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Beyond Antioxidant Supplementation: Oil Palm Phenolics, the Gut Microbiome, and the Emerging Path toward Precision Nutrition and Metabolic Health

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ABSTRACT

Oil palm phenolics (OPP) are water-soluble bioactive compounds recovered from aqueous streams generated during oil palm fruit processing. Unlike the lipid-soluble constituents conventionally associated with palm oil, OPP contains phenolic acids and related compounds that have attracted increasing biomedical attention. Recent human trials indicate short-term tolerability and suggest effects on antioxidant status, inflammatory biomarkers, and blood pressure. However, the pathways explaining these responses remain incompletely understood. This qualitative literature review critically examines OPP through the emerging polyphenol–gut microbiome–metabolite framework. Evidence concerning OPP composition, gastrointestinal bioavailability, microbial biotransformation, intestinal barrier regulation, short-chain fatty acids, bile-acid metabolism, metabolic endotoxemia, endothelial signaling, microbial metabotypes, and precision nutrition is synthesized. Particular emphasis is placed on protocatechuic acid and p-hydroxybenzoic acid as mechanistically informative phenolic compounds. The review proposes that future OPP research should move beyond conventional antioxidant endpoints toward chemically standardized interventions combined with metagenomics, metabolomics, foodomics, vascular and inflammatory phenotyping, and responder-stratified analysis. Such an approach could clarify whether microbial transformation explains interindividual variability in OPP responses. OPP therefore represents a potentially distinctive convergence of palm-processing valorization, functional-food development, microbiome science, and preventive nutrition, although current evidence remains insufficient for therapeutic claims.

Keywords: Oil palm phenolics; Gut microbiome; Polyphenols; Precision nutrition; Microbial metabolites; Protocatechuic acid; Metabolic inflammation; Cardiometabolic health; Functional foods; Circular bioeconomy

JEL Classification Codes: I12; I18; Q16; Q53; Q56

INTRODUCTION

Oil palm (Elaeis guineensis) is among the world's most economically important perennial crops, yet discussions of palm-derived compounds and human health have traditionally concentrated on the lipid fraction of the fruit. Palm oil contains fatty acids as well as minor lipid-soluble constituents such as tocopherols, tocotrienols,

carotenoids, phytosterols, squalene, and coenzyme Q-related compounds. This conventional lipid-centered perspective, however, captures only part of the chemical diversity of oil palm fruit. During sterilization, pressing, clarification, and other milling operations, a substantial portion of water-soluble phytochemicals is transferred to aqueous streams rather than retained in the commercially recovered oil. Among these compounds are phenolic acids and related molecules collectively described in the literature as oil palm phenolics (OPP) or water-soluble palm fruit extract.[1–3]

The distinction between OPP and conventional palm oil is scientifically important. OPP is not a dietary fat, nor is it equivalent to palm tocotrienol-rich fraction or red palm oil. It represents a hydrophilic bioactive fraction recovered primarily from palm-fruit vegetation liquor and related aqueous processing streams. Characterized constituents include caffeoylshikimic acid isomers, protocatechuic acid (PCA), p-hydroxybenzoic acid (p-HBA), hydroxytyrosol-related compounds, and other phenolic substances whose relative abundance depends on fruit biology, milling conditions, recovery processes, concentration technology, and formulation.[1,2] Consequently, the health effects of OPP cannot be inferred directly from research on palm oil fatty acids or other lipid-soluble palm-derived compounds.

Interest in OPP has increased because the evidence base has begun to move from experimental models toward controlled human research. A randomized, double-blind, placebo-controlled phase I study published in 2022 provided evidence that tested preparations of OPP were tolerated in healthy volunteers, thereby supplying an essential translational foundation for later efficacy-oriented work.[4] A randomized double-blind placebo-controlled study published in 2025 subsequently reported improved plasma antioxidant capacity and reduced TNF-α among individuals with minor hyperlipidaemia after OPP supplementation, while another 2025 clinical study involving 97 healthy adults reported blood-pressure and antioxidant effects at selected OPP doses.[5,6] These human findings remain preliminary, but they shift the scientific question from whether OPP has measurable biological activity toward the more difficult question of how those effects arise.

