	
		1 L	Nar: 48	5.0	Nar: 0.20	Nar: 7.87	
			Hesp: 222	5.8	Hesp: 1.28	Hesp: 6.41	
37	orange juice	211 g	Nar: 29	–	Nar: 0.11	–	39
	orange	1/2	Hesp: 132	–	Hesp: 0.33	–	
	mandarin	1/2					
8	orange juice	8 mL/kg bw	Nar: 0.33 mg/kg bw	5.5	Nar: 0.64	Nar: 1.10	44
			Hesp: 1.74 mg/kg bw	5.4	Hesp: 2.20	Hesp: 5.30	
5	grapefruit juice	8 mL/kg bw	Nar: 2.79 mg/kg bw	4.8	Nar: 5.99	Nar: 30.20	
2	grapefruit juice	1.5 L	Nar: 214	–	–	Nar: 14.00	46

[a]Abbreviations: Nar, naringenin; Hesp, hesperetin. [b]A molecular weight of 272 g/mol for naringenin and 302 g/mol for hesperetin was used for conversion.

INTEREST OF FLAVANONES IN CARDIOVASCULAR PREVENTION

Epidemiological Data. Several prospective studies have reported an inverse relationship between citrus consumption and the risk of coronary events or cerebrovascular disease.[47−50] In a recent epidemiological study involving 10623 Japanese participants, a strong inverse association between citrus fruit consumption and CVD incidence was observed (hazard ratios for almost daily versus infrequent citrus fruit intake: 0.57, 95% CI = 0.33−1.01, in men and 0.51, 95% CI = 0.29−0.88, in women).[51] In another study, grapefruit consumption has been associated with a reduced risk of death from coronary heart disease.[52] Because citrus fruits are the major dietary sources of flavanones, these data provide interesting insight into their potential benefits. However, few epidemiological studies have investigated the direct association between flavanone consumption and cardiovascular events. Recently, in a prospective study conducted among 69622 women from the Nurses' Health Study, flavanone intake was inversely related to risk of ischemic stroke. In this study, women in the top quintile of flavanone intake (>63.0 mg/day) had a relative risk of 0.81 compared with those in the lowest quintile (<13.7 mg/day).[53] Another prospective study conducted in Finland (10054 men and women) also revealed that individuals with a higher intake of flavanones (ranging from 4.7 to 26.8 mg aglycone/day depending on the type of flavanone and the sex of the participant) had a 20% reduction in the incidence of cerebrovascular disease.[54] However, this study did not find an association between flavanone consumption and ischemic heart disease. In a large cohort of postmenopausal women (34489), Mink et al. found no association for stroke but showed that flavanone consumption was inversely correlated with the risk of death from coronary heart disease, with a 15% reduction of death for a consumption reaching 50 mg/day.[52]

Table 2. Effects of Flavanones on Functional Parameters and Systemic Biomarkers Related to Cardiovascular Risk in Clinical Studies

subjects	study design	intervention	daily dose[a] (mg equiv)	period	functional and systemic parameters[b]		effects	ref
men and women with metabolic syndrome	controlled	placebo	–	3 weeks	vascular function	FMD	↑	58
(n = 24), 21–65 years	crossover	hesperidin	Hesp: 250			SBP	↔	
						DBP	↔	
						sICAM	↔	
						sVCAM	↔	
						sE-selectin	↓	
					lipid profile	TG	↔	
						HDL-C	↔	
						LDL-C	↔	
						TC	↓	
						apo B	↓	
						apo A1	↔	
						Lpa	↔	
					inflammation	hs-CRP	↓	
						SAA	↓	
						fibrinogen	↔	
						homocysteine	↔	
healthy men	controlled	CDP: control drink (500 mL) + placebo	–	4 weeks	vascular function	acute microvascular-endothelium related reactivity	↑ for both CDH and OJ	57
(n = 24), overweight, 50–65 years	crossover	CDH: control drink (500 mL) + hesperidin	Hesp: 146					
		OJ: orange juice (500 mL)	Hesp: 146			chronic microvascular-endothelium related reactivity	↔	
			Nar: 24					
						NO metabolites	↔	
						SBP	↔	
						DBP	↓ for both CDH and OJ	
						sICAM-1	↔	
						sVCAM-1	↔	
					lipid profile	TG	↔	
						HDL-C	↔	
						LDL-C	↔	
						TC	↔	
					inflammation	CRP	↔	
						vWF	↔	
						IL6	↔	
					antioxidant capacity	FRAP	↔	
hypercholesterolemic men and women	controlled	placebo	–	4 weeks	lipid profile	TG	↔	60
(n = 194), 18–75 years	parallel	hesperidin	Hesp: 400			HDL-C	↔	
		naringin	Nar: 250			LDL-C	↔	
						TC	↔	
						TC/HDL-C	↔	

