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REVIEWS

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Beneficial Effects of Flavonoids on Skeletal Muscle Health: A Systematic Review and Meta-Analysis

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ABSTRACT Skeletal muscle (SkM) is a highly dynamic tissue that responds to physiological adaptations or pathological conditions, and SkM mitochondria play a major role in bioenergetics, regulation of intracellular calcium homeostasis, pro-oxidant/antioxidant balance, and apoptosis. Flavonoids are polyphenolic compounds with the ability to modulate molecular pathways implicated in the development of mitochondrial myopathy. Therefore, it is pertinent to explore its potential application in conditions such as aging, disuse, denervation, diabetes, obesity, and cancer. To evaluate preclinical and clinical effects of flavonoids on SkM structure and function. We performed a systematic review of published studies, with no date restrictions applied, using PubMed and Scopus. The following search terms were used: ''flavonoids'' OR ''flavanols'' OR ''flavones'' OR ''anthocyanidins'' OR ''flavanones'' OR ''flavan-3-ols'' OR ''catechins'' OR ''epicatechin'' OR ''(−)-epicatechin'' AND ''skeletal muscle.'' The studies included in this review were preclinical studies, clinical trials, controlled clinical trials, and randomized-controlled trials that investigated the influence of flavonoids on SkM health. Three authors, independently, assessed trials for the review. Any disagreement was resolved by consensus. The use of flavonoids could be a potential tool for the prevention of muscle loss. Their effects on metabolism and on mitochondria function suggest their use as muscle regulators.

KEYWORDS: • ***flavonoids*** • ***polyphenols*** • ***skeletal muscle***

INTRODUCTION

FLAVONOIDS ARE POLYPHENOLIC compounds, chemically characterized by two aromatic rings linked by a heterocycle, and the differences in the functionalization of the heterocycle allow them to be distinguished into subfamilies such as the following: anthocyanins, flavan-3-ols, flavones, flavanones, and flavonols.[1] Flavonoids are found ubiquitously in a wide range of plants, fruits, and vegetables.

A large proportion of the food we consume in our daily diet contains a variable amount of flavonoids, for example, those rich in flavones and flavonols: citrus, plums, apples, onions, and green herbs such as lettuce, parsley, and coriander; flavan-3-ols such as tea, grapes, red wine, cocoa, and chocolate; and/or anthocyanins, mainly present in berries.[2]

The type of flavonoid and the proportion found in each food source are very diverse, however, according to the U.S. Department of Agriculture some examples include the following: (1) flavonols: onions, red, raw: 39.21 mg quercetin/100 g and peppers, ancho variety: 27.60 mg quercetin/100 g; (2) flavan-3-ols: cocoa, dry powder, unsweetened: 196.43 mg (−)-epicatechin/100 g and cacao beans: 8262 mg (+)-gallocatechin/100 mg; (3) anthocyanins: raspberries, black: 669.01 mg cyanidin/100 g and cabbage, red, raw: 209.83 mg cyanidin/100 g; (4) flavones: fresh parsley: 215.16 mg apigenin/100 g and dried Mexican

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oregano: 1028.75 mg luteolin/100 g; and (5) flavanones: orange raw: 27.25 mg hesperidin/100 g and grapefruit raw: 53 mg naringenin/100 g.[3]

The consumption of these molecules has emerged as a potential approach to preserve and/or improve overall health as they possess positive effects on cardiovascular risks.[4] Current evidence indicates that flavonoids and associated circulating metabolites may modulate molecular pathways involved in the preservation of muscle structure and function.[5]

The current recommended approach to treat sarcopenia is adequate protein intake and regular exercise to improve muscle mass and strength.[6] However, many older individuals are incapable of sustaining regular and healthy levels of exercise due to conditions and diseases such as excess weight and osteoarthritis. An apparent beneficial effect of sustained flavonoid consumption on muscle quality is based on two main actions: (1) the stimulation of mitochondrial biogenesis, leading to increased production of ATP and (2) reduction of generated reactive oxygen species, through chemical scavenger action; both leading to increased muscle performance.[7,8] However, not all reports have yielded consistent positive effects on muscle.

We therefore conducted a systematic review and meta-analysis of preclinical and clinical studies that explore the effects of flavonoids on indicators skeletal muscle (SkM) structure and/or function. We hypothesized that flavonoids may play a key role in prevention of age-related pathologies of SkM.

METHODS

We carried out a systematic search of studies, following the Cochrane methodology and presented it in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search strategy

Three investigators independently conducted the electronic database search, with no date restrictions applied, using PubMed and Scopus for published articles. The following medical subject headings (MESH) and non-MESH terms by these following keywords were used: ''flavonoids'' OR ''flavanols'' OR ''flavones'' OR ''anthocyanidins'' OR ''flavanones'' OR ''flavan-3-ols'' OR ''catechins'' OR ''epicatechin'' OR ''(–)-epicatechin'' AND ''skeletal muscle.'' Chinese language was excluded from this study. The search was completed on March 08, 2019, at 22:00 h (UTC/GMT -6 h).

Study selection

Studies included in this review were preclinical studies, clinical trials, controlled clinical trials, and randomized-controlled trials that investigated the influence of any flavonoid on SkM health. The types of studies included were those focused on the administration of flavonoid-rich foods (*e.g.,* cocoa) and pure flavonoids (natural, semisynthetic, or synthetic) or flavonoid formulations, as well as any pharmacological compound that contains an active flavonoid ingredient, whether administered orally or parenterally. We evaluated titles, abstracts, and methodology, and then, potential articles were assessed for inclusion independently by each reviewer.

Data extraction

Three reviewers independently assessed the studies for inclusion in the review, extracted data from the selected studies into a Google-based data collection tool, and stored them into a standardized Microsoft Excel spreadsheet. Any disagreement was resolved in consensus between the authors. Relevant data were extracted including general characteristics of the study and population (authorship, year of publication, type of study population, number of cases and controls, participants' gender, study design, study location, intervention duration, type of flavonoids, and supplement dosage).

Trial quality assessment for rodent studies

Based on the criteria described by Kilkenny *et al.*,[9] quality was analyzed based on brief descriptions of essential characteristics of all studies using animal models, such as theoretical and methodological basis, research objective, and improvement of analytical methods, statistical design, sample calculations, and outcome measures.

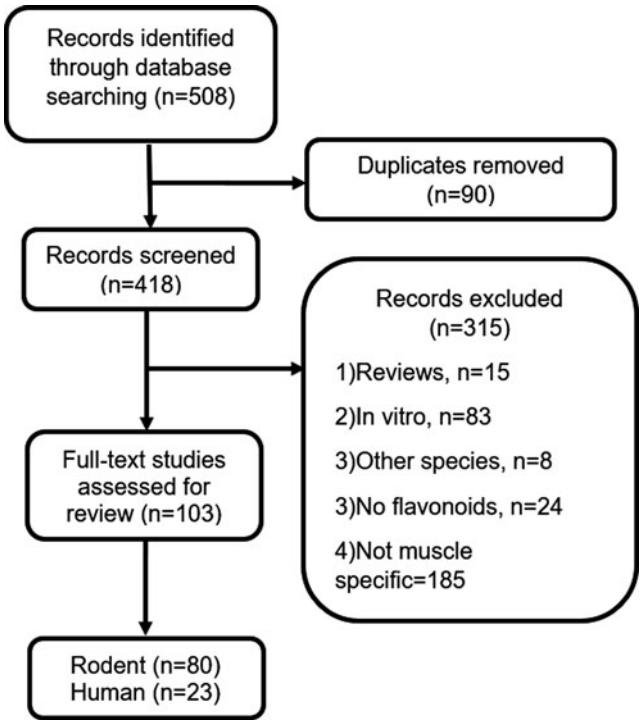

FIG. 1. Flowchart of the selection process of the studies for systematic review.

