

Exercise physiology meets sports nutrition: The flavonoid–gut–muscle axis and its implications for recovery and exercise adaptation

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ABSTRACT

Background: Dietary flavonoids undergo extensive host and microbial metabolism, producing circulating metabolites that differ from parent compounds and vary substantially between individuals. This variability may contribute to heterogeneous exercise responses, but the underlying causal sequence remains unproven. **Objective:** To examine whether variability in microbial flavonoid metabolism could explain interindividual differences in exercise recovery and adaptation. **Methods:** PubMed/MEDLINE, Scopus, and Web of Science were searched from inception to 30 August 2026. Of 110 unique records, 35 were excluded and 75 retained after full-text assessment. One reviewer conducted study selection and extraction, followed by a second criterion-based verification pass. Five principal human studies were appraised using the 2018 Mixed Methods Appraisal Tool. Evidence was synthesised narratively because of substantial heterogeneity. **Results:** Thirteen primary studies informed at least one component of the proposed model, including five human studies and eight animal or cellular experiments. Only two human studies combined flavonoid or polyphenol supplementation with exercise, and neither demonstrated mediation by a defined microbial metabolite or assessed functional recovery or performance outcomes. Two additional exercise studies examined gastrointestinal or microbiome responses without flavonoid exposure, while one non-exercise study investigated microbial flavan-3-ol metabolism. No observational study directly tested the complete model. Confidence in generalisability was limited by small samples, restricted populations, incomplete reporting of blinding procedures, and the absence of integrated mediator and functional outcome measures. **Conclusion:** Individuals may differ in exercise responses because they generate distinct systemic exposures to microbial flavonoid metabolites. Current evidence supports the early metabolic steps of the proposed pathway, but not microbial mediation of recovery or adaptation.

Keywords: flavonoids; gut microbiota; microbial metabolites; interindividual variability; skeletal muscle; exercise recovery; training adaptation; precision nutrition.

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INTRODUCTION

Flavonoids are structurally diverse dietary polyphenols found in fruits, vegetables, berries, tea, cocoa, and legumes. Intake alone is an incomplete measure of biological exposure because glycosylation, food matrix, intestinal absorption, host conjugation, and microbial catabolism determine which compounds subsequently circulate (Alqudah & Claesen, 2024; Carregosa et al., 2022; Oliveira, 2026; Quesada-Vázquez, 2024; Williamson, 2025; Zhang, 2024). Parent flavonoids may be transient or poorly absorbed, whereas lower-molecular-weight phenolic products and host-conjugated metabolites can appear later and persist longer. Two people receiving the same nominal dose may therefore experience different internal exposures.

The proposed gut–muscle axis is an emerging network rather than a single demonstrated pathway. It encompasses microbial products, intestinal barrier function, immune and endocrine signalling, vascular responses, and skeletal-muscle metabolism (Gao, 2025; Imdad, 2022; Li et al., 2024; Saponaro, 2024; Xie & Huang, 2024; Xu & He, 2025). Previous reviews have examined flavonoid bioavailability, polyphenol–microbiota interactions, the athlete microbiome, polyphenols and recovery, or the broader gut–muscle concept (Baky et al., 2022; Carey et al., 2021; Favari, 2024; Gonzalez, 2026; Howatson & Clifford, 2026; Narduzzi, 2022; Pérez-Castillo, 2024; Perrone & D'Angelo, 2026; Ruiz-Iglesias, 2021; Ticinesi, 2023). Combining all of these topics into one model, however, can imply a degree of integration that the evidence does not support.

The present review is organised around a narrower question: can variation in microbial flavonoid metabolism explain interindividual variation in exercise recovery or adaptation? This question requires evidence for a sequential chain: ingestion, microbial transformation, systemic appearance of defined metabolites, engagement of a biologically relevant target, and change in a functional exercise outcome. Demonstrating separate associations at each stage is insufficient to establish mediation.

The unique contribution of this review is therefore the proposed role of metabolite-exposure heterogeneity as a candidate explanation for variable exercise responses. The review does not propose that the general interaction among diet, microbiota, and muscle is novel. It instead evaluates whether microbial-derived flavonoid metabolites provide the missing measurable bridge between intake and functional adaptation. Direct and indirect evidence are separated throughout, and secondary pathways are retained only as hypotheses that could connect systemic metabolite exposure to an outcome.

REVIEW METHODOLOGY

Review design and organising question

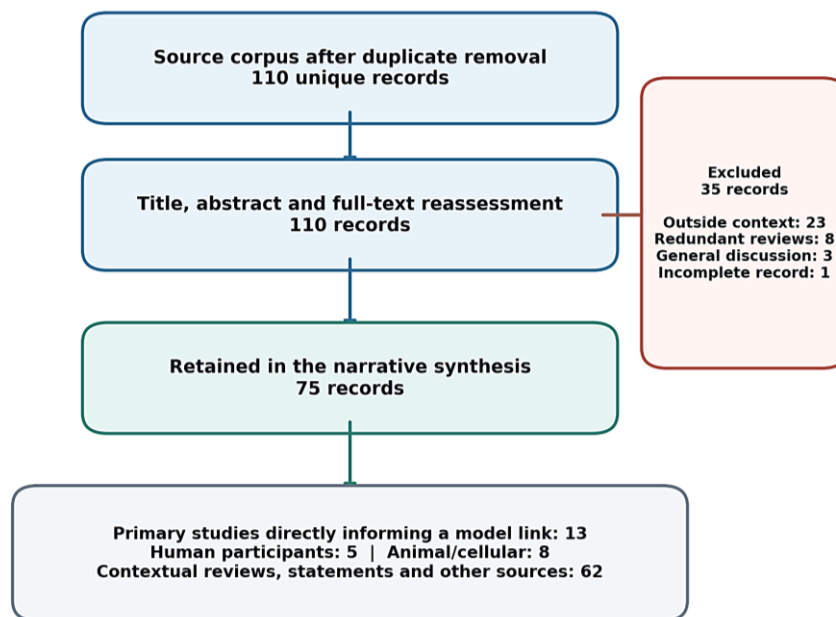
This work was conducted as a structured narrative review. The organising question was: among humans exposed to exercise or training, is there evidence that gut microbial transformation of flavonoids changes systemic metabolite exposure and thereby influences recovery, performance, or adaptation? A narrative design was retained because the corpus spans human interventions, pharmacokinetic studies, controlled exercise experiments, animal models, cellular studies, and mechanistic reviews with incompatible exposures and outcomes. The review was not registered as a systematic-review protocol and no meta-analysis was planned.

Information sources and search strategy

PubMed/MEDLINE, Scopus, and Web of Science Core Collection were searched from database inception to 30 August 2026. The core searches combined three concept blocks: (1) flavonoids or named subclasses and

compounds; (2) gut microbiota, microbial metabolites, phenolic metabolites, or metatypes; and (3) exercise, athletes, skeletal muscle, recovery, performance, fatigue, or training adaptation. Targeted searches added intestinal permeability, inflammatory or redox signalling, vascular function, mitochondrial dynamics, mitophagy, and metabolic flexibility. Backward citation screening was limited to potentially eligible records already represented in the review corpus. Complete database-specific strings, including field tags and Boolean operators, are reproduced in Supplementary Table S1.