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Table 2. continued

subjects	study design	intervention	daily dose[a] (mg equiv)	period	functional and systemic parameters[b]		effects	ref
hypertensive men and women (n = 12)	crossover	HF: sweetie juice high in flavonoids (500 mL)	Nar: 222	5 weeks	vascular function	SBP	↔	56
						DBP	↓ only in HF	
		LF: sweetie juice low in flavonoids (500 mL)	Nar: 58					
healthy (n = 30), 30−60 years	single arm	naringin	Nar: 200	8 weeks	lipid profile	TG	↔	59
						HDL-C	↔	
						LDL-C	↔	
						TC	↔	
						HDL-C/TC	↔	
						apo B	↔	
						apo A1	↔	
					oxidative stress	TBARS	↔	
						catalase	↔	
						glutathione peroxidase	↔	
						SOD	↔	
hypercholesterolemic (n = 30), 30−60 years	single arm	naringin	Nar: 200	8 weeks	lipid profile	TG	↔	59
						HDL-C	↔	
						LDL-C	↓	
						TC	↓	
						HDL-C/TC	↑	
						apo B	↓	
						apo A1	↔	
					oxidative stress	TBARS	↔	
						catalase	↑	
						glutathione peroxidase	↔	
						SOD	↑	

[a]Abbreviations: Nar, naringenin; Hesp, hesperetin. [b]Abbreviations: Apo A1, apolipoprotein A1; Apo B, apolipoprotein B; DBP, diastolic blood pressure; FMD, flow-mediated dilation; FRAP, ferric reducing ability of plasma; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; ICAM, intercellular adhesion molecule 1; IL, interleukin; LDL-C, low-density lipoprotein-cholesterol; Lpa, lipoprotein a; NO, nitric oxide; SAA, serum amyloid A; SBP, systolic blood pressure; SOD, superoxide dismutase; VCAM, vascular cell adhesion molecule; vWF, Von Willebrand factor; TBARS, thiobarbituric acid reactive substances; TC, total cholesterol; TG, triglycerides.

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Table 3. Effects of Flavanones on Parameters Related to Cardiovascular Risk in Animal Studies

parameter	effect[a]	compound	effective dose (%)	model	ref
vascular function	↓ systolic blood pressure	glucosyl hesperidin	50 mg/kg bw	SHR rats (hypertensive)	75, 77
lipid profile	↓ triglyceridemia	hesperidin	0,02	db/db mice (diabetic)	87
		naringenin	0.003, 0.006, 0.012	rats fed a diabetogenic diet	85
		naringenin	1.00	mice fed a diabetogenic diet	86
		naringenin	1.00, 3.00	LDLR−/− mice fed a high-fat diet	16, 83
		naringin	0.02	db/db mice (diabetic)	87
		naringin	50 and 100 mg/kg bw	streptozotocin-induced type 2 diabetic rats fed a high-fat diet	84
	↓ cholesterolemia	hesperidin	0.02	db/db mice (diabetic)	87
		naringenin	0.006	rats fed a diabetogenic diet	85
		naringenin	1.00	mice fed a diabetogenic diet	86
		naringenin	1.00, 3.00	LDLR−/− mice fed a high-fat diet	16, 83
		naringenin	3.00	mice fed a high-fat diet	83
		naringin	0.02	mice fed a high-fat diet	82
		naringin	0.02	mice fed a high-fat high-cholesterol diet	74
		naringin	0.02	db/db mice (diabetic)	87
		naringin	0.05	rabbits fed a high-cholesterol diet	81
		naringin	50−100 mg/kg bw	streptozotocin-induced type 2 diabetic rats fed a high-fat diet	84
		naringin and hesperidin	0.50	rats fed high-cholesterol diet	80
	↓ hepatic TG	hesperidin	0.02	db/db mice (diabetic)	87
		naringenin	1.00, 3.00	LDLR−/− mice fed a high-fat diet	16, 83
		naringenin	3.00	mice fed a high-fat diet	83
		naringin	0.02	db/db mice (diabetic)	87
		naringin	0.05	rabbits fed high-cholesterol diet	81
		naringin and hesperidin	0.50	rats fed high-cholesterol diet	80
	↓ hepatic cholesterol	hesperidin	0.02	db/db mice (diabetic)	87
		naringenin	0.006	rats fed a diabetogenic diet	85
		naringenin	1.00, 3.00	LDLR−/− mice fed a high-fat diet	16, 83
		naringenin	3.00	mice fed a high-fat diet	83
		naringin	0.02	mice fed a high-fat diet	82
		naringin	0.02	db/db mice (diabetic)	87
		naringin	0.05	rabbits fed high-cholesterol diet	81
		naringin and hesperidin	0.50	rats fed high-cholesterol diet	80
	↓ apo B secretion	naringenin	3.00	LDLR−/− mice fed a high-fat diet	83
insulin resistance	↓ glycemia	hesperidin	0.02	db/db mice (diabetic)	87
		naringenin	3.00	LDLR−/− mice fed a high-fat diet	16, 83
		naringenin	3.00	mice fed a high-fat diet	83
		naringin	0.02	db/db mice (diabetic)	87
		naringin	0.02	mice fed a high-fat diet	82
		naringin	50−100 mg/kg bw	streptozotocin-induced type 2 diabetic rats fed a high-fat diet	84
	↓ insulinemia	naringenin	3.00	LDLR−/− mice fed a high-fat diet	16, 83
		naringenin	3.00	mice fed a high-fat diet	83
		naringin	0.02	mice fed a high-fat diet	82
		naringin	25, 50, 100 mg/kg bw	streptozotocin-induced type 2 diabetic rats fed a high-fat diet	84
	↓ insulin resistance	naringenin	1.00, 3.00	LDLR−/− mice fed a high-fat diet	83
		naringin	0.02	mice fed a high-fat high-cholesterol diet	74
		naringin	0.02	mice fed a high-fat diet	82
		naringin	25, 50, 100 mg/kg bw	streptozotocin-induced type 2 diabetic rats fed a high-fat diet	84
oxidative stress	↑ paraoxonase	hesperidin	0.02	db/db mice (diabetic)	87
		naringenin	0.02	rats fed a high-cholesterol diet	97
		naringin	0.02	db/db mice (diabetic)	87
	↑ SOD	naringin	0.02	mice fed a high-fat diet	82