The answer may require moving beyond the traditional concept of dietary polyphenols as direct antioxidants. The antioxidant paradigm has historically provided an intuitively attractive explanation for the health effects of phenolic-rich foods and extracts: plant phenolics neutralize reactive oxygen species, thereby reducing oxidative damage. Contemporary pharmacokinetic, microbiological, and metabolomic evidence indicates that this model is incomplete. Many dietary phenolic compounds are poorly or incompletely absorbed as parent molecules in the small intestine. A substantial fraction enters the colon and becomes substrate for bacterial deconjugation, dehydroxylation, reduction, decarboxylation, ring cleavage, and other reactions that generate lower-molecular-weight compounds with different absorption, distribution, and signaling characteristics.[7–10] Recent cardiometabolic synthesis similarly argues that the in vivo actions of dietary polyphenols are better explained by bioavailability, signaling, and microbiota-derived metabolites than by direct antioxidant capacity alone.[11]

The gut microbiome is therefore not merely exposed to phenolics; it participates actively in determining their effective biological dose. Microorganisms can produce phenolic acids, valerolactones, urolithins, enterolignans, equol, and other metabolites whose systemic concentrations often vary dramatically among people despite

similar dietary exposure. Conversely, phenolic compounds may alter the ecological and metabolic properties of the intestinal microbiota through selective antimicrobial effects, microbial substrate utilization, modulation of ecological niches, and changes in microbial gene expression.[12–14] Polyphenols should therefore increasingly be considered components of a bidirectional food–microbiome interaction rather than chemically static antioxidants. A recent Nature Reviews Microbiology synthesis further emphasizes that dietary effects on the microbiome depend on the wider dietary pattern, geography, and host context, strengthening the case for interpreting OPP within the whole diet–microbiome system rather than as an isolated supplement exposure.[15]

This change in perspective is highly relevant to OPP. Existing human OPP studies have primarily measured conventional physiological endpoints including safety markers, antioxidant systems, inflammatory biomarkers, lipid profiles, and blood pressure. They have not yet systematically investigated microbiome composition, microbial functional genes, microbiota-derived phenolic metabolites, short-chain fatty acids (SCFAs), bile-acid transformation, microbial aromatic metabolites, or integrated host–microbial metabolomics.[4–6] Consequently, the OPP literature currently contains an important mechanistic gap: measurable systemic responses have been observed, but the potential contribution of the microbiome remains largely untested.

The gap is especially significant because metabolic and inflammatory disorders increasingly are understood as multisystem conditions involving interactions among diet, microbial ecology, intestinal permeability, inflammation, adipose tissue, liver metabolism, vascular biology, and host genetics. Gut microbial products such as SCFAs and modified bile acids can participate in metabolic regulation, while microbiota-derived compounds associated with endotoxemia or trimethylamine metabolism have been linked with cardiometabolic outcomes.[16–19] This does not imply that OPP necessarily changes each of these pathways, but it provides a strong scientific rationale for measuring them.

A further problem is interindividual variability. Individuals consuming an identical quantity of a phenolic compound can produce substantially different metabolite profiles because of differences in microbial composition and function, genetics, age, body composition, habitual diet, health status, medication use, geographic context, and other determinants. A systematic review of human studies demonstrated that gut microbiota contributes substantially to variability in polyphenol metabolism, producing patterns ranging from continuous high- versus low-excretor phenotypes to more discrete producer and non-producer metabotypes.[20] Such variability provides a conceptual bridge between microbiome research and precision nutrition.[21–23]

Against this background, this review addresses two primary questions. First, how could interactions between OPP, intestinal microorganisms, and microbial metabolites plausibly contribute to metabolic, inflammatory, antioxidant, and vascular outcomes? Second, what methodological and translational gaps must be addressed before OPP can be positioned responsibly within precision nutrition or preventive public health? The review does not assume that microbiome mediation of OPP effects has already been demonstrated. Instead, it develops a testable translational framework integrating direct OPP evidence with contemporary knowledge of polyphenol metabolism and microbiome-dependent phenotypes.

CONCEPTUAL AND THEORETICAL FOUNDATIONS

OPP as a chemically distinct bioactive resource

OPP should first be understood as a chemically heterogeneous mixture rather than as a single active molecule. Its composition reflects biological and technological determinants beginning with fruit genotype and maturity and continuing through sterilization, extraction, concentration, drying, encapsulation, and storage. Total phenolic content is useful as an aggregate indicator, but it is insufficient to guarantee that two OPP preparations contain equivalent proportions of biologically relevant constituents.[2,3]

This issue is increasingly recognized across functional-food research. Clinical trials may describe an intervention according to nominal milligrams of "polyphenols" while using relatively limited chemical characterization of the food or extract being administered. However, different varieties, agricultural conditions, post-harvest handling, processing temperatures, extraction methods, and matrices can alter both the concentration and chemical form of individual phenolics. Keohane et al.[24] observed that sophisticated omics analyses are increasingly used for participant biological samples while untargeted compositional analysis of the intervention food itself remains comparatively rare. For OPP, this imbalance is particularly problematic because its very identity depends on recovery and concentration from a processing stream.