The source file for the original submission contained 110 unique records after duplicate removal. The pre-deduplication exports were not archived; consequently, a raw pre-deduplication count cannot be reconstructed and is not claimed. For the present revision, all 110 records were treated as the identified corpus and rescreened from the beginning. Figure 1 reports the selection flow.



Raw pre-deduplication exports were not archived; no unrecoverable count is imputed.

Figure 1. Selection of evidence from the 110-record source corpus. The pre-deduplication count could not be reconstructed because raw database exports were not archived. All records were reassessed in full because they had appeared in the original submission corpus.

Eligibility criteria and study selection

Records were eligible when they directly informed at least one prespecified link: (1) microbial transformation of a flavonoid; (2) systemic exposure to a defined flavonoid-derived metabolite; (3) interindividual variation in that exposure; (4) modification of gastrointestinal physiology or microbiome function by exercise; (5) a metabolite-sensitive mechanism relevant to muscle; or (6) a recovery, performance, or adaptation outcome following flavonoid exposure. Peer-reviewed original studies, systematic reviews, meta-analyses, narrative reviews, and position statements were eligible, but original investigations were prioritised for claims about causality or efficacy.

Records were excluded if they concerned a disease-specific pathway with no defensible connection to the organising question; discussed phytochemicals only in general therapeutic terms; duplicated a closer and more relevant secondary source without adding unique evidence; addressed an unrelated gut–organ axis; or lacked sufficient bibliographic information for verification. All 110 records underwent title-and-abstract

screening and full-text reassessment because every record had appeared in the original reference corpus. Thirty-five were excluded and 75 were retained. Full-text exclusion reasons were: outside or disease-specific context with no direct transfer to the model ($n = 23$), redundant secondary evidence ($n = 8$), general pharmacological discussion without a relevant exercise or microbial-metabolite link ($n = 3$), and incomplete bibliographic information ($n = 1$). Supplementary Table S2 lists every excluded record and its reason.

Selection was undertaken by one reviewer (PJ), who also extracted the study characteristics. All eligibility and classification decisions were checked in a second pass against the prespecified criteria. Because there was one selector, between-reviewer disagreement resolution was not applicable. This process is reported explicitly because single-reviewer selection remains a potential source of error and narrative-selection bias.

Data extraction and evidence streams

For primary studies, extraction fields were population or experimental model, intervention or exposure, flavonoid or metabolite measurement, microbiome assessment, exercise context and outcome, principal finding, and the limitation most relevant to the proposed causal sequence. The resulting evidence table is presented in Table 1. Thirteen primary studies directly informed at least one central link. The remaining retained sources were used for pharmacokinetic, methodological, physiological, or interpretive context rather than as substitutes for direct evidence.

Evidence was separated into four streams. Direct human exercise evidence comprised intervention or controlled-exercise studies in humans. Human non-exercise evidence established microbial transformation or metabolite exposure without an exercise outcome. Observational evidence was defined prospectively as non-interventional human evidence relating flavonoid or metabolite exposure to an exercise phenotype; no retained study met this direct definition. Animal and cellular evidence was used solely for plausibility. Reviews and consensus statements contextualised consistency, terminology, and practical boundaries but were not treated as proof of an individual model link.

Table 1. Direct and indirect primary evidence informing the narrowed flavonoid–gut–muscle model.

Evidence stream / study	Population or model	Intervention or exposure	Metabolite measurement	Microbiome assessment	Exercise outcome	Principal finding	Evidential limitation
Human non-exercise: Lessard-Lord et al.	Faecal donors ($n = 34$); short human supplementation component	Aronia/cranberry flavan-3-ols; cranberry extract for 4 days (82.3 mg/day)	Phenyl- γ -valerolactones in fermentation; urinary microbial metabolites	Donor faecal fermentation; no integrated functional sequencing endpoint	None	<1% conversion of the studied polymers and no significant urinary metabolite increase	Compound-specific, short, non-athlete and no parallel control or exercise condition
Direct human exercise: Huang et al.	Adolescent athletes ($n = 80$)	12-week high-polyphenol blend (1200 mg/day) vs placebo during intensive training	Urinary conjugates, untargeted metabolomics and short-chain fatty acids	16S and shotgun metagenomic profiling	Immune and training-load context; no recovery or performance endpoint	Immune, metabolomic and microbial differences during training	Four-compound intervention; no defined microbial flavonoid mediator or functional outcome
Direct human exercise: Alipour et al.	Men with obesity ($n = 44$)	Fisetin 200 mg/day, concurrent training, both, or placebo for 12 weeks	None	None	Inflammatory and metabolic biomarkers; no performance or recovery outcome	Training and fisetin-containing arms changed Maresin-1, inflammatory and metabolic markers	Clinical population; no pharmacokinetics, microbiome or functional exercise endpoint

Human exercise context: Hart et al.	Resistance-trained adults ($n = 30$; 15 women)	Randomised counterbalanced resistance-exercise and non-exercise sessions	None	None	GI symptoms, I-FABP and lactulose/rhamnose permeability	Resistance exercise increased symptoms; sex-related differences occurred in AUC markers	No flavonoid exposure, microbial assessment or adaptation outcome
Human exercise context: Suther et al.	Healthy active men ($n = 10$)	Randomised crossover: 72 h high activity with energy balance or ~45% energy deficit	No flavonoid-derived metabolite measurement	Faecal microbiome assessment	Intestinal function and microbial responses during high energy demand	Energy status modified intestinal and microbial responses	Small male-only sample; no flavonoid exposure or functional performance outcome
Cellular: Krueger et al.	β -cell model exposed to donor-specific microbial flavanol-metabolite mixtures	Bioavailable microbial metabolite profiles	Defined flavanol-derived metabolite mixtures	Donor-derived profiles; no exercise microbiome assessment	None	Bioactivity varied across donor-derived metabolite profiles	Non-muscle in vitro model; does not establish athlete response
Cellular: Wilhelmsen et al.	Primary human myotubes from eight healthy adults	Urolithin A (0.002, 1 or 50 μ M) for 24 h	Applied metabolite, not in vivo exposure	None	Glucose uptake, protein synthesis and myostatin expression	The 50- μ M condition increased glucose uptake and reduced myostatin expression	No exercise; active concentration may not represent post-dietary muscle exposure
Animal exercise: Chen et al.	Female mice ($n = 8$ /group)	Red-clover isoflavones for 6 weeks	No defined microbial metabolite measurement	Gut microbial composition	Exhaustive swimming, grip strength and fatigue markers	Supplemented groups showed microbiome and exercise-related differences	High animal-equivalent doses; no metabolite mediation
Animal exercise: Li et al.	Intensive-exercise mouse model	Resveratrol during intensive exercise	No defined microbial metabolite mediator	Gut microbial composition	Fatigue-related and intestinal outcomes	Resveratrol altered fatigue, gut inflammation and barrier-related outcomes	Animal study; mediation and human exposure were not established
Animal exercise: Ruiz-Iglesias et al.	Intensively trained and exhausted rats	Cocoa-enriched diet with or without hesperidin	None	Not a direct flavonoid-metabolite analysis	Mucosal immune outcomes after training/exhaustion	Flavonoid-enriched diets modified selected mucosal immune responses	Animal immune endpoints; no functional performance or metabolite mediation
Animal/cellular barrier: Zhang et al.	LPS-challenged mice and intestinal cell systems	Quercetin	Parent compound exposure	None	None	Barrier and inflammatory signalling were modified	Disease model, no exercise and no microbial-derived metabolite
Animal muscle: Mo and Lee	Aged mice	Baicalin	Parent compound exposure	None	Grip strength and muscle morphology, not training adaptation	Muscle atrophy and DRP-1-related fission markers were modified	Ageing model without gut or exercise mediation
Animal/cellular exercise: Liu et al.	C57BL/6 mice and C2C12 myotubes	Icariin with exercise-related testing	Parent compound exposure	None	Fatigue/metabolic responses and mitochondrial clearance	TFEB-dependent mitochondrial and exercise-related measures changed	No microbiome or microbial metabolite measurement; preclinical only