Table 1. Animal Studies

Author, country, year	*Animal model/strain*	*Sex*	*Age/weight*	*Disease/model*	*Flavonoids*	*Source of flavonoid*	*Dose and route*	*Time of intervention*
Büttemeyer *et al.*, Germany, 2003[35]	Wistar rats	Male	200–380 g	Ischemia	EGCG	Purchased	4 mg/kg/jugular injection	60–120 min
Ashida *et al.*, Japan, 2004[36]	Wistar rats	Male	3-wk	No	Catechins	Bottled green tea	Dose nonspecified/oral	3-wk
Pinent *et al.*, Spain, 2004[37]	Wistar rats	Male	250 g	Diabetes	Procyanidins	Grape seed extract	250 mg/kg/oral	2 h
Murase *et al.*, Japan, 2005[38]	Balb/c mice	Male	8-wk	No	Catechins	GTE	0.2 and 0.5% chow diet/oral	10-wk
Murase *et al.*, Japan, 2006[39]	C57BL/6 mice	Male	6-wk	Obesity	Catechins	GTE	0.5% of HFD/oral	15 and 4-wk
Dorchies *et al.*, Switzerland, 2006[40]	mdx and C57BL/6J mice	Male	3-wk	Dystrophy	EGCG	GTE	0.05 and 0.25% of GTE and 0.1% of EGCG chow diet/oral	1 and 5-wk
Murase *et al.*, Japan, 2006[41]	Balb/c mice	Male	7-wk	No	Catechins	GTE	0.2 and 0.5% of chow diet/oral	10-wk
Ueda *et al.*, Japan, 2008[42]	Sprague-Dawley rats	Male	6-wk	No	EGCG	BTE	75 mg/kg/oral	1 h
Murase *et al.*, Japan, 2008[43]	SAMR1 and SAMP1 mice	Male	13-wk	Senescence	Catechins	GTE	0.35% of chow diet/oral	18-wk
Senthil Kumaran *et al.*, India, 2008[44]	Wistar rats	Male	4 and 24 mo	Aging	EGCG	Purchased	100 mg/kg/oral	4-wk
Chen *et al.*, Australia, 2009[26]	Sprague-Dawley rats	Male	7-wk	Obesity	Catechins and EGCG	GTE, BTE, EGCG purchased	1 mg/kg/oral	27-wk
Messina *et al.*, Italy, 2009[45]	mdx mice	Male	5-wk	Dystrophy	Baicalin and catechins	Flavocoxid	5 mg/kg/IP	5-wk
Wang *et al.*, Taiwan, 2011[46]	C57BL/6 mice	Male	8-wk	Cancer cachexia	EGCG	Purchased	0.2 and 0.6 mg/oral	4-wk
Si *et al.*, USA, 2011[47]	C57BL/6 mice	Male	5-wk	Obesity and diabetes	Epicatechin	Purchased	150 mg/kg/oral	15-wk
Ikarashi *et al.*, Japan, 2011[48]	KK-Ay mice	Male	5-wk	Obesity and diabetes	Flavanols	Acacia mearnsii extract	2.5 and 5%/oral	7-wk
Nogueira *et al.*, USA, 2011[49]	C57BL/6 mice	Male	12-mo	No	Epicatechin	Purchased	2 mg/kg BID/oral	2-wk
Ota *et al.*, Japan, 2011[50]	Balb/c mice	Male	10-wk	HLS	Catechins	GTE	0.5% of chow diet/oral	24 days
Haramizu *et al.*, Japan, 2011[51]	SAMR1 and SAMP1 mice	Male	47-wk	Aging	Catechins	GTE	0.35% of chow diet/oral	8-wk
Sae-tan *et al.*, USA, 2011[52]	C57BL/6 mice	Male	5-mo	Obesity, fatty-liver	EGCG	Purchased	3.2 g/kg chow diet/oral	15-wk
Li *et al.*, China, 2011[53]	Wistar rats	Male	250–300 g	FFAs-induced peripheral IR	EGCG	Purchased	5 and 10 mg/kg/ intravenous	72 h
Yan *et al.*, China, 2012[54]	GK rats	Male	1-mo	Diabetes	EGCG	Purchased	100 mg/kg/oral	12-wk
Friedrich *et al.*, Germany, 2012[55]	C57BL/6 mice	Male	12-wk	Obesity	EGCG	GTE	0.5% and 1.0% of chow diet/oral	5 and 7 days
Hüttemann *et al.*, USA, 2012[56]	C57BL/6 mice	Male	5-mo	HLS	Epicatechin	Purchased	1 mg/kg BID/oral	2-wk

(*continued*)

Table 1. (Continued)

Author, country, year	*Animal model/strain*	*Sex*	*Age/weight*	*Disease/model*	*Flavonoids*	*Source of flavonoid*	*Dose and route*	*Time of intervention*
Renno *et al.*, Kuwait, 2012[57]	Wistar rats	Male	250–300 g	Sciatic nerve crush injury	EGCG	Purchased	50 mg/kg/IP	3-wk
Yamashita *et al.*, Japan, 2012[58]	ICR and C57BL/6 mice	Male	1-mo	No	Procyanidins	Cacao liquor	0.5% and 1.0% of chow diet/oral	1-wk
Yamashita *et al.*, Japan, 2012[59]	C57BL/6 mice	Male	4-wk	Hyperglycemia and diabetes	Procyanidins	Cacao liquor	0.5% and 2.0% of chow diet/oral	13-wk
Jang *et al.*, Korea, 2013[60]	Sprague-Dawley rats	Male	6-wk	Obesity	Catechins and polyphenols	GTE and laminaria extract	100 mg/kg/oral	6- and 12-wk
Hüttemann *et al.*, USA, 2013[61]	LCR rats	Male	5-mo	HLS and low- capacity running	Epicatechin	Purchased	1 mg/kg BID/oral	4-wk
Sundaram *et al.*, India, 2013[62]	Wistar rats	Male	200 g	Diabetes	Catechins	GTE	75, 150 and 300 mg/kg/oral	4-wk
Haramizu *et al.*, Japan, 2013[63]	ICR mice	Male	2-mo	Diabetes	Catechins	GTE	0.5% of chow diet/oral	3-wk
Alway *et al.*, USA, 2013[64]	Fischer 344 Brown Norway rats	Male	34-mo	Aging and HLS	EGCG	GTE	50 mg/kg/oral	2-wk
Yamashita *et al.*, Japan, 2013[65]	ICR mice	Male	5-wk	Diabetes	Epicatechin and procyanidins	Purchased and cacao liquor	10 μg/kg/bw	18 h
Casanova *et al.*, Spain, 2014[66]	Wistar rats	Male	150 g	Obesity and diabetes	Proanthocyanidins	Grape seed extract	25 mg/kg/oral	3-wk
Gutierrez *et al.*, Mexico, 2014[67]	Wistar rats	Male	300 g	Obesity	Epicatechin	Purchased	1 mg/kg BID/oral	2-wk
Ramirez-Sanchez *et al.*, USA, 2014[68]	δ-SG null	Male	2.5-mo	Muscular dystrophy	Epicatechin	Purchased	1 mg/kg BID/oral	2-wk
Chalopin *et al.*, France, 2014[69]	ERα wild type mice	Female	12-wk	ERα deletion	Proanthocyanidins	Red wine extract	20 mg/kg/oral	4-wk
Watanabe *et al.*, Japan, 2014[70]	C57BL/6 mice	Male	7-wk	No	Flavanols	Cocoa powder	50 mg/kg/oral	2-wk
Sae-tan *et al.*, USA, 2014[71]	C57BL/J mice	Male	5-wk	Metabolic syndrome	Catechins	GTE	7.7 g/kg of chow diet/oral	16-wk
Matsumura *et al.*, Japan, 2014[72]	ICR mice	Male	40 g	Diabetes	Flavanols or epicatechin	Cocoa powder and purchased	10 mg/kg/oral	20 h
Always *et al.*, USA, 2015[73]	FBN rats	Male	32-mo	Aging and HLS	Catechins	GTE	50 mg/kg/oral	2-wk
Pence *et al.*, USA, 2015[74]	Balb/c mice	Male	17-mo	No	EGCG	GTE	182 mg/kg of chow diet/oral	41 days
Moreno *et al.*, USA, 2015[75]	C57BL/6 mice	Male	6- and 26-mo	Aging	Epicatechin	Purchased	1 mg/kg BID/oral	2-wk
Meador *et al.*, USA, 2015[76]	Sprague-Dawley rats	Male	20-mo	Aging and sarcopenia	EGCG	GTE	200 mg/kg of chow diet/oral	8-wk
Aminuddin *et al.*, Malaysia, 2015[77]	Sprague-Dawley rats	Male	200 g	Obesity and diabetes	Flavanols	Cocoa extract	600 mg/kg/oral	8-wk
Liu *et al.*, Taiwan, 2015[78]	SAMP8 and SAMR1 mice	Male	7-mo	Aging	EGCG	GTE	3.2 g/kg of chow diet/oral	12-wk
Lambert *et al.*, France, 2015[79]	CD4dnTGFβRII mice	Male	3-mo	Muscle atrophy	Catechins	Red grape extract	50 mg/kg/oral	4-wk

(*continued*)

TABLE 1. (CONTINUED)

Author, country, year	*Animal model/strain*	*Sex*	*Age/weight*	*Disease/model*	*Flavonoids*	*Source of flavonoid*	*Dose and route*	*Time of intervention*
Kudo *et al.*, Japan, 2015[80]	ICR mice	Male	10-wk	Diabetes	Theaflavin	Theaflavin mixture	10 mg/kg/oral	2 days
Assi *et al.*, France, 2016[81]	Balb/c mice	Male	7-wk	Cancer cachexia	Catechins	Antioxidant mixture	81.5 mg/kg/oral	22 days
Liu *et al.*, Japan, 2016[82]	C57BL/6 mice	Male	1-mo	Obesity	EGCG and oligonol	GTE, lychee fruit extract	50 mg/kg/oral	12-wk
Lee *et al.*, Korea, 2016[83]	C57BL/6 mice	Male	6-mo	HLS	Epicatechin	Purchased	1 mg/kg BID/oral	2-wk
Mohamad *et al.*, Malaysia, 2016[84]	ICR mice	Female	8-wk	Diabetes	Epicatechin	*M. citrifolia* leaves extract	200 and 400 mg/kg/oral	4-wk
Yamashita *et al.*, Japan, 2016[31]	ICR mice	Male	5-wk	Diabetes	Procyanidins, catechins, and epicatechin	Soybean PC and purchased	10 μg/kg/oral	2 h
Marinello *et al.*, Brazil, 2016[25]	Wistar rats	Male	250–290 g	Thyrotoxicosis-induced muscle wasting	Isoflavones	Purchased	1 mg/kg/IP	5 days
Lin *et al.*, Taiwan, 2017[85]	C57BL/6 mice	Male	4-wk	Diabetes	(-)-Epicatechin-3-O-β-D-allopyranoside	Davallia formosana extract	10,20, 40 mg/kg/oral	4-wk
Li *et al.*, China, 2017[32]	ICR mice	Male	20 g	Diabetes	Procyanidins	Lotus seed extract	150 mg/kg/oral	8-wk
Takahashi *et al.*, USA, 2017[86]	Fischer 344 Brown Norway rats	Male	34-mo	Aging	EGCG	GTE	50 mg/kg/oral	2-wk
Mizunoya *et al.*, Japan, 2017[87]	Sprague-Dawley rats	Male	12-wk	Healthy	Procyanidins	Apple polyphenols	5% (w/w)/oral	8-wk
Pence *et al.*, USA, 2017[88]	Balb/cByJ mice	Male	12-mo	Aging	EGCG	Commercial supplement	1.7 mg/g of chow diet/oral	24-wk
Dos Santos *et al.*, Brazil, 2017[33]	Wistar rats	Male	8-wk	Diabetes	Quercetin	Yacon leaf extract	100 mg/kg/oral	30 days
Kohara *et al.*, Japan, 2017[89]	ICR mice	Male	6-wk	Overload-induced hypertrophy	Enzymatically modified isoquercitrin	Purchased	4 or 40 mg/kg/oral	3-wk
Liu *et al.*, Taiwan, 2017[90]	C57BLKS/J (db/db) mice	Male	8-wk	Diabetes	Oligonol	Purchased diet	(20 mg or 200 mg/kg chow diet)	10-wk
Jung *et al.*, Korea, 2017[91]	C57BL/6 mice	Male	6-wk	Obesity	Puerarin	Radix Pueraria lobata extract	100 or 300 mg/kg	16-wk
Attakpa *et al.*, France, 2017[92]	C57BL/6 mice	Male	4-wk	Obesity	Quercetin and kaempferol	Moringa oleifera leaf extract	200, 400 or 600 mg/kg/oral	8-wk
Chen, *et al.*, China, 2017[34]	C57BL/6J mice	Male	8–12-wk	Sciatic nerve crush injury	Quercetin	Nonspecified	20 mg/kg/ intramuscular	7, 14, and 35 days
Chen, *et al.*, China, 2018[93]	C57BL/6 mice	Male	4–6-wk	Cancer cachexia	Luteolin	Purchased	20 mg/kg/oral	21 days
Choi, *et al.*, Korea, 2017[18]	C57BL/6 mice	Male	4-wk	Obesity	Apigenin	Nonspecified	0.1% (w/w)/oral	8-wk
da Costa, *et al.*, Brazil, 2017[94]	C57/BL6 mice	Male	4-wk	Metabolic disorders	Anthocyanins	*Vitis vinifera L.* grape skin	200 mg/kg/oral	12-wk
Ito *et al.*, Japan, 2017[95]	C57BL/6J mice	Male	17–19 wk	HLS	Flavanol	Cocoa powder	50 mg/kg/Intragastric	2-wk