PCA deserves special attention within OPP research because it occupies an unusual position at the boundary between plant chemistry and microbial metabolism. PCA can be ingested as a naturally occurring phenolic acid, but it may also be formed during microbial degradation of anthocyanins and other phenolic structures. As a result, circulating PCA or PCA-related conjugates after an OPP intervention could theoretically originate from direct absorption, microbial transformation of OPP constituents, metabolism of the background diet, or a combination of these processes. Understanding its provenance therefore requires controlled dietary assessment and isotopic or detailed metabolomic approaches rather than concentration measurement alone.[25–27]

p-HBA provides another potentially informative compound. Experimental work has linked p-HBA with mucosal-barrier effects that are substantially dependent on intestinal microorganisms. Han et al.[28] reported that p-HBA improved experimental colitis and mucosal integrity and that disruption of microbiota weakened the effect. Although such findings cannot be interpreted as proof of an OPP effect in humans, they demonstrate that small phenolic acids chemically relevant to OPP may act through host–microbial pathways rather than solely through direct systemic antioxidant mechanisms.

Bioaccessibility, bioavailability, and microbial transformation

A central theoretical issue is the distinction between the amount of a phenolic compound present in an OPP capsule and the amount of biologically relevant material eventually presented to human tissues. Bioaccessibility describes the fraction released from the food or formulation and made available for absorption, whereas bioavailability encompasses absorption, distribution, metabolism, and excretion. Phenolic compounds vary widely across both dimensions.[9,10]

A fraction of OPP phenolics may be absorbed in the upper gastrointestinal tract, metabolized by intestinal and hepatic enzymes, and circulated predominantly in conjugated forms. Other compounds may enter the colon in substantial quantities. There, bacterial enzymes can transform aromatic structures into lower-molecular-weight metabolites, which subsequently may enter host circulation and undergo additional phase II conjugation. Therefore, the biologically relevant "OPP exposure" should be conceptualized as a mixture of the administered parent compounds, host-derived conjugates, microbial transformation products, and microbial–host co-metabolites.[10,14,29]

Food technology can modify this exposure. Encapsulation, fermentation, enzymatic processing, co-administration with selected microorganisms, and other approaches can alter solubility, stability, release kinetics, microbial accessibility, and absorption. Polia et al.[30] emphasized that food-processing and biotechnology interventions may change polyphenol bioavailability significantly. The observation that encapsulated OPP has produced measurable human effects further strengthens the need to treat formulation as a biological variable rather than simply a manufacturing detail.[6] Recent evidence also shows that food processing can alter polyphenol stability, release, bioavailability, and subsequent microbial exposure, reinforcing the need to characterize processing history alongside nominal dose.[31]

The consequence is that chemical antioxidant capacity measured before ingestion cannot adequately predict systemic function. In-vitro radical-scavenging assays occur under conditions very different from physiological exposure, where circulating compounds often consist largely of metabolites rather than the parent phenolic structure. Contemporary reviews therefore emphasize signaling, gene regulation, enzyme modulation, inflammatory pathways, endothelial nitric-oxide regulation, and microbiome-dependent processes in addition to direct antioxidant activity.[32,33]

Gut microbiome regulation of metabolic and inflammatory physiology

The gut microbiome influences host physiology through numerous interconnected functions, including fermentation, vitamin metabolism, bile-acid transformation, maintenance of mucosal ecology, immune education, and synthesis of small molecules capable of entering systemic circulation. Because these functions vary between individuals and are altered in many metabolic disorders, microbial metabolism has become an important target in cardiometabolic and preventive nutrition research.[34,35]

SCFAs provide one of the clearest examples. Acetate, propionate, and butyrate arise predominantly from microbial fermentation and participate in epithelial metabolism, receptor signaling, immune regulation, and aspects of glucose and lipid homeostasis. Butyrate is a major fuel for colonocytes and is frequently linked with epithelial-barrier integrity and anti-inflammatory regulation. However, fecal concentrations are not equivalent to total production because much of the SCFA pool is absorbed and metabolized; measurement therefore requires careful interpretation.[16]