Table 3. continued

parameter	effect[a]	compound	effective dose (%)	model	ref
		naringin	0.05	rabbits fed a high-cholesterol diet	98
		naringin	50−100 mg/kg bw	streptozotocin-induced type 2 diabetic rats fed a high-fat diet	84
	↑ catalase	naringenin	0.02	rats fed a high-cholesterol diet	97
		naringin	0.02	mice fed a high-fat diet	82
		naringin	0.05	rabbits fed a high-cholesterol diet	98
	↑ glutathione peroxydase	naringin	0.02	mice fed a high-fat diet	82
		naringin	0.05	rabbits fed a high-cholesterol diet	98
		naringin	50−100 mg/kg bw	streptozotocin-induced type 2 diabetic rats fed a high-fat diet	84
	↑ glutathione reducatase	naringenin	0.02	rats fed a high-cholesterol diet	97
inflammation	↓ TNFα	naringin	0.02	mice fed a high-fat diet	82
		naringin	50−100 mg/kg bw	streptozotocin-induced type 2 diabetic rats fed a high-fat diet	84
	↓ IL6	naringin	50−100 mg/kg bw	streptozotocin-induced type 2 diabetic rats fed a high-fat diet	84
	↓ CRP	naringin	50−100 mg/kg bw	streptozotocin-induced type 2 diabetic rats fed a high-fat diet	84
	↓ VCAM-1	naringenin	0.05	rabbits fed a high-cholesterol diet	73
		naringin	0.10	rabbits fed a high-cholesterol diet	73
	↓ ICAM-1	naringin	0.02	mice fed a high-fat high-cholesterol diet	74
		naringin	0.50	rabbits fed a high-cholesterol diet	72
	↓ E-selectin	naringin	0.02	mice fed a high-fat high-cholesterol diet	74
	↓ MCP1	naringenin	0.05	rabbits fed a high-cholesterol diet	73
		naringin	0.10	rabbits fed a high-cholesterol diet	73
atherosclerosis development	↓ atherosclerotic lesions	naringenin	0.05	rabbits fed a high-cholesterol diet	73
		naringenin	3.00	LDLR−/− mice fed a high-fat diet	16
		naringin	0.02	mice fed a high-fat−high-cholesterol diet	74
		naringin	0.10	rabbits fed a high-cholesterol diet	73
		naringin	0.50	rabbits fed a high-cholesterol diet	72

[a]Abbreviations: Apo B, apolipoprotein B; CRP, C-reactive protein; ICAM, intercellular adhesion molecule 1; IL, interleukin; MCP1, monocyte chemotactic protein-1; SOD, superoxide dismutase; TNFα, tumor necrosis factor alpha; VCAM, vascular cell adhesion molecule.

Clinical Studies. Several clinical trials have demonstrated an improvement in cardiovascular risk factors after consumption of flavanone-rich foods or isolated flavanones (Table 2).