(*continued*)

Table 1. (Continued)

Author, country, year	*Animal model/strain*	*Sex*	*Age/weight*	*Disease/model*	*Flavonoids*	*Source of flavonoid*	*Dose and route*	*Time of intervention*
Kou, *et al.*, China, 2017[27]	Sprague-Dawley rats	Male	8-wk	Atrophy induced by D-gal	Ampelopsin	Purchased	100 or 200 mg/kg/IP	6-wk
Ng *et al.*, Australia, 2017[96]	Sprague-Dawley rats	Male	9-wk	Hindlimb perfusion or hyperinsulinemic -euglycemic clamp	EGCG	Nonspecified	0.1, 1, 10, 100 μM perfusion	0–120 min
Zheng *et al.*, Germany, 2017[97]	Wistar rats	Female	250 g	Ovariectomized	Isoflavone	Soy	Enriched chow diet	46 days
Duan *et al.*, China, 2017[98]	Sprague-Dawley rats	Male	20–22 mo	Stress injury	Luteolin-6-C-neohesperidoside	Moso bamboo leaf	25, 50 and 75 mg/kg/oral	3-wk
Ogawa *et al.*, Japan, 2017[99]	Kwl:ddY mice	Male and female	7–8 wk	Ovariectomized	Daidzein	Purchased	0.1% of chow diet/oral	1-wk
Onishi *et al.*, Japan, 2018[100]	SAMP8 and SAMR1 mice	Male	4-wk	HFD-induced muscle atrophy	EGCG	GTE	269 mg/kg/oral	16-wk
Chen, *et al.*, China, 2018[127]	Sprague-Dawley rats	Male	160–180 g	Diabetes	Puerarin	Purchased	100 mg/kg/IP	4-wk
Kim, *et al.*, South Korea, 2018[101]	C57BL/6 mice	Male	6-wk	Atrophy	Quercetin	Purchased	0.05% (w/w)/oral	9-wk
Huang *et al.*, China, 2018[17]	Sprague-Dawley rats	Male	200 g	Atrophy induced by dexamethasone	Dihydromyricetin	Purchased	100 and 200 mg/kg/oral	14 days
Londzin *et al.*, Poland, 2018[102]	Wistar rats	Female	14–15 wk	Diabetes	Phloridzin	Purchased	20 and 50 mg/kg/oral	4-wk
Si *et al.*, USA, 2018[15]	C57BL/6 mice	Male	9 and 20 mo	Aging	Epicatechin and EGCG	Purchased	Epicatechin (0.25% w/v) or EGCG ($\sim$150 mg/kg)/oral	37 and 44 wk
Yoshioka *et al.*, Japan, 2018[103]	KK-Ay mice	Male	Nonspecified	Diabetes	Glabridin	Glycyrrhiza root extract	1 and 1.5 g/kg	4-wk

BID, BH3 interacting domain death agonist; BTE, black tea extract; EGCG, epigallocatechin gallate; FBN, Fisher Brown Norway Rats; FFA, free fatty acids; GK, glucokinase; GTE, green tea extract; HFD, high–fat diet; HLS, hindlimb suspension; LCR, low-capacity running; PC, procyanidin; wk, weeks; mo, months.

Table 2. Human Studies

Author, country, year	*Study design*	*Subjects*	*Sex*	*Age (yo)*	*Flavonoid*	*Dosage form*	*Dose*	*Time of intervention*
Kerksick *et al.*, USA, 2009[104]	Double-blind, prophylactic, and parallel	Healthy, nonresistance trained	Men	20	EGCG	Commercial supplement	1800 mg/day	14 days
Taub *et al.*, USA, 2011[105]	Open label	HF and DM2	Men	47–71	Epicatechin	Cocoa powder	100 mg/day	12-wk
Kim *et al.*, Japan, 2012[106]	Randomized-controlled trial	Sarcopenic	Women	75	Catechins	Bottled green tea	540 mg/day	12-wk
Taub *et al.*, USA, 2013[107]	Open label	HF and DM2	Men	61	Epicatechin	Cocoa powder	100 mg/day	12-wk
Kerksick *et al.*, USA, 2013[108]	Double-blind, prophylactic, and parallel	Healthy, nonresistance trained	Men	20	EGCG	Commercial supplement	1800 mg/day	14 days
Ramirez-Sanchez *et al.*, USA, 2013[109]	Open label	HF and DM2	Men	47–71	Epicatechin	Cocoa powder	100 mg/day	12-wk
Peschek *et al.*, USA, 2013[110]	Randomized, single-blind, crossover	Well-trained runners and triathletes	Men	18–44	Flavanols	Cocoa powder	350 mg of flavanols	24 h, 48 h and 5 km test
Mahler *et al.*, Germany, 2015[111]	Randomized, double-blind, placebo-controlled, crossover	Relapsing-remitting MS	Men and women	20–60	EGCG	Capsules	600 mg/day	12-wk
Most *et al.*, Netherlands, 2015[112]	Randomized, double-blind, crossover	Overweight	Men and women	30	EGCG	Capsules	282 mg/day	3 days
Aizawa *et al.*, Japan, 2016[113]	Randomized, placebo-controlled, parallel-group	Healthy	Men and women	20	Theaflavin and catechins	Capsules	100 or 200 mg/day of TF and 800 mg/day of CAT	10-wk
Kim *et al.*, Japan, 2016[114]	Randomized-controlled trial	Sarcopenic obesity	Men and women	>70	Catechins	Bottled green tea	540 mg/day	12-wk
Most *et al.*, Netherlands, 2016[115]	Randomized, double-blind, controlled study	Overweight and obese	Men and Women	20–50	EGCG + RES	Capsules	282 mg +80 mg/day	12-wk
Martin *et al.*, Canada, 2016[116]	Double-blind, crossover	Overweight	Men	34	Catechins	Capsules	900 mg/day	1-wk
Ota *et al.*, Japan, 2016[117]	Randomized double-blind, placebo-controlled, crossover	Healthy	Men	25–47	Catechins	GT beverage	570 mg/day	8-wk
Taub *et al.*, USA, 2016[118]	Randomized, double-blind, placebo-controlled	Healthy	Men	40–75	Flavanols	Cocoa powder	175 mg/day	12-wk
Romain *et al.*, France, 2017[119]	Randomized, double-blind, crossover	Healthy trained	Men and women	20	Xanthones, ellagitannins, and anthocyanins	Capsules	500 mg/day	5-wk
Beyer *et al.*, USA, 2017[120]	Randomized, double-blind, placebo-controlled	Healthy untrained	Men	18–31	EGCG (from tea extract)	Capsules	2 g/day	4-wk

(*continued*)

Table 2. (Continued)

Author, country, year	*Study design*	*Subjects*	*Sex*	*Age (yo)*	*Flavonoid*	*Dosage form*	*Dose*	*Time of intervention*
Hadi *et al.*, Iran, 2017[121]	Randomized double-blind	Healthy trained	Men	18–25	Catechins	Capsules	450 mg/day	6-wk
Kinoshita *et al.*, Japan, 2017[122]	Randomized, double-blind, placebo-controlled	Under rehabilitation for knee osteoarthritis	Men and women	54–90	Licorice	Capsules	300 mg/day	16-wk
Patrizio *et al.*, Italy, 2018[123]	Randomized, double-blind, crossover	Healthy trained	Men	22	Quercetin	Capsules	1 g/day	2-wk
Townsend *et al.*, USA, 2018[124]	Randomized, placebo-controlled	Healthy	Men	18–35	Catechins	Capsules	2 g/day	4-wk
Cavarretta *et al.*, Italy, 2018[125]	Randomized controlled, crossover	Healthy trained athletes	Men	17	Flavanols	Dark chocolate	40 g/day	30 days
da Silva *et al.*, Brazil, 2018[126]	Randomized triple-blinded, placebo-controlled	Healthy untrained	Men	25	Catechins	Capsules	500 mg/day	48 h

RESULTS

The search from PubMed and Scopus identified 508 potentially eligible studies, of which 90 duplicates were excluded. A large number of studies were excluded (315) based on title and methodology screening and at least one of the following reasons: (1) reviews that were not filtered in the initial search; (2) *in vitro*, *in silico*, or other species studies (not humans or rodents); (3) only abstract or not available; and (4) unclear methodology.