Formal critical appraisal

The five principal studies involving human participants were appraised with the 2018 Mixed Methods Appraisal Tool, using the relevant quantitative randomised or quantitative non-randomised domain. Each criterion was judged yes, no, or cannot determine from the report. The appraisal evaluated randomisation or representativeness, baseline comparability or control of confounding, completeness of outcome data, appropriateness and blinding of outcome measurement, and adherence to the assigned intervention or fidelity of exposure. Consistent with MMAT guidance, no numerical summary score was calculated; domain judgments and their consequences for interpretation are reported in Table 2.

The appraisal materially constrained the synthesis. The adolescent-athlete trial had several design strengths, including randomisation, placebo control, repeated multi-omics sampling, high retention, and intention-to-treat analysis (Huang, 2026). Nevertheless, it used a four-compound intervention, did not isolate microbial-derived flavonoid metabolites, and did not measure functional recovery or performance. The fisetin trial supported inflammatory and metabolic responses during training but provided no microbiome or pharmacokinetic data and involved men with obesity rather than trained athletes (Alipour, 2026). The two controlled exercise studies had appropriate within-person designs and objective gastrointestinal or microbiome measurements, but neither administered flavonoids (Hart et al., 2022; Suther et al., 2025). The short cranberry study directly quantified microbial metabolite formation but lacked exercise, a parallel control group, and an athlete population (Lessard-Lord, 2024). Consequently, even internally credible results support only isolated early links and cannot be combined into a demonstrated causal pathway.

Synthesis and language of inference

Because of heterogeneity in design, intervention, matrix, dose, biological sampling, exercise modality, and outcome, findings were synthesised narratively. Supported denotes direct human evidence for the stated link in the stated context. Suggestive denotes convergent but incomplete human evidence or a supported observation that has not been tested as a mediator. Proposed denotes a link supported primarily by animal, cellular, or theoretical evidence. These labels apply to individual links, not to the full model.

Table 2. Formal critical appraisal of the principal human studies using the 2018 mixed methods appraisal tool.

Study / design	C1	C2	C3	C4	C5	Methodological interpretation	Effect on conclusions
Huang et al.; randomised parallel trial	Y	Y	Y	U	Y	Generally low risk; assessor blinding not fully clear	Supports biological responsiveness during training only; no functional or microbial-flavonoid mediation claim
Alipour et al.; randomised parallel trial	Y	U	Y	U	U	Some concerns regarding concealment, assessor blinding and adherence reporting	Biochemical findings are retained but not generalised to athletes, performance or gut mediation
Hart et al.; randomised crossover	Y	Y	Y	N	Y	Some concern from unblinded subjective symptom assessment; objective measures strengthen inference	Supports acute GI context only, not flavonoid biotransformation
Suther et al.; randomised crossover	Y	Y	Y	U	Y	Some concern from limited blinding information and restricted sample	Supports energy status as a gut-response modifier only
Lessard-Lord et al.; non-randomised exposure	U	Y	Y	N	Y	Higher concern because the short human component lacked a parallel control and confounding control	Supports compound-specific conversion measurement, not general metabolite or exercise claims

Note. Y = yes; N = no; U = cannot determine. For randomised studies: C1, appropriate randomisation; C2, comparable baseline groups or periods; C3, complete outcome data; C4, appropriate and blinded outcome measurement; C5, adherence to the assigned intervention. For the non-randomised study: C1, representative participants; C2, appropriate exposure and outcome measurement; C3, complete data; C4, confounding addressed; C5, exposure delivered as intended. MMAT domain judgments were not converted to a numerical score.

WHAT THE EVIDENCE DIRECTLY SHOWS

Microbial conversion and variable systemic exposure

Many flavonoids reach the colon and undergo deglycosylation, ring cleavage, dehydroxylation, demethylation, and reduction by microbial consortia (Alqudah & Claesen, 2024; Kiriya, 2024; Stevens &

Maier, 2016; Zeng et al., 2026). The resulting phenolic products are further conjugated by the host. Human circulation therefore contains a time-varying mixture of parent-derived conjugates and microbial products, often at concentrations and time courses that differ from those of the ingested compound (Carregosa et al., 2022; Williamson, 2025). This early part of the model is supported as general flavonoid pharmacology.

The retained primary evidence also warns against assuming extensive conversion for every flavonoid matrix. Lessard-Lord and colleagues used faecal fermentations from 34 donors and a four-day cranberry intervention and found less than 1% conversion of the studied oligomeric and polymeric flavan-3-ols into measured microbial products, with no significant change in urinary microbial flavan-3-ol metabolites (Lessard-Lord, 2024). This compound- and matrix-specific result supports direct measurement rather than the presumption that a given flavonoid exposure necessarily generates abundant circulating microbial metabolites.

Interindividual variability in polyphenol metabolism is repeatedly documented in human evidence syntheses (Favari, 2024; Narduzzi, 2022; Perrone & D'Angelo, 2026). However, a metabotype is currently a descriptive pattern of metabolite production, not a validated predictor of an exercise response. No retained human study prospectively classified athletes by microbial flavonoid-metabolite profile and then tested recovery or adaptation.

Human exercise studies with flavonoid or polyphenol exposure

Only two retained primary human studies combined flavonoid or polyphenol exposure with a structured exercise or training context. In adolescent athletes, a 12-week high-polyphenol blend administered during high-intensity training altered immune biomarkers, multi-omics signatures, gut microbial features, short-chain fatty acids, and urinary conjugated polyphenol markers (Huang, 2026). The design is valuable because it integrates training and biological profiling. It does not, however, identify a microbial-derived flavonoid metabolite as a mediator, distinguish the contribution of four compounds, or establish a change in performance, recovery kinetics, or training adaptation.

In men with obesity, 12 weeks of fisetin supplementation, concurrent interval resistance–aerobic training, or their combination changed Maresin-1, inflammatory markers, and indices of glucose regulation (Alipour, 2026). This study provides direct human evidence that a flavonoid intervention can accompany biochemical changes during training. It does not include trained athletes, metabolite pharmacokinetics, microbiome assessment, objective recovery, or performance outcomes. It therefore cannot support a gut-mediated mechanism or an athlete-specific recommendation.