Impact on Vascular Function. Endothelial function tightly controls both vascular reactivity and integrity, and any alteration of these capacities is highly involved in the initiation of atherosclerosis.[55] Notably, endothelial dysfunction has been associated with the occurrence of hypertension, a well-recognized cardiovascular risk factor. In individuals with stage I hypertension, a double-blind crossover trial evaluated the effect on blood pressure of the consumption of a high-flavonoid citrus juice compared to a low-flavonoid citrus juice.[56] Only consumption of the high-flavonoid citrus juice during 5 weeks resulted in a significant reduction in diastolic blood pressure (DBP, −3.7 mmHg) (Table 2). In agreement with this, another intervention study with a randomized crossover design demonstrated a lower DBP after a 4 week supplementation with hesperidin (292 mg; equivalent to the amount found in 500 mL of orange juice) compared to placebo in overweight subjects.[57] The magnitude of the decrease of DBP after hesperidin consumption (−4 mmHg) was similar to that observed after the consumption of 500 mL of orange juice. In addition, hesperidin ingestion significantly improved the postprandial microvascular endothelial reactivity compared to the placebo, and these changes were positively correlated with plasma hesperetin concentrations. Importantly, this study showed that the flavanone hesperidin may be causally linked to the vascular protective effects observed with orange juice. Recently, another controlled crossover trial involving individuals with metabolic syndrome has shown an improvement in flow-mediated dilation after a 3 week supplementation with 500 mg of hesperidin but with no effect on blood pressure.[58] In this study, hesperidin supplementation also reduced sE-selectin concentrations, a soluble biomarker of endothelial dysfunction. The clinical data available to date indicate that the impact of flavanones is focused on endothelium-dependent vasorelaxation without any changes in vascular smooth muscle cell function.[57,58]

Impact on Blood Lipid Profile. Clinical studies on the effects of flavanones on the blood lipid profile are not consistent. In healthy individuals receiving 400 mg of naringin daily for 2 months, no change in plasma lipid concentration was observed (Table 2).[59] By contrast, the same dose of naringin significantly lowered plasma low density lipoprotein-cholesterol (LDL-C) and total cholesterol (TC) concentrations and increased the high density lipoprotein-cholesterol (HDL-C)/TC ratio in hypercholesterolemic subjects. In individuals with the metabolic syndrome, a 3 week supplementation with 500 mg of hesperidin also significantly reduced TC and apolipoprotein

Table 4. Effects of Flavanones on Parameters Related to Cardiovascular Risk in Cell Studies

parameter	effect[a]	compound	effective dose (μM)	model[a]	ref
vascular function	↑ endothelium-dependent vasodilatory response	hesperetin	10	aortic ring of SHR rats	75
	↑ NO production	hesperetin	0.01−10	BAEC	58
		hesperetin	12.5−100	HUVEC	78
lipid profile	↓ apo B secretion	hesperetin	200	HepG2	94
		hesperetin	200[b]	HepG2	92
		naringenin	75	HepG2	90
		naringenin	100	HepG2	89
		naringenin	100	HepG2	88
		naringenin	100−200	HepG2	94
		naringenin	200	Huh7	93
		naringenin	200	wild-type mouse hepatocytes	91
		naringenin	200	LDLR−/− mouse hepatocytes	91
		naringenin	220[b]	HepG2	92
		naringenin	200	primary rat hepatocytes	93
	↓ cholesteryl ester	hesperetin	200	HepG2	94
		hesperetin	200[b]	HepG2	92
		naringenin	200	HepG2	94
		naringenin	220[b]	HepG2	92
insulin resistance	insulin-like activity	naringenin	50−200	HepG2	89
		naringenin	100	HepG2	88
		naringenin	200	HepG2	91
inflammation	↓ VCAM-1	hesperetin	10	TNFα-stimulated BAEC	58
		hesperetin	50	TNFα-stimulated HUVEC	105
		hesperidin	550	TNFα-stimulated HUVEC	106
		hesperidin	50	TNFα-stimulated HUVEC	105
		naringenin	50	TNFα-stimulated HUVEC	105
		naringin	50	TNFα-stimulated HUVEC	105
	↓ monocyte adhesion	hesperetin	10	TNFα-stimulated BAEC	58
		hesperidin	550	TNFα-stimulated HUVEC	106
		naringenin	1	TNFα-stimulated HUVEC	74
	↓ TNFα	hesperetin	50	LPS-stimulated macrophages	100
		hesperetin	50	LPS-stimulated macrophages	101
		naringenin	90−180[b]	LPS-stimulated macrophages	99
	↓ IL6-IL1β	naringenin	90−180[b]	LPS-stimulated macrophage	99
	↓ PGE2	naringenin	550	LPS-stimulated macrophage	102

[a]Abbreviations: Apo B, apolipoprotein B; BAEC, bovine aortic endothelial cell; HUVEC, human umbilical vein endothelial cells; IL, interleukin; PGE2, prostaglandine E2; TNFα, tumor necrosis factor alpha; VCAM, vascular cell adhesion molecule. [b]A molecular weight of 272 g/mol for naringenin and 302 g/mol for hesperetin was used for conversion.