The study identification and selection processes are shown in Figure 1.

Study covered those articles published between 2003 and 2019. Of the 103 included studies, 54 were conducted in Asia, 30 in America, 17 in Europe, and 2 in Oceania. According to the type of study, 80 were performed in rodents and 23 in humans. The duration of trials ranged between 2 and 72 h for acute effects, and 1 to 44 weeks for chronic/accumulative effects. Characteristics of rodent and human eligible studies are summarized in Tables 1 and 2, respectively.

Data are presented as the direct or indirect effects of flavonoids, type of flavonoid derived from a variety of sources such as green tea, black tea, and cacao, among others. Results are grouped into the following tables:

Table 3 summarizes the reported effects on body composition, physical performance, and muscle in rodent studies.

Table 4 shows reported effects on body composition, physical performance, aerobic capacity, inflammation, muscle damage, apoptosis, oxidative stress, glucose profile, and lipid profile in human studies.

Table 5 summarizes the biomarkers modulated by flavonoids in autophagy, differentiation, ubiquitin/proteasome system, apoptosis, inflammation, and oxidative stress in rodents.

Table 6 summarizes reported effects in mitochondria (changes in activity, signaling pathways, or transcription factors).

Table 7 summarizes metabolic changes in rodent studies.

Table 8 shows the effects on SkM metabolism (carbohydrates, lipids, and protein synthesis).

Figure 2 provides an integrated panorama of reported flavonoid-induced activation or inactivation of signaling pathways, related to their induced effects showing the possible interaction of signaling pathways and mitochondrial bioenergetics and biogenesis.

Figure 3 shows an integrated participation in three possible signaling pathways. (1) Interaction of flavonoids in apoptosis through an increase in the activity of B cell lymphoma and promoting degradation of damaged cells. (2) The ubiquitin/proteasome system through the reduction of MAFbx and MuRF1 expression and reduction of protein ubiquitination and hence reduction of protein degradation. (3) Myogenesis through myostatin/activin by clocking the myostatin activity and an increase in follistatin expression.

Meta-analysis

Overall, the meta-analysis reported in the present study suggested an improvement in muscle health; it must be

Table 3. Summary of Effects on Body Composition and Skeletal Muscle in Rodent Studies

	Outcome	*Flavonoid*	*Reference*
Body composition	↓ Weight gain	Flavan-3-ols	38,39,59,71,90
		Anthocyanidin	94
		Isoflavones	91,97
	↓ Weight loss due to muscle waste	Flavanonols	17
	↓ Fat mass	Flavan-3-ols	26
	↓ WAT	Flavan-3-ols	59
	↑ Visceral fat	Flavan-3-ols	15
	↓ Energy efficiency	Isoflavones	91
	↓ Epididymal adipose tissue	Isoflavones	91
Physical performance	↑ Exercise endurance	Flavan-3-ols	38,41,43,49,56,63,84
		Flavones	98
	↓ Time to exhaustion	Flavan-3-ols	88
	↑ Traveling distance	Flavan-3-ols	15
	↑ Running distance	Flavones	18
Muscle	↓ Fiber atrophy	Flavan-3-ols	50,73
		Isoflavones	25
		Flavonols	34
		Flavanonols	27
		Flavones	18
	↑ Fiber perimeter	Flavan-3-ols	49
	↑ Fiber diameter	Isoflavones	91
		Flavonols	89
	↑ Cross-sectional area	Flavan-3-ols	49,64,73,76,79,90
		Flavonols	89
		Flavanonols	27,17
		Flavones	18
	↑ Regenerating fiber area	Flavan-3-ols	45
	↑ Protection against necrosis	Flavan-3-ols	40,45
	↑ Tetanic force and peak twitch force	Flavan-3-ols	40,73
	Recover maximal isometric force	Flavan-3-ols	64
	↑ Muscle mass	Flavan-3-ols	46,49,56,95,100
		Isoflavones	97,99
		Flavonols	89
		Licorice	104
		Flavanonols	27,17
		Flavones	18
	↓ Muscle waste	Isoflavones	91
	↑ Capillary indices	Flavan-3-ols	56,61
	↓ Pain and recovery rate	Flavan-3-ols	57
	↑ Intermediate and slow MyHC	Flavan-3-ols	87
	↑ Myoglobin protein expression	Flavan-3-ols	87
	↓ Fiber shift	Flavan-3-ols	90
	↓ Lipid accumulation	Flavan-3-ols	90

WAT, white adipose tissue.

considered that we only reported the analysis on three parameters: physical performance, cross-sectional area, and muscle mass.

Nine studies including a total of 154 rodents (experimental = 80, and control = 74) reported performance as an outcome measure. Combined results from the random-effects model showed a significant improvement in the endurance exercise following flavonoid consumption (mean difference [MD]: +10 min, 95% CI: 4.70–15.30, $P < .0002$), with significant heterogeneity among the studies ($I^2 = 97\%$, $P < .00001$) (Fig. 4).

Ten studies including a total of 198 rodents (experimental = 98, and control = 100) reported cross-sectional area as an outcome measure. Combined results from the random-effects model showed a significant improvement in the muscle area following flavonoid consumption (MD: +317.29 μm^2, 95% CI: 184.48–450.11, $P < .00001$), with significant heterogeneity among the studies ($I^2 = 89\%$, $P < .00001$) (Fig. 5).

Seven studies including a total of 120 rodents (experimental = 59, and control = 61) reported muscle weight as an outcome measure. Combined results from the random-effects model showed a significant improvement in the muscle mass following flavonoid consumption (MD: +14.23 mg, 95% CI: 1.98–26.48, $P = .02$), with significant heterogeneity among the studies ($I^2 = 81\%$, $P < .0001$) (Fig. 6).

DISCUSSION

SkM gives strength and movement to the body. Throughout human existence, tribute has been paid to its relationship with vigor and youth. Currently, it is recognized as an endocrine organ capable of influencing the metabolism. The reduction of the muscular mass leads to loss of autonomy, development of chronic comorbidities, and a lower quality of life. Therefore, the study of interventions that promote muscle health is relevant and necessary. The present systematic review and meta-analysis summarize the effects of flavonoid supplementation on SkM quality indicators. In the setting of sarcopenia, the preservation of SkM structure (mass) and strength is now recognized as key to countering the effects of aging, leading to a reduction in the risk for falls, institutionalization, disability, and mortality.[10]

In this review, we focused on the effects of flavonoids on muscle health, and we divided these effects in the regulation

Table 4. Summary of Effects in Human Studies

	Outcome	*Flavonoid*	*Reference*
Body composition	↓ Weight	Flavan-3-ols	113,120
	↓ Fat mass	Flavan-3-ols	113,114
	↑ Muscle mass in the body trunk	Licorice	122
	↓ Body fat percentage	Licorice	122
Physical performance	↑ Walking speed	Flavan-3-ols	106,114
	↓ Up & go time	Flavan-3-ols	106
	↓ Postexercise muscle soreness	Flavan-3-ols	104
	↑ Relative squad strength	Flavan-3-ols	120
	↑ Leg extension strength	Flavan-3-ols	120
	↑ Torque–velocity of knee extensors	Flavonols	123
	↑ Total volume of the resistance exercises	Flavonols	123
	↓ Postexercise muscle soreness	Anthocyanins	119
Aerobic capacity	↑ VO_2 max	Flavan-3-ols	117,118
	↑ Power exercise (Watts)	Flavan-3-ols	118
	↓ Muscle recovery period	Flavan-3-ols	110
Inflammation	↓ Cortisol, neutrophil count, and the neutrophil/lymphocyte ratio	Flavan-3-ols	104
Muscle damage	↓ Myoglobin	Anthocyanins	119
	↓ Creatinine	Anthocyanins	119
	↓ CK	Anthocyanins	119
	↓ Myoglobin	Flavan-3-ols	125
	↓ CK	Flavan-3-ols	125
	↓ LDH	Flavan-3-ols	125
Apoptosis	↓ BAD phosphorylation	Flavan-3-ols	124
	↑ JNK phosphorylation	Flavan-3-ols	124
	↑ Bcl-2 phosphorylation	Flavan-3-ols	124
Oxidative stress	↑ GSH	Flavan-3-ols	118
	↓ Carbonylation levels	Flavan-3-ols	118
	↑ CAT	Flavan-3-ols	109
	↑ SOD	Flavan-3-ols	109
	↓ H_2O_2	Flavan-3-ols	125
	↓ HBA%	Flavan-3-ols	125
	↓ Nox2dp	Flavan-3-ols	125
	↑ Total antioxidant capacity	Flavan-3-ols	120
	↓ MDA	Flavan-3-ols	121
Glucose profile	↓ Glycerol	Flavan-3-ols	112
	↓ Glucose AUC	Flavan-3-ols	116
Lipid profile	↓ Triglycerides	Flavan-3-ols	111
	↓ HDL	Flavan-3-ols	105,107,118

BAD, BCL2–associated agonist of cell death; BCL2, B cell lymphoma 2; CAT, catalase; CK, creatine kinase; Glucose AUC, glucose area under the curve; GSH, reduced glutathione; H_2O_2, hydrogen peroxide; HBA%, glycated hemoglobin; HDL, high-density lipoprotein; JNK, c-Jun N-terminal; LDH, lactate dehydrogenase; MDA, malondialdehyde; Nox2dp, nitric oxide derived peptide; SOD, superoxide dismutase; VO_2, volume of oxygen.

of autophagy, ubiquitin/proteasome system, apoptosis, inflammation, oxidative stress, muscle metabolism, and bioenergetics. Although the exact mechanisms by which flavonoids may exert their reported beneficial effects on muscle quality remain unclear, according to the data reported, the suggested pathways involved in metabolism, mitochondrial bioenergetics, apoptosis, ubiquitin/proteasome system, and autophagy are summarized in Figures 2 and 3.