Evidence syntheses of flavonoid interventions report heterogeneous effects on exercise-induced muscle damage, immune and inflammatory biomarkers, and performance (Carey et al., 2021; Howatson & Clifford, 2026; Ruiz-Iglesias, 2021). These reviews are useful for context but do not replace the missing integrated primary design. The central conclusion from the retained primary evidence is therefore negative but informative: no human exercise study in the corpus measures the complete sequence from microbial flavonoid transformation to a defined circulating metabolite and a functional outcome.

Human exercise studies without flavonoid exposure

Two primary human studies inform the exercise-to-gut context but not flavonoid efficacy. In 30 resistance-trained adults, a randomised counterbalanced exercise–control study found increased gastrointestinal symptoms after resistance exercise and sex-related differences in permeability and epithelial-damage area-under-the-curve measures (Hart et al., 2022). In ten healthy men, a randomised crossover study of

consecutive high-activity days showed that energy balance modified intestinal and microbial responses to substantial physical demand (Suther et al., 2025).

These studies support the proposition that exercise context and energy status can modify the gastrointestinal environment. They do not show that such changes alter flavonoid biotransformation. Extrapolation should be further limited by small samples, sex restrictions in the energy-balance study, and the acute or short-duration nature of the protocols. Evidence from reviews of endurance exercise, heat stress, and athlete microbiota similarly indicates substantial dependence on modality, heat, hydration, training status, and diet (Alsinani et al., 2026; Costa, 2020; Dmytriv et al., 2024; Keirns et al., 2020; Pérez-Castillo, 2024; Ribeiro et al., 2021).

Animal and cellular evidence

Animal and cellular studies supply mechanistic hypotheses but cannot establish human exercise mediation. Red-clover isoflavones altered gut microbial composition and exercise-related measures in female mice, while resveratrol affected gut inflammation, barrier-related outcomes, microbial features, and fatigue in an intensive-exercise mouse model (Chen et al., 2021; Li et al., 2025). Diets enriched with cocoa and hesperidin modified mucosal immunity in trained and exhausted rats (Ruiz-Iglesias, 2025). These are among the closest preclinical approximations to the proposed model, yet none establishes that a quantified microbial flavonoid metabolite caused the functional response.

Other experiments isolate individual mechanisms. Quercetin influenced LPS-induced intestinal inflammation and barrier disruption in mice and cellular systems (Zhang, 2022). Baicalin modified muscle atrophy and DRP-1-related mitochondrial fission in aged mice, and icariin affected exercise-related metabolic responses and TFEB-dependent mitochondrial clearance in mice and C2C12 myotubes (Liu et al., 2026; Mo & Lee, 2025). A gut-derived ellagitannin metabolite, urolithin A, altered glucose uptake and myostatin expression in primary human myotubes, but the active 50- μ M condition does not establish that equivalent muscle exposure follows dietary intake (Wilhelmsen et al., 2025). Donor-specific mixtures of microbial flavanol metabolites also produced heterogeneous effects in a β -cell model, illustrating biological variability without demonstrating a muscle or exercise outcome (Krueger et al., 2023).

These experiments justify candidate targets, not practical recommendations. Their main translational limitations are high or uncertain tissue exposure, parent compounds rather than measured human metabolites, non-athletic disease or ageing models, and the absence of formal mediation.

A NARROWED FLAVONOID–GUT–MUSCLE MODEL

Core causal sequence and unique contribution

The revised model is intentionally limited to four core steps: flavonoid exposure $\rightarrow$ microbial transformation $\rightarrow$ systemic metabolite exposure $\rightarrow$ functional recovery or adaptation. The first two transitions are supported as general pharmacokinetic phenomena, although the extent of conversion is compound- and matrix-specific. The transition from systemic microbial metabolite exposure to a functional exercise outcome remains untested in humans.

The model's distinctive proposition is that variation at the microbial-transformation step may create variation in systemic exposure and thereby contribute to responder heterogeneity. It differs from prior reviews by treating this proposition as a mediator question with explicit measurement requirements, rather than describing the general health effects of flavonoids, the athlete microbiome, or the gut–muscle axis in parallel. Figure 2 shows this narrowed sequence and separates secondary hypotheses from the core claim.

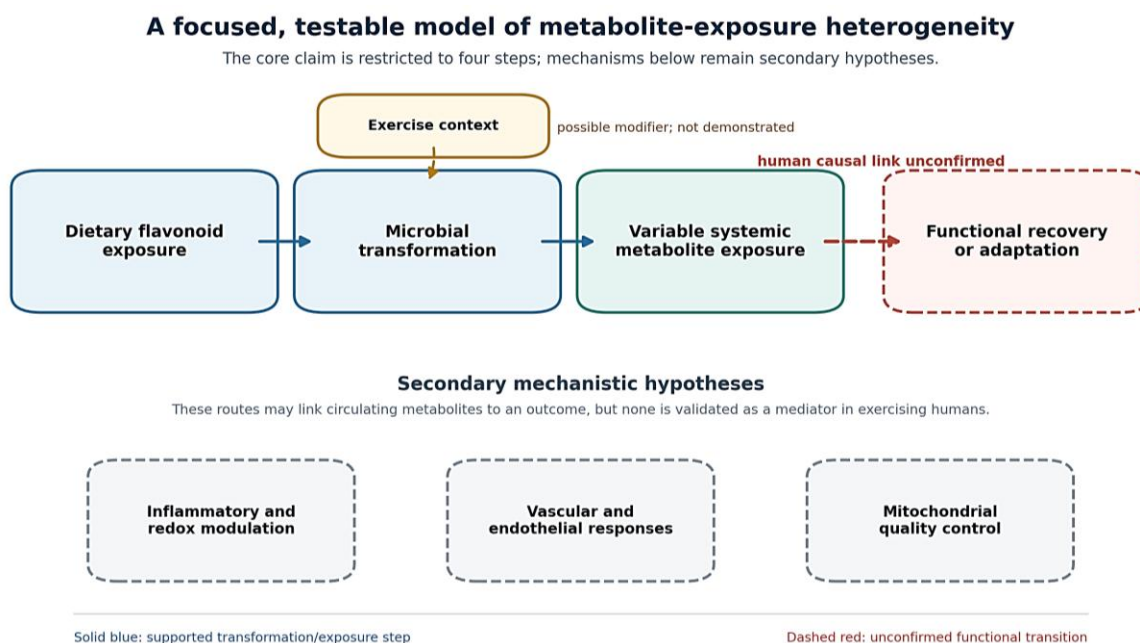


Figure 2. Narrowed flavonoid–gut–muscle model. Solid blue arrows denote supported early metabolic steps; the dashed red arrow denotes the unconfirmed transition from systemic microbial metabolite exposure to functional recovery or adaptation. The lower boxes are secondary mechanistic hypotheses rather than established components of one integrated pathway. Exercise may modify the gut environment, but an effect on flavonoid biotransformation has not been demonstrated.

Exercise as a potential modifier of biotransformation

Exercise may modify the luminal and absorptive environment through changes in splanchnic perfusion, transit, epithelial integrity, substrate availability, hydration, and energy balance (Costa, 2020; Dmytriv et al., 2024; Hart et al., 2022; Keirns et al., 2020; Suther et al., 2025). This is supported for selected gastrointestinal responses under defined conditions. Whether those changes alter the identity, amount, or timing of a microbial flavonoid metabolite is only suggestive because no retained human study compares the pharmacokinetics of the same flavonoid exposure at rest and after exercise.