B (apo B) concentrations.[58] However, hypercholesterolemic subjects receiving 800 mg of hesperidin or 500 mg of naringin,[60] as well as overweight men supplemented with 292 mg of hesperidin,[57] both during 4 weeks, did not show any modification in their blood lipid profile. Given the high similarity of the baseline characteristics of the study subjects and conditions of exposure, such a discrepancy is surprising. A possible explanation might be related to the high variability in flavanone bioavailability among individuals. Even though animal studies support a potential lipid-lowering effect of flavanones (see below), further clinical intervention studies are necessary to clarify their impact on blood lipids in humans.

Impact on Parameters Related to Oxidant/Antioxidant Status and Inflammation. Oxidative stress and chronic inflammation are pathological processes that contribute to atherogenesis and the progression of atherosclerosis.[61,62] In healthy men with cardiovascular risk factors, no changes were observed in the plasma antioxidant capacity following hesperidin supplementation (292 mg) for 4 weeks (Table 2).[57] This result, which does not support a direct antioxidant effect of flavanones in vivo, is not surprising considering both the low antioxidant capacity of the native flavanone structure, further reduced by the conjugation process, and the low circulating levels of conjugated metabolites. Jung et al. investigated the impact of an 8 week supplementation with 400 mg of naringin on antioxidant enzymes and reported a significant increase in erythrocyte catalase and superoxide dismutase (SOD) activities in hypercholesterolemic subjects.[59] This study suggests that flavanones may improve endogenous antioxidant defense systems in dyslipidemic subjects, which may positively affect cardiovascular function. Additional data are needed to confirm these effects.

With regard to inflammation, in subjects with metabolic syndrome, a 500 mg hesperidin supplementation was shown to

reduce the plasma levels of two inflammatory biomarkers, C-reactive protein (CRP) and serum amyloid A (SAA).[58] In healthy, middle-aged, moderately overweight men, despite no effect on circulating inflammatory markers,[57] hesperidin intake (292 mg/day for 4 weeks) tended to modulate gene expression in white blood cells toward an anti-inflammatory profile.[63] In this study the supplementation notably affected the expression of genes involved in processes such as adhesion, chemotaxis, and cell proliferation. Even if clinical data are still insufficient to resolve the anti-inflammatory effect of flavanones in humans, several preclinical studies further support this hypothesis and are discussed below.

Together with clinical trials performed with isolated flavanones, some studies have also been conducted with citrus juices rich in these polyphenols. Interestingly, these later studies revealed modifications of some intermediate biomarkers of cardiovascular risk similar to the studies of isolated flavanones.[57,64−71] This further suggests that flavanones are one of the bioactive compounds responsible for CVD prevention by citrus. It should be noted that the beneficial effects of flavanones are clearer in subjects presenting cardiovascular risk factors. A large interindividual variability regarding flavanone bioavailability could also explain some of the discrepancies observed between the results from clinical studies. Finally, the effects of flavanones on intermediate risk factors for CVD in humans appear interesting and promising, but data are still scarce. Moreover, the impact of dietary flavanones on other key targets of interest for the prevention of CV risk, for example, platelet function, has not been investigated in humans.

Preclinical and in Vitro Studies. Results from numerous in vivo and in vitro studies of the effects of flavanones in relation to cardiovascular protection confirm most of the effects observed in clinical trials and provide clues about their mechanisms of action.

Impact on Atherosclerosis. As suggested by studies performed in various animal models, flavanone consumption may influence the progression of atherosclerosis (Table 3). A 60−70% reduction in the extent of the atherosclerotic lesion was observed in rabbits fed a high-cholesterol diet supplemented with naringin (0.1−0.5%)[72,73] as well as in low-density lipoprotein receptor knockout (LDLR−/−) mice receiving a Western diet supplemented with 3% naringenin.[16] Recently, our group demonstrated a 41% reduction in plaque progression in mice fed a high-fat−high-cholesterol diet supplemented with a nutritional dose of naringin (0.02%, equivalent to the human consumption of half a grapefruit), whereas the same dietary treatment did not affect the extent of the lesion in Apo E−/− mice.[74] Overall, these studies suggest antiatherogenic effects of dietary flavanones, even at doses that could be easily achievable in human diets.