Physical performance

In rodents, flavonoids appear to improve the physical performance, cross-sectional area, and muscle mass. In humans, improved physical performance with reduction of postexercise muscle soreness and the time of recovery. Although currently only diet and exercise are recognized as effective means to counteract muscle loss, it is important to mention that exercise in the elderly can produce exercise-induced muscle damage with reduction of muscle force and delayed-onset muscle soreness.[11] The inflammatory response from the injured muscle involves neutrophils, macrophages, and cytokines such as TNF-α, IL-1β, and IL-6, which contribute to low-grade systemic inflammation and oxidative stress.[12] Therefore, in specific populations where the preservation of muscle is crucial, flavonoids may be potentially useful to prevent loss of muscle mass and function.

Table 5. Summary of Plasma and Skeletal Muscle Biomarkers Modulated in Rodent Studies

Skeletal muscle	*Outcome*	*Flavonoid*	*Reference*
Autophagy	↓ Akt1, ATG4b, ATG4c, ATG7, Gabarap, Gabarapl2 and Rab24 mRNA expression	Flavan-3-ols	86
	↑ ATG16L2, SNCA, TM9SF1, Pink-1, PI3Kγ, PIM-2, Dapk1, IFNγ, IRGM and Cdkn2A mRNA expression	Flavan-3-ols	86
	↓ Beclin1, LC3-II/LC3-I, ATG12 and ATG7 protein expression	Flavan-3-ols	86
	↓ DRP1 and Beclin1 protein expression	Flavan-3-ols	54
	↑ AMPK phosphorylation	Flavanonols	27
		Flavan-3-ols	47
	↑ Beclin1 protein expression	Flavanonols	27
	↑ LC3-II/LC3-I protein expression	Flavanonols	27
Differentiation	↑ MyoD protein and mRNA expression	Isoflavones	97
	↑ Myogenin mRNA expression	Isoflavones	97
Ubiquitin/proteasome	↓ NF-kB protein expression	Flavan-3-ols	46,90
	↓ NF-kB activation	Flavonols	101
	↑ Nrf2 activation	Flavonols	101
	↓ NF-kB mRNA expression	Flavan-3-ols	46
	↓ Myostatin protein expression	Flavan-3-ols	76
		Flavanonols	27
	↓ MuRF1 protein expression	Flavan-3-ols	46,76,95
		Licorice	103
		Flavones	18,93
		Flavonols	101
		Flavanonols	17
	↓ MAFbx protein expression	Flavan-3-ols	46,76
		Flavones	93
		Flavanonols	17,27
		Licorice	103
	↓ MuRF1 and MAFbx mRNA expression	Flavan-3-ols	46,90
		Flavones	93
	↓ MuRF1 and Atrogin-1 mRNA expression	Flavones	18
	↓ Proteasome 20S and 19S protein expression	Flavan-3-ols	76
	↓ FOXO1 and GSK3β protein expression	Flavan-3-ols	83
	↓ FOXO3a protein expression	Flavan-3-ols	90
		Flavanonols	17
	↓ FOXO3a phosphorylation	Licorice	103
	↑ Sirt1 protein expression	Flavan-3-ols	75,90
		Flavanonols	27
	↑ S6K phosphorylation	Flavan-3-ols	95
		Licorice	103
		Flavanonols	17
	↑ Akt phosphorylation	Licorice	103
		Flavanonols	17
		Flavan-3-ols	53,64
		Anthocyanins	94
	↓ USP19 protein expression	Isoflavones	99
	↓ p38 phosphorylation	Flavones	93
		Licorice	103
	↓ p65 phosphorylation	Flavones	93
	↓ Free ubiquitin E3 protein expression	Flavanonols	27
Apoptosis	↑ Bak1, Bid, Caspase 3, TNF-α, Htt, Bcl-2, Bcl-XL, Map1lc3a and FADD mRNA expression	Flavan-3-ols	86
	↓ Bax mRNA expression	Flavan-3-ols	57
	↑ Cytochrome c mitochondria/cytoplasm ratio	Flavan-3-ols	68
	↓ Bcl-2 mRNA expression	Flavan-3-ols	57
	↑ Bax cytoplasm/mitochondria ratio	Flavan-3-ols	68
	↑ p53 mRNA expression	Flavan-3-ols	57
	↓ p53 phosphorylation	Licorice	103
	↓ Caspase 3 and caspase 9 protein expression	Flavan-3-ols	64

(*continued*)

TABLE 5. (CONTINUED)

Skeletal muscle	*Outcome*	*Flavonoid*	*Reference*
	↓ Caspase 3 and caspase 9 mRNA expression	Flavan-3-ols	79
	↓ AIF protein expression	Flavan-3-ols	64,73
	↓ FADD protein expression and apoptotic index	Flavan-3-ols	64
	↓ Bax protein expression	Flavanonols	27
		Flavan-3-ols	64,73
	↑ Bcl-2 protein expression	Flavanonols	27
		Flavan-3-ols	64
Inflammation	↑ IL-10 protein expression	Flavones	98
	↓ IL-6 protein expression	Flavones	18,98
	↑ IL-6	Flavonols	33
	↓ TNF-α protein expression	Flavones	18,98
		Flavan-3-ols	63
	↓ IL-1β protein expression	Flavones	98
		Flavan-3-ols	47,63
	↓ CRP-1 protein expression	Flavan-3-ols	47
	↑ IL-4 and IL-10 mRNA expression	Flavan-3-ols	84
	↓ MCP-1 and TNF-α mRNA expression	Flavan-3-ols	51
	↓ MCP-1 protein expression	Flavan-3-ols	63
	↑ Itgam (macrophage marker CD11b) mRNA expression	Flavan-3-ols	74
	↑ mRNA expression of IL-15 and IGF-1	Flavan-3-ols	76
	↑ HO-1 protein expression	Flavonols	98,101
	↑ HO-1 mRNA expression	Flavones	98
	↑ Nrf2 mRNA and protein expression	Flavones	98
	↑ Nrf2 protein expression	Flavan-3-ols	75
	↓ TNF-α and IL-1β mRNA expression	Flavones	18
Oxidative stress	↑ SOD2 protein expression	Flavan-3-ols	68,75
	↑ SOD2 mRNA expression	Flavan-3-ols	84
	↑ SOD2 activity	Flavan-3-ols	68
	↑ SOD1 activity	Anthocyanins	94
	↑ Total SOD activity	Flavan-3-ols	44
	↓ Total SOD protein expression	Isoflavone	25
		Flavones	98
	↑ CAT protein expression	Flavonols	33
		Flavan-3-ols	75
	↑ CAT activity	Anthocyanins	44,94
		Flavan-3-ols	68,75
	↑ GSH/GSSG ratio	Flavan-3-ols	51,68,75
	↑ GSH protein levels	Isoflavone	25
	↑ Glutathione reductase protein expression	Flavan-3-ols	51
	↑ GPx protein expression	Flavones	98
		Flavonols	33
	↑ GPx activity	Anthocyanins	94
		Flavan-3-ols	44
	↓ ROS	Flavones	98
	↓ Myeloperoxidase activity	Flavan-3-ols	63
	↓ Cytochrome c oxidase activity	Isoflavone	25
	↓ MDA levels	Flavonols	33
		Flavan-3-ols	51,54,63
		Flavanonols	17
		Flavones	98
		Anthocyanins	94
		Isoflavone	25
	↓ Carbonylation levels	Flavan-3-ols	44,50,51,54,68,75,79
		Isoflavone	25
		Anthocyanins	94
		Flavanonols	17

(*continued*)

Table 5. (Continued)

Skeletal muscle	*Outcome*	*Flavonoid*	*Reference*
Plasma			
Oxidative stress	↓ MDA levels	Flavan-3-ols	35,51,53,84
		Anthocyanins	94
		Flavanonols	27
	↑ SOD activity	Anthocyanins	94
		Flavanonols	27
		Flavan-3-ols	53
	↑ CAT activity	Anthocyanins	94
	↑ GPx activity	Anthocyanins	94
		Flavan-3-ols	53
Inflammation	↑ IL-10 protein levels	Flavan-3-ols	51
		Flavones	98
	↓ IL-6 protein levels	Flavan-3-ols	51
	↓ IL-6	Flavones	18,93
		Anthocyanins	94
	↓ TNF-α protein levels	Flavones	18,93
		Anthocyanins	94
	↓ Leptin and resistin protein levels	Anthocyanins	94
	↑ Adiponectin protein levels	Anthocyanins	94