The appropriate next test is therefore an exercise-by-exposure interaction study, not another cross-sectional comparison of microbial diversity. A standardised flavonoid challenge should be administered at rest and after a specified endurance, interval, or resistance session, with serial plasma and urine metabolomics, dietary control, functional microbial profiling, and appropriate washout. Taxonomic change without metabolite measurement cannot establish altered biotransformation.

Secondary mechanistic hypotheses

Three secondary routes have the clearest translational relevance. First, metabolite exposure could modulate excessive or unresolved inflammatory and redox signalling. Exercise-generated reactive species and inflammatory mediators also participate in adaptation, so the relevant hypothesis is context-sensitive modulation rather than maximal suppression (Liu & Jiao, 2025; Mănescu, 2026; Özdemir & Demir, 2025; Vrankova, 2026; Zhou et al., 2024). Second, selected metabolites could influence endothelial function and oxygen delivery; flavanol-related vascular effects are plausible but do not demonstrate microbial mediation (Al-Dashti, 2018). Third, metabolites could affect mitochondrial quality control, including biogenesis,

dynamics, and mitophagy (Anchimowicz et al., 2025; Carrillo-Garmendia et al., 2024; de Oliveira, 2025; Kumar, 2024; Lin, 2024; Liu, 2025; Ritenis et al., 2025; Sahariah, 2026; Victoria-Montesinos et al., 2026).

These routes are secondary because the human evidence does not establish target-tissue exposure or mediation. Barrier function and immune signalling can shape systemic responses, but Zonulin assays alone are not adequate evidence of permeability and should not be used as a surrogate for a gut-to-muscle mechanism (Arumugam, 2025; Markovich, 2024; Massier, 2021; Tripathi, 2009). Myokines and broader microbial products may also contribute to systemic communication (Chang, 2024; Hoseini, 2026; Kim et al., 2024; Rekha et al., 2024; Saponaro, 2024), but they do not specifically establish a flavonoid-derived signal. Table 3 summarises the evidence status of each retained link.

Table 3. Evidence status of the narrowed causal sequence.

Narrowed link	Direct evidence	Current status	Permitted inference
Ingested flavonoid → microbial transformation	Human non-exercise and microbial chemistry evidence (Alqudah & Claesen, 2024; Carregosa et al., 2022; Lessard-Lord, 2024; Stevens & Maier, 2016)	Supported, compound- and matrix-specific	Transformation occurs, but its magnitude cannot be assumed from dose alone.
Microbial transformation → variable systemic exposure	Human metabolism and variability evidence (Favari, 2024; Lessard-Lord, 2024; Narduzzi, 2022; Perrone & D'Angelo, 2026; Williamson, 2025)	Supported for heterogeneity; predictive value untested	Individuals can differ in exposure, but athlete responder status is not validated.
Exercise state → altered flavonoid biotransformation	Exercise–gut studies without flavonoid exposure (Dmytriv et al., 2024; Hart, 2022; Suther, 2025)	Suggestive	Exercise can change the gut environment; an effect on flavonoid pharmacokinetics is unproven.
Systemic microbial metabolite → muscle-relevant target	Cellular and preclinical evidence (Krueger, 2023; Liu et al., 2026; Mo & Lee, 2025; Wilhelmsen, 2025; Zhang, 2022)	Proposed	Candidate targets exist, but physiological muscle exposure and in vivo target engagement are uncertain.
Metabolite-mediated target engagement → recovery/adaptation	No integrated human study; indirect exercise literature (Alipour, 2026; Carey et al., 2021; Howatson & Clifford, 2026; Huang, 2026; Ruiz-Iglesias, 2021)	Unconfirmed	No causal or practical claim is justified.

EXERCISE-RELEVANT OUTCOMES

Recovery and performance

Functional recovery should be defined by outcomes such as restoration of maximal force, rate of force development, repeated-bout capacity, soreness accompanied by objective function, illness-related training availability, or subsequent performance. Biomarker changes alone are insufficient. Reviews and meta-analyses suggest that selected flavonoid-containing interventions can influence recovery from exercise-induced muscle damage, but effects vary with product, dose, exercise model, training status, and sampling time (Carey et al., 2021; Howatson & Clifford, 2026; Ruiz-Iglesias, 2021). The retained primary human studies do not establish microbial mediation of these effects.

The practical interpretation must therefore be narrow. The current corpus does not support a claim that microbiome testing can identify a flavonoid responder, that a specific flavonoid should be prescribed to improve recovery, or that greater antioxidant exposure necessarily improves adaptation. Any use of a flavonoid-rich food or supplement should be interpreted as a product-specific intervention supported, if at all, by direct evidence for that product and outcome—not as validation of the proposed axis.

Longitudinal adaptation

Training adaptation requires repeated exposure and longitudinal endpoints such as change in strength, fatigue resistance, performance, mitochondrial function, or training tolerance. Acute changes in inflammatory markers, microbial diversity, or metabolite abundance cannot substitute for these outcomes. The evidence

relating flavonoids to mitochondrial dynamics is predominantly preclinical, and the evidence relating exercise to mitochondrial remodelling does not show that microbial flavonoid metabolites mediate the response (Liu et al., 2026; Mo & Lee, 2025; Ritenis et al., 2025; Wilhelmsen et al., 2025).

Accordingly, the model should not be described as an emerging nutritional paradigm. It is a falsifiable research framework. A decisive study would need to show that a flavonoid intervention changes a defined microbial metabolite, that the metabolite reaches the circulation and plausibly the target tissue, that the change precedes a functional adaptation, and that mediation analysis or an experimentally justified perturbation supports the proposed route.

Consequences of study quality for inference

The formal appraisal prevents high confidence even where a study reports positive findings. Stronger internal validity in a placebo-controlled trial cannot overcome a mismatch between measured and required outcomes. The adolescent-athlete trial supports biological responsiveness during training but not functional recovery or metabolite mediation (Huang, 2026). The fisetin trial supports biochemical change in a clinical population but not athlete performance or gut involvement (Alipour, 2026). The crossover exercise studies support context-dependent gastrointestinal responses but contain no flavonoid exposure (Hart et al., 2022; Suther et al., 2025). The non-exercise metabolism study supports compound-specific microbial conversion but not exercise translation (Lessard-Lord, 2024).

The conclusion is therefore determined by the missing intersection of otherwise informative studies. Evidence is not upgraded merely because separate links are individually plausible. This approach reduces the risk of assembling a causal narrative from studies that tested different populations, exposures, mediators, and outcomes.

PRACTICAL IMPLICATIONS AND RESEARCH BOUNDARIES

What can be stated now

Direct human exercise evidence in the retained corpus supports only cautious, product- and outcome-specific statements. A multi-polyphenol intervention can alter immune and multi-omics markers during intensive training, and fisetin combined with training can alter inflammatory and metabolic markers in men with obesity (Alipour, 2026; Huang, 2026). Neither finding establishes a microbial mechanism or a functional benefit. General sports-nutrition priorities—adequate energy and macronutrient intake, hydration, sleep, and appropriate training progression—remain primary (Gonzalez, 2026; Pérez-Castillo, 2024).