Impact on Vascular Function. Some studies have examined the impact of an acute oral administration of glucosyl hesperidin on vascular function in spontaneously hypertensive rats (SHR) or Wistar rats (Table 3).[75] Of note, glucosyl hesperidin is not a natural compound, but a hesperidin derivative obtained by enzymatic synthesis bearing an additional glucose residue (linkage β 1→4); its solubility and bioavailability are higher than those of hesperidin.[76] After a single oral intake of 50 mg/kg glucosyl hesperidin, a significant reduction in systolic blood pressure was observed in SHR rats.[75] The chronic administration of the same dose of glucosyl hesperidin (50 mg/kg) over 8 weeks also resulted in a moderate reduction in systolic blood pressure (−3%) in SHR rats.[77] Furthermore, 10 μM hesperetin induced an increase in endothelium-dependent vasorelaxation of aortic rings from SHR rats (Table 4).[75]

Vascular tone depends on the balance between vasorelaxing agents such as nitric oxide (NO) and vasoconstrictive agents such as endothelin-1. NO bioavailability in the arterial wall is determined by the balance between its synthesis by endothelial nitric oxide synthase (eNOS) and its inactivation by reactive oxygen species generated by vascular NADPH-oxidase. In agreement with its beneficial effect on vascular tone and endothelial function described clinically and experimentally, hesperetin (0.1−100 μM) was shown to increase both NO production and eNOS expression or activity in endothelial cells (Table 4).[58,78] Rizza et al. reported that hesperetin acutely stimulated phosphorylation of Akt, AMP kinase, and eNOS, which mediate NO production in endothelial cells.[58] The effect of hesperetin on NO production by endothelial cells may also be mediated by estrogen receptor α.[78] Furthermore, in vivo data obtained with glucosyl hesperidin demonstrated its ability to reduce mRNA expression of aortic NADPH oxidase subunits, thus potentially reducing NO inactivation.[77] In agreement, improved NO bioavailability was supported by the lower urinary excretion of 8-hydroxy-2′-deoxyguanosine, a biomarker of oxidative stress, in SHR rats fed glucosyl hesperidin.[77] Studies investigating the effect of naringenin on vascular function are scarce. In LDLR−/− mice fed a Western diet, naringin supplementation (3%) had no effect on blood pressure; nevertheless, these animals were not hypertensive.[16] In vitro, no change in endothelial NO production was observed in response to naringenin.[78,79] Overall, these results suggest that among flavanones, hesperetin may improve endothelium-dependent vasorelaxation by increasing the availability of NO.

Impact on Lipid Profile. Several studies have reported a lipid-lowering effect of flavanones (Table 3) in animals with dyslipidemia due to their diet or genetic characteristics. Supplementation with naringin (0.05%) or a mix of naringin and hesperidin (0.5%) in rabbits or rodents fed a cholesterol-rich diet reduced cholesterolemia by 30−55%.[80,81] In rodent models fed a high-fat or high-fat−high-cholesterol diet, a low dietary supplementation with naringin (0.02%) decreased cholesterolemia (from −13 to −25%) without an effect on triglycerides (TG) levels.[74,82] In contrast, treatment with 1−3% naringenin or 50 mg/kg naringin decreased TC (from −17 to 50%) and TG (from −36 to −68%).[16,83,84] The supplementation of diabetogenic diets with 0.012% naringenin in rats led to a decrease in plasma TG concentration (−56%) and with 1% naringenin in mice resulted in a reduction in TG (−46%) and cholesterol (−20%) concentrations.[85,86] In this latter study, however, supplementation of the diet with 1% hesperetin had no effect on lipidemia. Additionally, lipid-lowering effects of dietary flavanones have also been observed in animal models of type 2 diabetes. Indeed, hesperidin or naringin supplementation (0.02%) decreased plasma TG and cholesterol concentration.[87] Several studies also reported a reduction in hepatic cholesterol (−30% to −80%) and/or TG (−20% to −80%) concentration[16,80−83,85,87] after flavanones supplementation (Table 3). Furthermore, flavanones increased hepatic fatty acid β oxidation in vivo[83,86] and reduced apo B lipoprotein secretion (very low density lipoprotein, VLDL) both in vivo and in vitro (Table 4).[83,88−94] Thus, the impact of flavanones on both the hepatic metabolism of TG and cholesterol is likely to be involved in plasma lipid-lowering effect.

The lipid-lowering effects of flavanones may be mediated through their ability to alter the expression or activity of nuclear receptors involved in the control of lipid metabolism. In vivo naringenin and naringin supplementations have been shown to increase hepatic peroxisome proliferator-activated receptor α (PPARα) mRNA or protein levels as well as its downstream targets carnitine palmitoyltransferase (CPT1), acyl-CoA oxidase (Aco), and uncoupling protein (2UCP2), which control fatty acid oxidation and energy metabolism.[82,83,85,86] Strengthening these results, exposure of hepatic cells to naringenin induced PPARα activation and expression of its target gene Aco.[93] Activation of PPARα is known to decrease apo B and VLDL production and to induce fatty acid oxidation,[95] thus explaining the reduced hepatic and plasma TG concentrations and decreased VLDL secretion observed under flavanone supplementation.