Bile acids represent a second major host–microbiome interface. The liver synthesizes primary bile acids that are secreted into the intestine, where bacteria deconjugate and chemically modify them. Secondary and otherwise transformed bile acids interact with signaling receptors involved in glucose homeostasis, lipid metabolism, immune regulation, and energy balance. The bile-acid pool simultaneously influences microbial ecology, creating another bidirectional system.[17,19,36]

A third pathway concerns compounds associated with metabolic endotoxemia. Increased intestinal permeability can facilitate systemic exposure to bacterial components, particularly lipopolysaccharide-related molecules, which can stimulate innate immune responses. Polyphenol-rich interventions have been associated in some studies with changes in intestinal permeability and endotoxin-related markers, although findings vary by intervention and population.[37–39] Such markers may be particularly informative in future OPP trials if anti-inflammatory effects are reproduced.

Trimethylamine-related metabolism illustrates another microbiome-linked cardiometabolic pathway. Gut bacteria transform dietary precursors into trimethylamine, which the host converts into trimethylamine-N-oxide (TMAO). Elevated circulating TMAO is associated with several cardiovascular and metabolic outcomes, although causal interpretation remains complex because kidney function, dietary patterns, and other host variables substantially influence circulating concentrations.[18] For OPP research, TMAO should be regarded as an exploratory functional biomarker rather than a presumed mechanism.

The bidirectional polyphenol–microbiome relationship

Polyphenol–microbiome interactions are inherently reciprocal. Intestinal bacteria transform phenolic molecules, but phenolic molecules can also influence bacterial growth, ecological competition, and metabolic activity. Certain bacteria possess enzymes involved in phenolic degradation and can use phenolic structures directly or indirectly. Polyphenols may suppress some organisms while creating ecological opportunities for others, leading Rodríguez-Daza et al.[12] to propose the concept of “duplibiotic” action to capture combined antimicrobial and substrate-related effects.

Clinical evidence increasingly demonstrates that these interactions can be biologically meaningful. In the MaPLE randomized crossover trial, a polyphenol-rich diet in older adults was associated with reduced intestinal permeability together with microbiome and metabolomic changes.[37,38] Follow-up analysis showed that the same intervention increased the microbial tryptophan metabolite indole-3-propionic acid among participants with preserved kidney function and linked the change with microbial and inflammatory features, illustrating how host phenotype can modify the metabolic response to diet.[40]

Other human studies provide methodological models for future OPP research. Le Sayec et al.[41] investigated Aronia polyphenol supplementation together with arterial function and the gut microbiome, while Wood et al.[42]

integrated wild-blueberry polyphenols with vascular, cognitive, microbiome, and metabolite outcomes. Cortés-Martín et al.[43] demonstrated that medication can modify the microbial response to a pomegranate polyphenol intervention in metabolic syndrome, showing why drug exposure should not be treated merely as a nuisance variable. Contemporary cardiometabolic reviews likewise identify reciprocal polyphenol–microbiota signaling as a plausible route through which dietary phenolics may affect inflammatory, metabolic, and vascular pathways.[44]

Meta-analytic findings confirm both promise and heterogeneity. Mao et al.[39] reported microbiome and inflammatory effects of polyphenol supplementation among individuals with overweight or obesity, while González-Gómez et al.[45] similarly identified effects influenced by dose, duration, and intervention characteristics. A large 2026 synthesis of 50 randomized trials reported frequent increases in total fecal SCFAs and butyrate and changes in selected commensal taxa, but also highlighted considerable between-study variability.[46] Consequently, OPP should be described as potentially microbiome-modulating rather than presumed to have a universal prebiotic effect.

Microbial metabotypes and the rationale for precision nutrition

A central implication of microbial metabolism is that an identical dose does not necessarily generate an identical internal exposure. Some individuals harbor microbial communities capable of producing particular metabolites, whereas others produce very little or none. This phenomenon has been studied most extensively for urolithins, equol, and several other microbial products, but it may have broader relevance to phenolic acids and complex polyphenol extracts.[20,47]

The term microbial metabotype describes a subgroup defined by functional metabolic production rather than simply by taxonomic composition. This distinction is valuable because two microbial communities that appear taxonomically different can perform similar metabolic functions, while superficially similar communities may differ in key genes. Perrone and D'Angelo[48] argue that microbial metabotypes may eventually become useful biomarkers for precision nutrition, although standardization of challenge tests, concentration thresholds, analytical platforms, and clinical validation remains insufficient.