AIF, apoptosis inducing factor; Akt, RAC-alpha serine/threonine-protein kinase; AMPK, 5' AMP-activated protein kinase; ATG12, ubiquitin-like protein ATG12; ATG16L2, autophagy-related protein 16–2; ATG4b,c, autophagy-related 4B/4C cysteine peptidase; ATG7, ubiquitin-like modifier-activating enzyme; Bak1, Bcl-2 homologous antagonist killer; Bax, Bcl2 associated X; Bcl-2, B cell lymphoma 2; Bcl-XL, B cell lymphoma extra-large; CAT, catalase; Cdkn2A, cyclin-dependent kinase inhibitor 2A; CRP-1, cysteine-rich protein 1; Dapk1, death-associated protein kinase 1; DRP1, dynamin-1-like protein; FADD, Fas associated via death domain; FOXO1, forkhead box protein O1; FOXO3a, forkhead box O3a; Gabarap, gamma-aminobutyric acid receptor-associated protein; Gabarapl2, gamma-aminobutyric acid receptor-associated protein-like 2; GPx, glutathione peroxidase; GSH, glutathione; GSK3β, glycogen synthase kinase 3 beta; GSSG, disulfide glutathione; HO-1, heme oxygenase 1; Htt, Huntingtin; IFNγ, interferon gamma; IGF-1, insulin-like growth factor I; IL, interleukin; IRGM, immunity-related GTPase family M protein; Itgam, integrin alpha-M precursor; LC3-II/LC3-I/Map1lc3a, microtubule-associated proteins 1A/1B-light chain 3; MAFbx, muscle atrophy F-box; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde.; mRNA, messenger ribo nucleic acid; MuRF1, muscle RING-finger protein-1; MyOD, myoblast determination protein 1; NF-kB, nuclear factor kB; Nrf2, nuclear factor-erythroid factor 2-related factor 2; p38, p38 mitogen-activated protein kinase; p53, cellular tumor antigen p53; p65, nuclear factor NF-kappa-B p65 subunit; PI3Kγ, phosphatidylinositol 3-kinase catalytic subunit gamma isoform; PIM-2, serine/threonine-protein kinase pim-2; Pink-1, PTEN-induced putative kinase protein 1; Rab24, Ras-related protein Rab-24; ROS, reactive oxygen species; S6K, ribosomal protein S6 kinase; SIRT1, sirtuin 1; SNCA, alpha synuclein; SOD, superoxide dismutase; TM9SF1, transmembrane 9 superfamily member 1; TNF-α, tumor necrosis factor alpha; USP19, ubiquitin carboxyl-terminal hydrolase 19.

In this regard, resveratrol and (–)-epicatechin have been defined as exercise mimetics based on many similarities between the effects of exercise and the consumption of these flavonoids, such as AMP-activated protein kinase activation and an increase in mitochondrial biogenesis, angiogenesis, and vasodilatation.[13,14] In addition, flavonoids could stimulate muscle remodeling through the AMPK–SIRT1–PGC1α–PPARδ pathway and myokines (*e.g.,* Il-6, IGF1, and cathepsin B).[2,14] Our data agree with this statement, associating the consumption of flavonoids with an increase in muscle mass, muscle area, and exercise endurance.

All the evidence reveals that regular exercise significantly increases β-oxidation (fatty acid metabolism) in SkM.[13] Considering that two important flavonoids (resveratrol and (–)-epicatechin) have been defined as partial exercise mimetics,[14] and besides acting on beta-oxidation, they could modulate the expression of proteins involved in related lipid metabolism pathways and the expression of energy expenditure-related genes, such as the PPAR family.[15] The evidence suggested that flavonoids increase fat oxidation (metabolism) at rest and/or during exercise and subsequently decreasing the carbohydrate oxidization rate and improving the exercise capacity.

Based on the results reported here, we hypothesize that since flavonoids have been reported to have vasodilatory effects by increasing endothelial nitric oxide synthesis, they may improve muscle perfusion during exercise and therefore improve endurance and the reduction of the recovery period.

Changes in body composition and increased muscle quality are strong predictors of a change in physical function,[16] and in concordance with this evidence, flavonoids included in this review induced improvements in both.

Effects on SkM mitochondria

It has been suggested that (–)-epicatechin, an abundant flavan-3-ol found in cacao, could enhance the effects of exercise improving muscle performance and possibly attenuating the effects of aging induced muscle loss and maintaining mitochondrial integrity and metabolism homeostasis.

In addition, dihydromyricetin an important flavanonol prevents dexamethasone-induced muscle atrophy through mitochondrial biogenesis and mitochondrial fusion, enhances mitochondrial respiratory chain complex activity,

Table 6. Summary of Muscle Mitochondrial Effects in Rodent Studies

Outcome	*Flavonoid*	*Reference*
↑ Complex I	Flavan-3-ols	49,54,56,71,75
	Flavanonols	17
	Flavones	18
↑ Complex II	Flavan-3-ols	49,54,56,71
	Flavanonols	17
	Flavones	18
↑ Complex III	Flavan-3-ols	49,54,56,71
↑ Complex IV	Flavanonols	17
↑ Complex V	Flavan-3-ols	49,54,56,71,75
↑ mRNA expression of complexes I and IV	Flavan-3-ols	78
↑ ATPase activity	Flavan-3-ols	66
	Flavanonols	17
↑ CcO activity	Flavan-3-ols	56,61,83
↑ Citrate synthase	Flavan-3-ols	49,56,66
	Flavones	18
↑ Cristae, inner membrane surface and volume density	Flavan-3-ols	49
	Flavones	18
↑ TFAM	Flavan-3-ols	67,78
	Flavanonols	17
	Flavones	18
↑ SIRT1	Flavan-3-ols	67,69,78,82
	Flavanonols	27
↑ PGC1α	Flavan-3-ols	52,67,69,71,72,74
	Flavanonols	17,27
	Flavones	18
↑ mRNA levels of PGC1α	Flavan-3-ols	80
No effect on mRNA levels of PGC-1α	Flavan-3-ols	26,38
No effect on protein levels of PGC-1α	Flavan-3-ols	54,78
↑ UCP1	Flavan-3-ols	67
↑ UCP2	Flavan-3-ols	66
↑ UCP3	Flavan-3-ols	52
↑ mRNA expression UCP1	Flavan-3-ols	80
↑ mRNA expression UCP3	Flavan-3-ols	48,72,80
↑ mRNA expression of PPARα	Flavan-3-ols	60
↑ Mitofilin	Flavan-3-ols	67,75
↑ AMPK expression and activity	Flavan-3-ols	82
↑ AMPKα phosphorylation	Flavan-3-ols	31,47,53,59,66,69,78,80,85
↓ Protein carbonyls and MDA	Flavanonols	17
↑ Nrf1	Flavan-3-ols	52,78
	Flavonols	101
↑ Mfn2 and OPA1 gene expression	Flavan-3-ols	54
↑ Mitochondrial DNA copy number	Flavan-3-ols	70
↓ DRP1	Flavanonols	17
↑ TOM 20	Flavanonols	17

CcO, cytochrome c oxidase; Mfn2, mitofusin-2; OPA1, mitochondrial dynamin-like GTPase; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PPARα, peroxisome proliferator-activated receptor α; TFAM, mitochondrial transcription factor A; TOM20, mitochondrial import receptor subunit TOM20; UCP1, 2, 3, uncoupling protein isoforms 1, 2, 3.

Table 7. Associated Metabolic Changes in Rodent Studies

Outcome	*Flavonoid*	*Reference*
↓ Glucose	Flavan-3-ols	48,52,54,60,62,67,70,77,78,82
	Flavonols	33,92
	Isoflavones	91,100
	Anthocyanins	94
↓ Postprandial glucose	Flavan-3-ols	31,32,37,58,59,77,85
↓ Insulin	Flavan-3-ols	39,43,48,52,58,59,60,62,65,66,78,82,100
	Isoflavones	91
	Anthocyanins	94
↑ Insulin	Flavonols	92
	Isoflavones	101
↓ HOMA-IR	Flavan-3-ols	48,59,66,71,100
	Flavonols	33
	Anthocyanins	94
↑ Glucose uptake	Flavan-3-ols	36,53
↑ Glucose tolerance	Isoflavones	91
↓ HbA1C	Flavan-3-ols	32,62,85
	Anthocyanins	94
↓ HK, PK, Glucose-6P-DH	Flavan-3-ols	62
↓ LECT2	Flavan-3-ols	100
↑ IGF-1	Isoflavones	97
↑ IGF-1R	Isoflavones	97
↑ Irisin	Flavanonols	27
↑ HDL	Flavan-3-ols	32,36,77
	Isoflavones	91
↓ LDL	Flavan-3-ols	32,36,47,77
	Anthocyanins	94
↓ VLDL	Anthocyanins	94
↓ Total cholesterol	Flavan-3-ols	32,36,47,59,77,85
	Isoflavones	91
	Anthocyanins	94
↑ PPARα	Flavonols	92
↓ Triglycerides	Flavan-3-ols	32,39,55,67,77,85
	Anthocyanins	94
↑ Lipid oxidation	Flavan-3-ols	38,39
↓ FFA	Flavan-3-ols	32,36
↓ NEFA	Flavan-3-ols	26,39,55
↓ HDL/LDL ratio	Phloridzin	102

Glucose-6P-DH, glucose 6 phosphate dehydrogenase; HbA1C, glycated hemoglobin; HDL, high-density lipoprotein; HK, hexokinase; HOMA-IR, homeostatic model assessment of insulin resistance; IGF-1R, insulin-like growth factor-1 receptor; LDL, low-density lipoprotein; LECT2, leukocyte cell-derived chemotaxin 2; NEFA, nonesterified fatty acids; PK, pyruvate kinase; VLDL, very low-density lipoprotein.

and prevents collapse of mitochondrial membrane.[17] Also, flavones such as apigenin suppress mitochondrial dysfunction and reduce muscle atrophy.[18]

In this sense, many flavonoids enhance mitochondrial function through diverse signaling pathway changes.