In mice fed a high-fat diet, flavanone supplementation also inhibited the hepatic activity of liver X receptor alpha (LXRα) and its downstream effector sterol regulatory element binding protein 1c (SREBP1c), thereby down-regulating lipogenic genes. Indeed, naringenin supplementation has been associated with a reduction in the expression of SREBP1c in mice.[82,83] Sharma et al. reported reduced SREBP1c and LXRα protein expression following naringin feeding.[84] Naringin and hesperidin treatment led to reduced expression or activity of SREBP1c targets such as fatty acid synthase (FAS), acetyl-coA carboxylase (ACC), glucose-6-phosphate dehydrogenase, and the phosphatidate phosphohydrolase, involved in different steps of lipogenesis.[82,87] In support of these results, naringenin was shown to inhibit LXRα activity and reduce mRNA levels of LXRα-regulated genes controlling cholesterol and fatty acid availability including ABCA1, ABCG1, HMGCoA reductase, and FAS in hepatic cells.[93] Other studies demonstrated that flavanones inhibit the hepatic activity of HMGCoA reductase, the limiting enzyme of cholesterogenesis.[80,87] Overall, inhibition of the LXR pathway by flavanones can reduce lipogenesis and cholesterogenesis. Such effects may account for the reduced hepatic TG and cholesterol content and the limited VLDL secretion observed in response to flavanone supplementation.

In vitro studies of hepatocytes also showed that flavanones inhibited apo B-containing lipoprotein secretion by reducing the expression and activity of microsomal TG transfer protein (MTTP; involved in the assembly and secretion of apo B lipoproteins) and acyl CoA cholesterol acyl transferase (ACAT; responsible for cholesterol esterification).[88,94] Reduced cholesteryl ester synthesis has also been observed after exposure of hepatocytes to flavanones (Table 4).[92,94] In addition, naringenin increased the expression and activity of LDLR, which is involved in remnant lipoprotein clearance from the plasma.[91,93,94]

In summary, several animal studies have reported an improved lipid profile after supplementation with a nutritional dose of flavanones.[74,82,85] According to experimental data, flavanones may exert their lipid-lowering activities through changes in both the expression and activity of key mediators involved in the control of hepatic lipid homeostasis.

Impact on Insulin Resistance. Insulin resistance plays a crucial role in the development of atherosclerosis and cardiovascular risk. Interestingly, several studies revealed that flavanones can exert insulin-like effects (Table 3). In diabetic animals[84,87] as well as models of insulin resistance induced by a high-fat diet,[82,83] supplementation with flavanones (0.02−3% during 4 or more weeks) reduced glycemia and/or insulinemia. The animals supplemented with flavanones had reduced insulin resistance and improved glucose tolerance.[74,82−84] Insulin-like properties of naringenin have also been described in vitro (Table 4).[88,89,91]

Flavanones have been shown to activate PPARγ, a nuclear receptor involved in the control of glucose homeostasis and the activationof which increases insulin sensitivity.[96] Indeed, supplementation of diabetic animals with naringin or hesperidin significantly induced the hepatic expression of PPARγ[84,87] and increased the mRNA levels as well as the activity of glucokinase, a key enzyme in the regulation of hepatic glucose utilization.[87] Furthermore, exposure of hepatic cells to naringenin activated PPARγ as assessed by a gene reporter assay.[93] In diabetic rodents, naringin supplementation also resulted in the down-regulation of expression of key gluconeogenic enzymes such as glucose-6-phosphatase and phosphoenolpyruvate carboxykinase.[82,87] These changes could be related to the lowering of blood glucose observed with flavanones. Alternatively, naringenin also induced the activation of insulin signaling pathways such as MAPK and PI3Kinase, without affecting insulin receptor activity; this was associated with reduced apoB secretion.[88,89,91] Overall, by exerting insulin-like activity, dietary flavanones may improve insulin sensitivity and have a positive impact on both glucose and lipid homeostasis.

Impact on Oxidative Stress and Inflammation. In addition to their insulin sensitizing, antihypertensive, and lipid-lowering effects, flavanones may also act on oxidative stress and inflammation. In both dyslipidemic and diabetic rodent models, dietary flavanone supplementation was reported to increase the activity of antioxidant enzymes, such as plasma paraoxonase, SOD, and glutathione peroxidase,[84,87,97] and erythrocyte catalase,[97] as well as hepatic SOD, catalase, glutathione reductase, and glutathione peroxidase (Table 3).[82,84,97] Interestingly, supplementation with flavanones seemed without effect in healthy animals.[59,82] Increases in the hepatic gene expression of SOD, catalase, and glutathion peroxidase were also observed after naringin supplementation in rabbits that were fed a high-cholesterol diet.[98]