This review therefore makes no compound-specific dose or timing recommendation. It also does not recommend commercial microbiome testing, stool-based responder classification, or supplementation based on a presumed metabolotype. These positions follow directly from the absence of validated human mediation and prediction studies.

What remains exclusively a research agenda

Metabolotype-guided prescribing would require a reproducible challenge test, serial plasma and urine metabolomics, functional microbial profiling, stable within-person classification, and prospective evidence that the classification predicts a meaningful exercise outcome better than conventional information such as diet, training status, sleep, and baseline performance. A single stool sample or taxonomic diversity measure is insufficient (Favari, 2024; Narduzzi, 2022; Perrone & D'Angelo, 2026).

The proposed precision application becomes credible only if phenotype-guided care outperforms a conventional evidence-based approach in an independently replicated trial. Until then, precision flavonoid nutrition should describe a research objective rather than a service or clinical practice.

PRIORITISED RESEARCH QUESTIONS

Which microbial metabolites reach relevant systemic and tissue exposures?

Studies should identify metabolite appearance, peak concentration, persistence, conjugation state, and between- and within-person variability after a standardised food or supplement challenge (Carregosa et al., 2022; Favari, 2024; Kiriyaama, 2024; Lessard-Lord, 2024). Candidate compounds should then be tested at those measured concentrations in relevant human tissues or models. This order prevents mechanistic emphasis on parent compounds or concentrations that are not achieved in vivo.

Does exercise modify flavonoid biotransformation?

Randomised crossover studies should compare an identical flavonoid exposure at rest and after a clearly specified exercise condition. Diet, energy availability, hydration, heat, transit, and recent training should be controlled. Serial metabolomics should be paired with functional microbial measures. A reproducible exercise-by-exposure interaction is required before exercise can be described as a modifier of flavonoid metabolotype.

Do metabolite responses predict recovery or adaptation?

Prospective training studies should test whether early metabolite exposure predicts force recovery, fatigue resistance, illness-related training availability, training tolerance, mitochondrial function, or performance change. Repeated baselines are needed to distinguish stable response heterogeneity from measurement noise. Mediation analysis should be prespecified and should include the complete sequence from intake to microbial function, circulating metabolite, candidate target, and functional outcome.

Can a metabolite-guided strategy improve decisions?

Only after predictive validity is established should trials compare a metabolite-guided intervention with a conventional strategy. Such trials should prespecify the decision rule, clinically meaningful outcome, safety monitoring, and independent validation. Failure to outperform standard practice would falsify the practical value of the precision model even if metabolite variability remains biologically interesting.

LIMITATIONS OF THE REVIEW

This review has several limitations. First, selection and appraisal were performed by one reviewer, creating a risk of missed studies and subjective classification. The complete search syntax, selection counts, exclusion log, and study-to-link map are supplied to make this limitation visible and the decisions auditable. Second, the review corpus was reconstructed from the 110 unique records assembled for the original submission; raw pre-deduplication database exports were unavailable. Third, the retained literature is dominated by secondary and mechanistic sources because few primary human studies test the central question. Secondary sources were therefore restricted to context, while causal claims were anchored to the primary-study table.

Fourth, the MMAT appraisal addresses methodological features but does not correct indirectness. A well-conducted study can remain irrelevant to microbial mediation if it lacks metabolite, microbiome, or functional exercise measurements. Fifth, the heterogeneity of compounds, matrices, doses, populations, and outcomes precluded quantitative pooling. Finally, absence of an integrated study in this corpus should be interpreted as an evidence gap, not proof that microbial mediation is biologically impossible.

CONCLUSION

Human evidence supports extensive host and microbial transformation of dietary flavonoids and substantial interindividual variation in metabolite exposure. Controlled exercise studies also show that gastrointestinal physiology and microbial responses can vary with exercise mode and energy status. These observations justify studying their intersection, but they do not establish a causal flavonoid–gut–muscle axis.

The review's unique and testable proposition is that microbial metabolite exposure may explain part of the interindividual variation in exercise recovery or adaptation. Evidence is strongest for the early steps—transformation and variable exposure—and weakest for the transition to muscle-specific and functional outcomes. No retained human study measures the complete sequence or demonstrates mediation.

Current evidence therefore does not support metatype-based prescribing or a specific practical flavonoid strategy for athletes. The most informative next studies are those that identify physiologically relevant metabolites, determine whether exercise changes their production, and test whether the resulting exposure prospectively predicts or mediates a functional outcome. Until that evidence exists, the flavonoid–gut–muscle axis should remain a focused conceptual model and research agenda.

AUTHOR CONTRIBUTIONS

All authors meet the criteria for authorship in accordance with established ethical guidelines. Contributions are specified according to the CRediT (Contributor Roles Taxonomy) as follows:

Conceptualisation: Parham Jalali, Aida Mohammadi, Goran Sporiš, Hadi Nobari. Methodology: Parham Jalali, Aida Mohammadi, Mohammad Ali Izadi, Javad Mehrabani. Formal analysis: Not applicable in this review article; no new formal statistical analysis or meta-analysis was performed. Investigation: Parham Jalali, Aida Mohammadi, Mohammad Ali Izadi, Sara Miyahi, Pawel Chmura, Javad Mehrabani. Data curation: Parham Jalali, Aida Mohammadi, Mohammad Ali Izadi, Sara Miyahi. Writing – original draft: Parham Jalali, Aida Mohammadi. Writing – review & editing: Parham Jalali, Aida Mohammadi, Mohammad Ali Izadi, Sara Miyahi, Pawel Chmura, Javad Mehrabani, Walaa Juma Alkasasbeh, Arunas Emeljanovas, Goran Sporiš, Hadi Nobari. Supervision: Goran Sporiš, Hadi Nobari.

Equal contribution statement: Parham Jalali and Aida Mohammadi contributed equally to this work and share first authorship.

All authors have critically reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

AI USE DISCLOSURE

In accordance with current publishing ethics and transparency recommendations, artificial intelligence (AI) tools were used solely to assist with translation and language editing, with the aim of improving clarity and readability. No AI tools were used in the generation of scientific content, including the study design, data collection, analysis, interpretation of results, or the formulation of conclusions. The authors retain full responsibility for the content of the manuscript and confirm its originality, integrity, and accuracy.

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SUPPLEMENTARY MATERIAL

Supplementary Table S1. Complete database-specific search strings.