Effect on SkM metabolism-associated parameters

Several reviews have got together evidence of different studies demonstrating the beneficial effects of daily flavonoid consumption on cardiometabolic health, highlighting the probable mechanism that let those molecules regulate

Table 8. Effects on Metabolism in Skeletal Muscle in Rodent Studies

	Outcome	*Flavonoid*	*Reference*
Carbohydrates	↑ GLUT4	Flavan-3-ols	32,78,85
		Anthocyanidin	94
	↑ GLUT4 translocation	Flavan-3-ols	31,42,53,58,59
		Isoflavones	101
	↑ mRNA expression of GLUT4	Flavan-3-ols	48
		Flavonols	92
	↑ IRS	Flavan-3-ols	31,65
		Anthocyanidin	94
	↓ IRS phosphorylation	Flavan-3-ols	53,82
	↑ IRS phosphorylation	Isoflavones	101
		Anthocyanidin	94
	↑ GK and PFK	Flavan-3-ols	32
	↑ Akt	Flavonols	92
	↑ phospho-Akt	Flavan-3-ols	54,82,85,100
		Flavonols	92
		Isoflavones	101
		Anthocyanidin	94
	↑ phospho-S6K	Flavan-3-ols	100
	↑ phospho-AMPK	Anthocyanidin	94
	↑ AMPKα mRNA expression	Flavan-3-ols	90
	↑ PPARα mRNA expression	Flavan-3-ols	90
	↓ GSK3β	Flavan-3-ols	54
	↓ PI3K	Anthocyanidin	94
Lipids	↑ β-oxidation	Flavan-3-ols	38,39,41,43
	↑ CPT	Flavan-3-ols	15,48,66,70
		Laminaria	60
	↑ Acyl-CoA oxidase	Flavan-3-ols	71
	↑ mRNA FAT/CD36	Flavan-3-ols	38
	↑ mRNA MCAD	Flavan-3-ols	38,52,70
	↑ mRNA expression of LPL	Flavan-3-ols	66
	↑ CD36 gene expression	Flavan-3-ols	66
	↑ mRNA ACO	Flavan-3-ols	15,48
		Laminaria	48
	↑ mRNA expression of PPARα	Flavan-3-ols	15,48
	↑ mRNA expression of PPARδ	Flavan-3-ols	48
	↑ PPAR-γ gene expression	Flavan-3-ols	77
	No effect on PPARα	Flavan-3-ols	26
	↑ mRNA expression of PPARα	Laminaria	60
	↑ phospho-AMPK	Isoflavones	91
Protein synthesis	↑ mTOR phosphorylation	Licorice	103
	↑ p70S6K phosphorylation	Licorice	103

ACO, peroxisomal acyl-CoA oxidase; Akt, protein kinase B; CPT, carnitine palmitoyl transferase; FAT/CD36, fatty acid translocase; GLUT4, glucose transporter 4; IRS, insulin receptor substrate; LPL, lipoprotein lipase; MCAD, medium-chain acyl-CoA dehydrogenase; mTOR, mechanistic target of rapamycin; p70-S6K, ribosomal protein S6 kinase; PFK, phospho fructo kinase; PI3K, phosphoinositide 3-kinase; PPARα, δ, γ, peroxisome proliferator-activated receptor α, δ, γ isoforms.

different pathways involved in metabolism and the maintenance of cardiac health.[19–23] Some of these mechanisms include regulation of vascular health through nitric oxide synthase activation/deactivation and weight maintenance, and glucose-insulin homeostasis via regulation of Akt/PI3K, AMPK, and PGC1-α signaling cascades.[2] By the way, effects regulating different SkM processes have also been described, enriching the functional value of inclusion of different polyphenol sources in our diet. Information obtained in this review indicates that.

Flavonoids increase GLUT4 expression or stimulate its translocation by activating the PI3K/Akt-dependent signaling pathway. The analysis reported here strongly suggests that flavonoids may enhance muscle glucose uptake and improve adipocyte function by modulating pathways such as AMPK and PPAR-γ and decrease the expression of genes involved in the biosynthesis of fatty acids, cholesterol, and lipogenesis by limiting the *de novo* lipogenesis and increasing fatty acid β-oxidation.[24]

Dosage

The most challenging issue in flavonoid use is the broad range of doses used, using ranges between 1 mg/day (using isoflavones and catechins)[25,26] and up to 200 mg/day using dihydromyricetin,[17,27] making it difficult to interpret results in studies and their replication. We believe that (at least for (–)-epicatechin) many, if not all, of its induced effects are mediated through its specific interaction with acceptors/receptors, supporting the hypothesis of needing only low doses.

The use of low doses minimizes the antioxidation effects of these molecule types, however, given the specificity of the induced effects, the interaction with receptors needs to be analyzed molecule by molecule.[28,29] Interestingly, although positive effects have been observed with low doses of flavonoids, most of the analyzed studies utilized high doses of the flavonoids and suggest necessary association with physical training to improve physical performance parameters. However, in our hands, doses as low of 1 mg/kg/day induce the improvements in physical performance.[30]

With regard to rodents, 59 of the 80 studies administered flavanols either isolated in their monomeric form (epicatechin or epigallocatechin gallate [EGCG]) or in a mixture of monomeric and dimeric/polymeric forms (catechins or procyanidins), with a procyanidin dose ranging between 10 and 150 μg/kg (total dose for procyanidin-rich extracts).[31,32] Major differences in daily flavanols dosage utilized were observed among the studies, ranging between 10 and 400 mg/kg/bw for epicatechin, 0.05% in chow diet to 269 mg/kg/bw for EGCG, 0.05% in chow diet to 600 mg/kg/bw for catechins, on the other hand the authors report quercetin doses between 20 mg/kg intramuscular and 100 mg/kg oral.[33,34]

Meta-analysis

The results of the meta-analysis suggested that flavonoid supplementation is associated with improvements in muscle

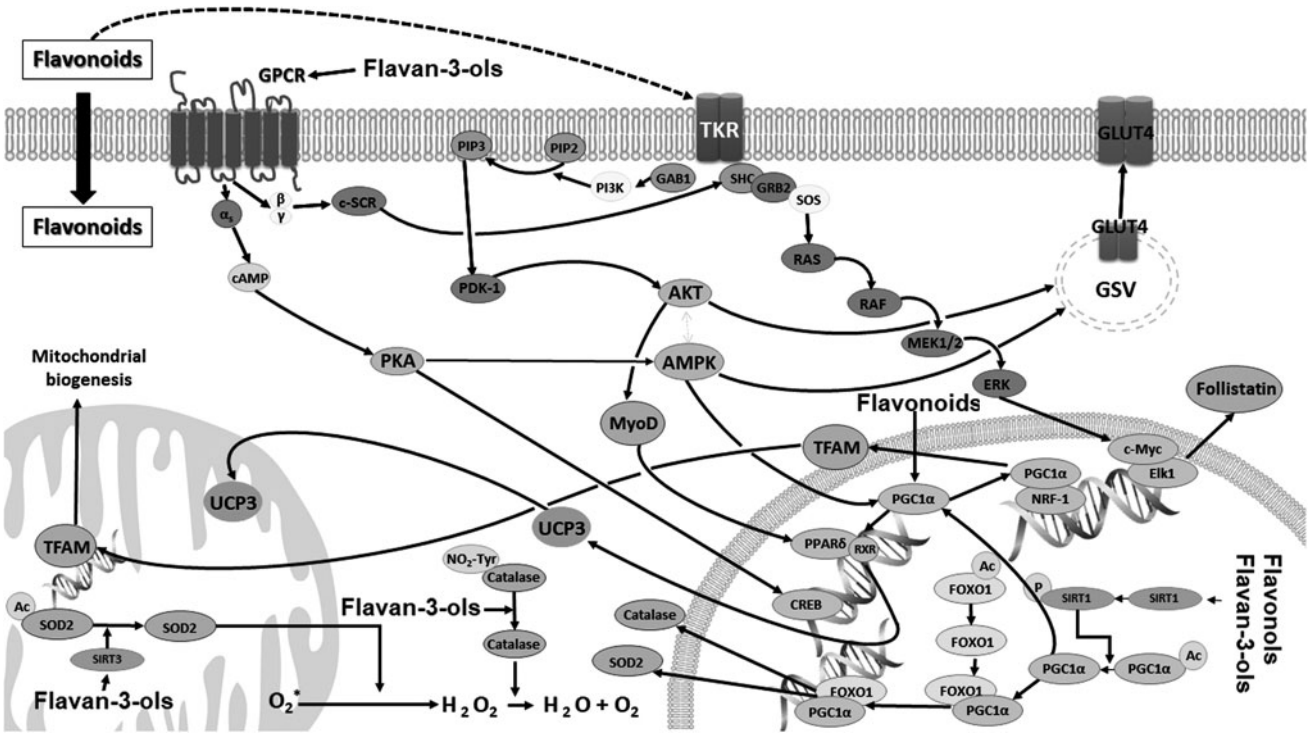

FIG. 2. Proposed mechanism for signaling pathway modulating mitochondrial biogenesis and bioenergetics.