Several in vivo studies have shown that flavanones can reduce vascular or systemic levels of chemokines as well as inflammatory and adhesion molecules,[72−74,82,84] the expression of which is tightly controlled by the pro-inflammatory factor NF-κB (Table 3). Flavanones have been reported to exert potential anti-inflammatory actions in various cell types involved in atherogenesis including endothelial and smooth muscle cells as well as monocytes/macrophages (Table 4). Indeed, in LPS-stimulated macrophages exposed to 90 μM naringenin, the production of pro-inflammatory cytokines (interleukin 1beta (IL1β), interleukin 6 (IL6), and tumor necrosis factor alpha (TNFα)) was reduced.[99] Other studies have also reported a decrease in TNFα production after exposure of activated macrophages to 50 μM hesperetin.[100,101] Furthermore, the exposure of macrophages to more physiological concentrations of naringenin, for example, 5 μM, decreased prostaglandin E2, a pro-inflammatory eicosanoid, production and reduced the expression of COX2, the enzyme required for its synthesis.[102] The exposure of inflammation-stimulated macrophages to naringenin (30−100 μM) inhibited NF-κB activation.[103,104] Surprisingly, hesperetin (100 μM) did not have such an effect, suggesting that other anti-inflammatory pathways may be involved.[100] With regard to the effects described in hepatic cells, PPARs, which also control

inflammation, could be one of these alternative molecular targets. In endothelial cells exposed to inflammatory stress, hesperidin and naringin reduced VCAM-1 expression without affecting ICAM-1 or E-selectin (Table 4).[105,106] Particularly, hesperidin has been shown to reduce TNFα-induced VCAM-1 expression through the regulation of the Akt and PKC pathways.[106] However, the observed effect of flavanone glycosides on reduced adhesion of monocytes to endothelial cells yielded inconsistent results.[105,106] In TNFα-stimulated endothelial cells, some studies reported a reduction of the expression of adhesion molecules and/or of monocyte adhesion to endothelial cells after exposure to aglycones including with physiological concentrations (effects observed with 1−50 μM hesperetin or naringenin),[58,74,105] whereas others did not observe this effect.[107] Data are scarce regarding the impact of flavanones on the activity of smooth muscle cells. One study indicated that 15 μM naringenin or naringin reduced matrix metallopeptidase 9 (MMP9) expression, thereby reducing smooth muscle cell migration, a step involved in lesion progression during atherosclerosis.[108] The observed reduction of MMP9 gene expression by naringin was partly due to the suppression of the DNA-binding activity of NF-κB.[108] These data suggest that flavanones may exert anti-inflammatory activities in the various cell types involved in atherosclerosis development in part through the inhibition of the NF-κB pathway. This modulatory effect may be related to the reduced progression of atherosclerosis observed in animals fed flavanones. However, these in vitro data were mostly obtained using supraphysiological concentrations of aglycone compounds or flavanone glycosides (see Table 1); thus, their biological relevance is limited. The underlying mechanisms by which flavanones may antagonize inflammation and oxidative stress have not yet been fully elucidated. Moreover, despite one promising study showing that hesperetin was a potent inhibitor of platelet aggregation and COX1 activity,[109] few data are available regarding the impact of dietary flavanones on platelet function, another cell type playing an important role in CVD.

A body of evidence from epidemiological, clinical, and experimental data suggests that flavanones may contribute to the prevention of CVD through a reduction of various cardiovascular risk factors. The few human intervention studies performed to date indicate a possible role of flavanones in regulating blood pressure and improving endothelial function. As is the case for many other flavonoids, these clinical data are insufficient to draw conclusions about the effectiveness of flavanones. The modes of action by which dietary flavanones may positively affect vascular health are more widely documented in studies performed in animal models. From these studies, flavanones were shown to exhibit antiatherogenic properties, to improve vascular reactivity, and to exert antihypertensive, insulin-sensitizing, and lipid-lowering effects. These beneficial effects may be mediated through genomic and nongenomic pathways, and most of them are related to anti-inflammatory and antioxidative activities.

In conclusion, further clinical studies in different populations using isolated compounds are needed to clarify the effect of flavanones in humans. Given the high interindividual variability of flavanone bioavailability, it would be particularly important to correlate the magnitude of the observed phenotypic changes with plasma concentrations achieved. Long-term intervention studies should also been conducted to substantiate future health claims regarding flavanone-rich products. To improve the physiological relevance of the preclinical and in vitro data, additional studies investigating the impact of nutritional doses of flavanones in vivo and the effect of nutritionally achievable concentrations of flavanone metabolites in vitro are required. These studies will be crucial to identify the underlying cellular and molecular mechanisms of the cardiovascular protective effects of flavanones.

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Notes

The authors declare no competing financial interest.

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