Database / search	Complete string
PubMed/MEDLINE – core	((flavonoid[Title/Abstract] OR polyphenol[Title/Abstract] OR anthocyanin[Title/Abstract] OR flavan-3-ol[Title/Abstract] OR quercetin[Title/Abstract] OR hesperidin[Title/Abstract] OR catechin[Title/Abstract] OR fisetin[Title/Abstract] OR resveratrol[Title/Abstract]) AND ("Gastrointestinal Microbiome"[Mesh] OR microbiot*[Title/Abstract] OR microbiome[Title/Abstract] OR "microbial metabolite"[Title/Abstract] OR "phenolic metabolite"[Title/Abstract] OR metabotype[Title/Abstract]) AND ("Exercise"[Mesh] OR exercise*[Title/Abstract] OR athlete[Title/Abstract] OR "Skeletal Muscle"[Mesh] OR "skeletal muscle"[Title/Abstract] OR recover*[Title/Abstract] OR performance[Title/Abstract] OR fatigue[Title/Abstract] OR "training adaptation"[Title/Abstract]))
PubMed/MEDLINE – targeted mechanisms	((flavonoid[Title/Abstract] OR polyphenol[Title/Abstract] OR quercetin[Title/Abstract] OR hesperidin[Title/Abstract] OR catechin[Title/Abstract] OR fisetin[Title/Abstract] OR resveratrol[Title/Abstract]) AND (exercis*[Title/Abstract] OR athlete[Title/Abstract] OR "skeletal muscle"[Title/Abstract] AND ("intestinal permeability"[Title/Abstract] OR inflamm*[Title/Abstract] OR redox[Title/Abstract] OR endothelial[Title/Abstract] OR vascular[Title/Abstract] OR mitochondri*[Title/Abstract] OR mitophagy[Title/Abstract] OR "metabolic flexibility"[Title/Abstract] OR recover*[Title/Abstract] OR fatigue[Title/Abstract]))
Scopus – core	TITLE-ABS-KEY((flavonoid OR polyphenol OR anthocyanin OR flavan-3-ol OR quercetin OR hesperidin OR catechin OR fisetin OR resveratrol) AND (microbiot* OR microbiome OR "microbial metabolite" OR "phenolic metabolite" OR metabotype) AND (exercis* OR athlete OR "skeletal muscle" OR recover* OR performance OR fatigue OR "training adaptation"))
Scopus – targeted mechanisms	TITLE-ABS-KEY((flavonoid OR polyphenol OR quercetin OR hesperidin OR catechin OR fisetin OR resveratrol) AND (exercis* OR athlete OR "skeletal muscle") AND ("intestinal permeability" OR inflamm* OR redox OR endothelial OR vascular OR mitochondri* OR mitophagy OR "metabolic flexibility" OR recover* OR fatigue))
Web of Science Core Collection – core	TS=((flavonoid OR polyphenol OR anthocyanin OR flavan-3-ol OR quercetin OR hesperidin OR catechin OR fisetin OR resveratrol) AND (microbiot* OR microbiome OR "microbial metabolite" OR "phenolic metabolite" OR metabotype) AND (exercis* OR athlete OR "skeletal muscle" OR recover* OR performance OR fatigue OR "training adaptation"))
Web of Science Core Collection – targeted mechanisms	TS=((flavonoid OR polyphenol OR quercetin OR hesperidin OR catechin OR fisetin OR resveratrol) AND (exercis* OR athlete OR "skeletal muscle") AND ("intestinal permeability" OR inflamm* OR redox OR endothelial OR vascular OR mitochondri* OR mitophagy OR "metabolic flexibility" OR recover* OR fatigue))

Supplementary Table S2. Full-text exclusions from the original review corpus.

Corpus record	Bibliographic record	Reason for full-text exclusion
6	Chaachouay, N. (2025). Synergy, additive effects, and antagonism of drugs with plant bioactive compounds. <i>Drugs and Drug Candidates</i> , 4(1), 4. https://doi.org/10.3390/ddc4010004	General pharmacological discussion without a specific exercise or microbial-metabolite link.
7	Vergara Nieto, Á. A., et al. (2025). Molecular mechanisms, physiological effects, gut microbiota interplay and nutritional strategies of anthocyanins as modulators of muscle protein synthesis: A narrative review. <i>Current Nutrition Reports</i> , 14(1), 105.	Redundant secondary evidence; no unique primary evidence for the narrowed model.
8	Chakraborty, P., et al. (2024). Flavonoids and their metabolites: Impact on gut microbiota in connection with chronic metabolic diseases. <i>Role of Flavonoids in Chronic Metabolic Diseases: From Bench to Clinic</i> , 347–374.	Redundant disease-focused secondary evidence; no unique exercise contribution.
10	Ling, Y., et al. (2024). CLDN5: From structure and regulation to roles in tumors and other diseases beyond CNS disorders. <i>Pharmacological Research</i> , 200, 107075. https://doi.org/10.1016/j.phrs.2024.107075	Disease-specific molecular topic outside the narrowed causal sequence.
12	Shi, C., et al. (2024). Lipocalin 2 (LCN2) confers acquired resistance to almonertinib in NSCLC through LCN2-MMP-9 signaling pathway. <i>Pharmacological Research</i> , 201, 107088. https://doi.org/10.1016/j.phrs.2024.107088	Cancer drug-resistance mechanism unrelated to flavonoid metabolism or exercise.
14	Ceballos Rodriguez-Conde, F., Zhu, S., & Dikicioglu, D. (2025). Harnessing microbial division of labor for biomanufacturing: A review of laboratory and formal modeling approaches. <i>Critical Reviews in Biotechnology</i> , 45(6), 1249–1267.	Microbial biomanufacturing topic without a relevant host or exercise link.
15	Sá-Pessoa, J., Calderón-González, R., Lee, A., & Bengoechea, J. A. (2025). Klebsiella pneumoniae emerging anti-immunology paradigms: From stealth to evasion. <i>Trends in Microbiology</i> , 33(5), 533–545. https://doi.org/10.1016/j.tim.2025.01.003	Pathogen immune-evasion topic outside the review question.
16	Ysrafil, Y., et al. (2025). Flavonoids and their advancement in pharmaceutical sciences. <i>Plant Secondary Metabolites</i> , 310–340.	General pharmaceutical book chapter without a direct model link.
19	Wang, T., et al. (2024). Derlin-1 promotes diet-induced non-alcoholic fatty liver disease via increasing RIPK3-mediated necroptosis. <i>Free Radical Biology and Medicine</i> , 217, 29–47. https://doi.org/10.1016/j.freeradbiomed.2024.03.014	Liver-disease necroptosis mechanism outside the review question.
20	Liu, X., et al. (2025). Substituent group-modified pectins: Targeted modifications for enhanced functional properties. <i>Trends in Food Science & Technology</i> , 157, 104920. https://doi.org/10.1016/j.tifs.2025.104920	Pectin modification study unrelated to the flavonoid–gut–muscle sequence.
21	Hou, Q., et al. (2024). Autophagic degradation of DHCR7 activates AKT3 and promotes sevoflurane-induced hippocampal neuroinflammation in neonatal mice. <i>Free Radical Biology and Medicine</i> , 222, 304–316. https://doi.org/10.1016/j.freeradbiomed.2024.06.012	Anaesthetic neuroinflammation mechanism outside the review question.
22	Annunziata, G., et al. (2025). Antioxidants and exercise performance: Focus on Mediterranean diet. <i>Antioxidants</i> , 15(1), 10.	Broad secondary discussion superseded by closer exercise-flavonoid sources.