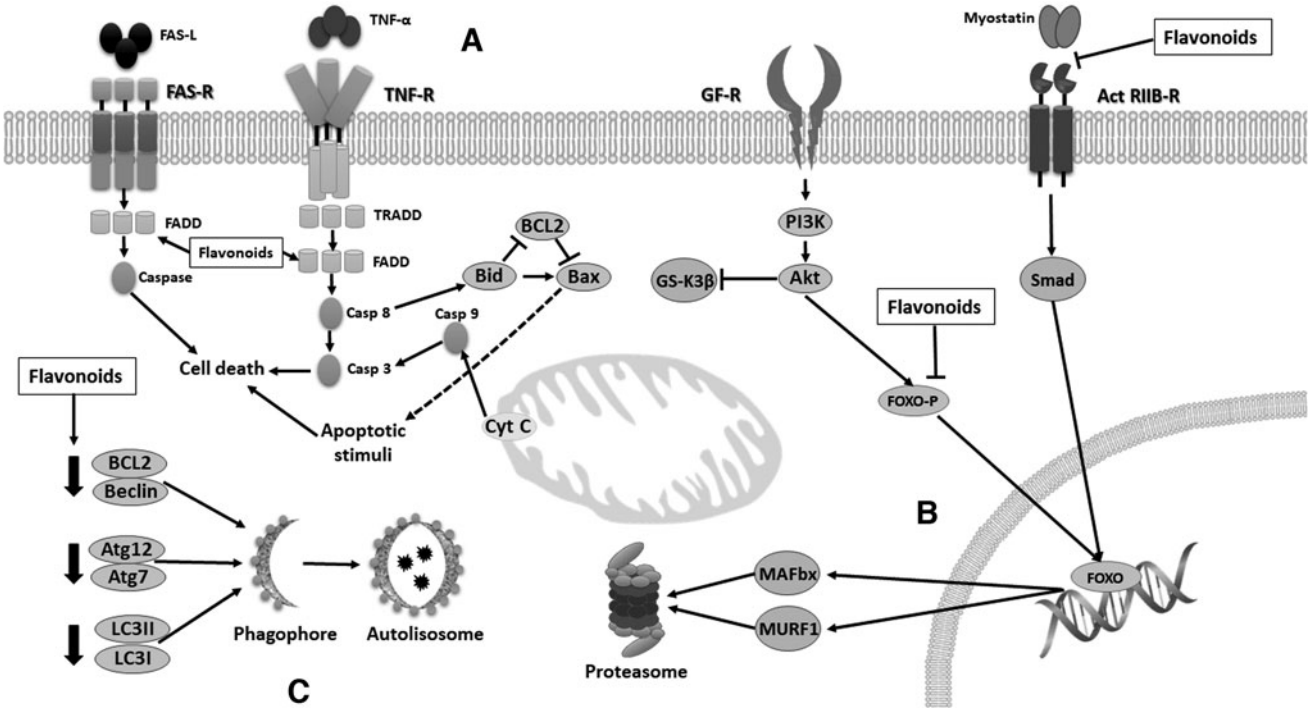

FIG. 3. Proposed signaling pathways where flavonoids modulate muscle homeostasis. **(A)** Interaction of flavonoids in apoptosis through increase in the activity of BCL and promoting degradation of damaged cells. **(B)** Ubiquitin/proteasome system through reduction of MAFbx and MuRF1 expression and reduction of protein ubiquitination, and hence, reduction of protein degradation. **(C)** Myogenesis through myostatin/activin by clocking myostatin activity and an increase in follistatin expression. BCL, B cell lymphoma, MAFbx, muscle atrophy F-box, MuRF1: muscle RING-finger protein-1.

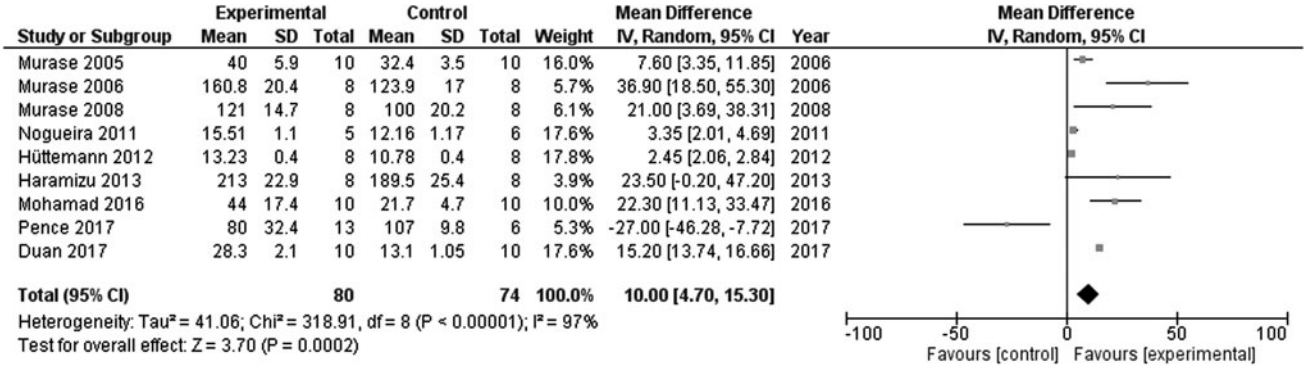

FIG. 4. Forest plot of the meta-analysis for the exercise performance. Mean differences in time (min) between flavonoids and control. Combined results from the random-effects model showed a significant improvement in the endurance exercise following flavonoid consumption (MD: +10 min, 95% CI: 4.70–15.30, $P < .0002$), with significant heterogeneity among the studies ($I^2 = 97\%$, $P < .00001$). MD, mean difference.

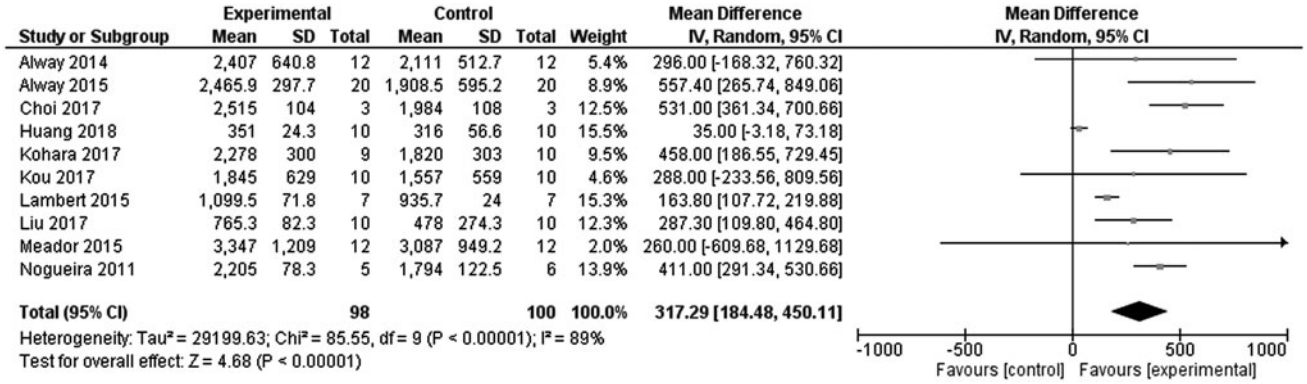

FIG. 5. Forest plot of the meta-analysis for the SkM cross-sectional area. Mean differences reported muscle fiber cross-sectional area (μm^2) between flavonoids and control. Combined results from the random-effects model showed a significant improvement in the muscle area following flavonoid consumption (MD: +317.29 μm^2, 95% CI: 184.48–450.11, $P < .00001$), with significant heterogeneity among the studies ($I^2 = 89\%$, $P < .00001$). SkM, skeletal muscle.

health parameters such as performance, cross-sectional area, and muscle mass, with no reported adverse effects. Because the data show different muscle conditions that involve aging, obesity, and atrophy, the use of flavonoids, particularly flavan-3-ols, could be clinically relevant for diseases such as sarcopenia-frailty, cachexia, or dystrophy.

CONCLUSIONS

Although the clinical evidence is still scarce, the results of preclinical studies focused at improving muscle mass and physical performance are promising. The analysis reported here strongly suggested that the use of flavonoids could be a

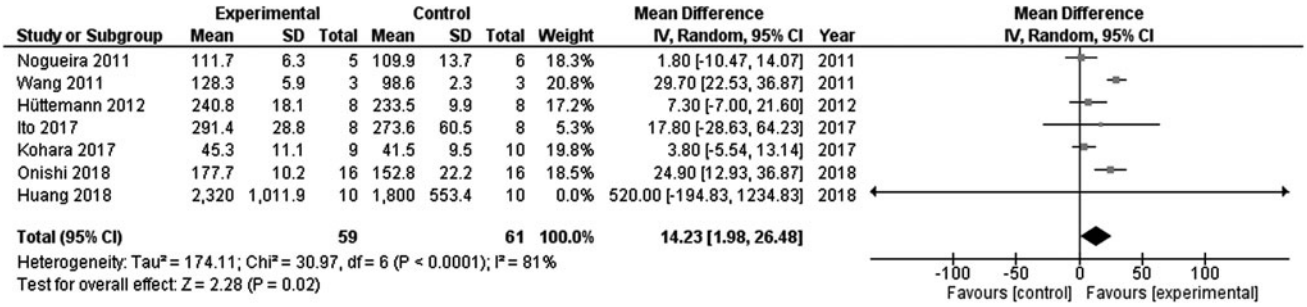

FIG. 6. Forest plot of the meta-analysis for the SkM weight. Mean differences reported weight (mg) between flavonoids and control. Combined results from the random-effects model showed a significant improvement in the muscle mass following flavonoid consumption (MD: +14.23 mg, 95% CI: 1.98–26.48, $P = .02$), with significant heterogeneity among the studies ($I^2 = 81\%$, $P < .0001$) (Fig. 6).

potential tool for the prevention of muscle loss. Their effects on metabolism and on mitochondrial function suggest their use as cardiometabolic regulators. However, larger clinical trials are necessary to support the use of flavonoids in the treatment of the muscle dysfunction.

AUTHOR DISCLOSURE STATEMENT

Villarreal is a cofounder and stockholder of Epirium Inc., and Ceballos is a stockholder.

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