23	Jung, D. H., et al. (2024). Tailored meal-type food provision for diabetes patients can improve routine blood glucose management in patients with type 2 diabetes: A crossover study. <i>Nutrients</i> , 16(8), 1190. https://doi.org/10.3390/nu16081190	Diabetes meal-provision study without flavonoid, microbiome or exercise mediation.
26	Bas, T. G. (2026). Dietary polyphenols (flavonoids) derived from plants for use in therapeutic health: Antioxidant performance, ROS, molecular mechanisms, and bioavailability limitations. <i>International Journal of Molecular Sciences</i> , 27(3), 1404.	General therapeutic flavonoid discussion without a direct model link.
28	Pais, M. L., Castelo-Branco, M., & Gonçalves, J. (2025). Brain-related sexual dimorphism in tuberous sclerosis complex: An overlooked matter. <i>Trends in Molecular Medicine</i> , 31(10), 882–884. https://doi.org/10.1016/j.molmed.2025.01.002	Neurological sexual-dimorphism topic outside the review question.
29	Min, Y., & O'Neill, L. A. J. (2024). Itaconate boosts malaria via induction of PD-L1. <i>Cell Metabolism</i> , 36(3), 457–458. https://doi.org/10.1016/j.cmet.2024.02.005	Malaria immune-metabolism topic outside the review question.
30	Nazzaro, F., et al. (2025). Polyphenols bioactive metabolites, and their anti-biofilm and neuroprotective potential. <i>Foods</i> , 14(22), 3976.	Antibiofilm and neuroprotection topic outside the review question.
33	Tran, N., & Mills, E. L. (2024). Redox regulation of macrophages. <i>Redox Biology</i> , 72, 103123.	Macrophage redox review without a specific flavonoid or exercise link.
34	Sun, L.-w., Geng, Q., & Zheng, G.-h. (2024). Research progress in signaling of gut microbiota-gut-brain-muscle axis.	Redundant broad gut-brain-muscle review without unique direct evidence.
43	Kalkan, H. (2026). Gut microbiota and skeletal muscle interaction: The role of short-chain fatty acids, G-protein receptor signaling and metabolic adaptation. <i>Skeletal Muscle Biology and Therapeutics</i> .	Redundant secondary/book source on short-chain-fatty-acid signalling.
44	Almutawif, Y. A., & Eid, H. M. (2026). Microbiome-metabolite signaling networks in gastrointestinal disease: Systems biology, network rewiring, and precision therapeutics. <i>Archives of Microbiology</i> , 208(10), 483.	Gastrointestinal disease network review outside the athlete-focused question.
45	Li, Y., Gasaly, N., & Vos, P. d. (2026). Experimental models for intestinal host-microbe interactions. <i>EMBO Molecular Medicine</i> , 1–14.	Experimental-model review without a direct flavonoid or exercise result.
51	Shi, Z., et al. (2025). Evaluation of the protective role of resveratrol on LPS-induced septic intestinal barrier function via TLR4/MyD88/NF- κ B signaling pathways. <i>Scientific Reports</i> , 15(1), 828.	Sepsis barrier model without exercise or microbial flavonoid mediation.
52	Yang, S., Liu, H., & Liu, Y. (2025). Advances in intestinal epithelium and gut microbiota interaction. <i>Frontiers in Microbiology</i> , 16, 1499202.	General intestinal epithelium review superseded by closer barrier sources.
70	Cheatham, C. L., et al. (2022). Enhancing the cognitive effects of flavonoids with physical activity: Is there a case for the gut microbiome? <i>Frontiers in Neuroscience</i> , 16, 833202.	Cognitive-flavonoid hypothesis outside the skeletal-muscle outcome focus.
71	Liu, X., et al. (2025). (Poly)phenol-gut microbiota interactions and their impact on human health. <i>Current Opinion in Clinical Nutrition & Metabolic Care</i> , 28(4), 316–322.	Broad health review redundant with closer polyphenol-microbiota sources.
82	Valdenassi, L., & Chirumbolo, S. (2025). Phytochemicals as chemical promoters of the adaptive chaos in health recovery: A modelling investigation. <i>Chemistry & Biodiversity</i> , 22(8), e202500078.	Theoretical phytochemical modelling without direct empirical evidence.
85	Shivani, D., et al. (2026). Redox reprogramming of the diseased liver by dietary flavonoids: From molecular signalling to gut-liver crosstalk. <i>Biology</i> , 15(8), 625.	Gut-liver disease review outside the narrowed model.
88	Fu, J., et al. (2026). Organ-specific regulation of systemic aging: Focus on the brain, skeletal muscle, and gut. <i>Cells</i> , 15(2), 153.	Broad organ-ageing review without a direct flavonoid exercise link.
90	Ritenis, E. (2026). Exercise and nutrition stimuli for the augmentation of mitochondrial quality control in skeletal muscle. <i>Swinburne</i> .	Thesis-level secondary source superseded by peer-reviewed evidence.
96	Jun, L., et al. (2024). Mitochondrial adaptation in skeletal muscle: Impact of obesity, caloric restriction, and dietary compounds. <i>Current Nutrition Reports</i> , 13(3), 500–515.	Broad secondary review superseded by exercise-specific mitochondrial sources.
97	Delgadillo-Puga, C., et al. (2026). Purple sweet potato (<i>Ipomoea batatas</i> L. Lam) leaves extract prevents weight gain and lipotoxicity in mice fed a high-fat diet by increasing metabolic flexibility and oxidative metabolism in skeletal muscle and brown adipose tissue. <i>Nutrition & Metabolism</i> .	Mouse obesity study without microbial mediation or exercise adaptation.
100	Liu, W., et al. (2025). Polyphenols and exercise in autophagy regulation: Potential benefits for cancer management and healthspan. <i>Frontiers in Nutrition</i> , 12, 1618813.	Cancer and health span autophagy review outside the athlete-focused question.
101	Bi, M., & Lin, S. Integrating polyphenols and exercise in cancer prevention, treatment, and rehabilitation: Cellular and molecular mechanisms linking the injury-recovery-musculoskeletal resilience axis. <i>Frontiers in Oncology</i> , 16, 1801640.	Cancer prevention/rehabilitation review outside the narrowed question.
107	Netto, D. P., et al. Major relationships among polyphenols, gut microbiota and sports performance: A systematic review.	Incomplete bibliographic record; direct contribution could not be verified reliably.

Supplementary Table S3. Studies directly informing each link in the narrowed model.

Model link	Primary studies directly informing the link	Context-only sources	Residual gap
Flavonoid exposure → microbial transformation	Lessard-Lord et al.	Bioavailability and microbial-chemistry literature	Matrix-specific conversion and tissue exposure remain incompletely measured.
Interindividual metabolite variation	Krueger et al.; Lessard-Lord et al.	Metabotype and variability literature	No prospective athlete classification or response threshold.
Reciprocal flavonoid–microbiome interaction	Chen et al.; Huang et al.	Mechanistic and narrative context	Taxonomic change is not equivalent to metabolite mediation.
Exercise → gastrointestinal or microbial environment	Hart et al.; Suther et al.	Exercise-gut context	No rest-versus-exercise flavonoid pharmacokinetic comparison.
Barrier and immune route	Zhang et al.; Ruiz-Iglesias et al.; Li et al.; Huang et al.	Signalling and measurement context	No defined microbial flavonoid metabolite shown to mediate a human exercise outcome.
Vascular, redox and mitochondrial routes	Mo and Lee; Liu et al.; Wilhelmsen et al.	Exercise and mechanistic context	Human muscle exposure, target engagement and adaptation are unverified.
Flavonoid exposure → functional exercise outcome	Chen et al. and Li et al. in animals; no integrated human study	Human intervention and synthesis context	No microbial mediation of recovery, performance or adaptation in humans.



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