Precision nutrition should therefore not be confused with generating a completely unique diet for every person. Zeisel[21] defines the more defensible objective as stratifying people into biologically meaningful subgroups based on determinants of metabolic heterogeneity. Gut microbiome data can contribute to this stratification, but it must be integrated with diet, genetics, metabolic phenotype, age, medication, behavior, and other variables.[22,23,49] Large-scale precision-nutrition research has also demonstrated marked person-to-person variation in postprandial metabolic responses to identical meals and has identified microbiome-related features as one component of predictive models, supporting the broader rationale for response stratification.[50]

The emerging field also requires caution. Commercial microbiome testing has developed more rapidly than clinically validated microbiome-guided dietary recommendations. Methodological differences in sampling, sequencing, taxonomy, functional annotation, and statistical pipelines remain substantial, and a universally accepted definition of a "healthy" microbiome does not exist.[35] Precision OPP research must therefore be hypothesis-driven and experimentally validated rather than based on descriptive stool profiles alone.

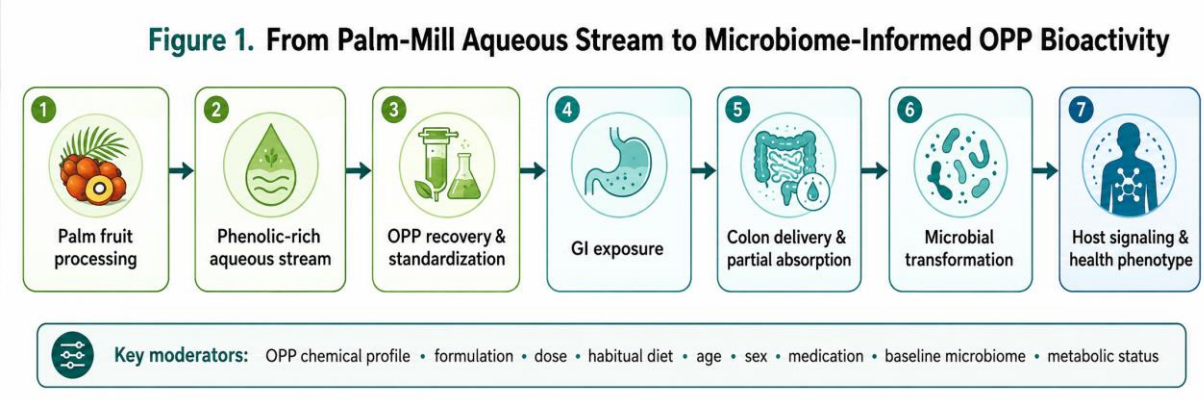

Figure 1 conceptually positions OPP within a multistage pathway beginning with palm-fruit processing and ending with host phenotype. The figure emphasizes that the biological effect of OPP may depend sequentially on recovery technology, chemical standardization, gastrointestinal exposure, intestinal microbial transformation, microbial metabolite production, and subsequent intestinal and systemic signaling. It also shows that host characteristics and baseline microbiome composition may modify virtually every downstream stage.

The principal implication of Figure 1 is that inconsistent clinical findings would not necessarily indicate that OPP is biologically inactive. Differences in the composition of the administered OPP preparation, microbial transformation capacity, habitual diet, medication use, or host phenotype could produce different internal exposures after an apparently equivalent external dose. Consequently, chemically characterizing the intervention and biologically characterizing the recipient should become complementary components of future OPP trials.[24,51,52]

METHOD

This study employed a qualitative literature review rather than a systematic literature review. The purpose was interpretive and integrative: to connect several bodies of evidence that have largely developed in parallel, including OPP chemistry and human trials, polyphenol bioavailability, microbial transformation, cardiometabolic microbiome research, microbial metabotypes, precision nutrition, and palm-processing valorization. The review was therefore not intended to produce a PRISMA flow diagram, pooled intervention estimate, or exhaustive risk-of-bias assessment.

Literature identification was iterative and concept-driven. Relevant peer-reviewed literature was considered from major academic databases and publisher platforms, including PubMed/MEDLINE, Scopus-indexed sources, Web of Science-indexed journals, ScienceDirect, Springer Nature, Wiley Online Library, Taylor & Francis, and other established academic platforms. Search concepts included combinations of "oil palm phenolics," "water-soluble palm fruit extract," "oil palm phenolics clinical trial," "polyphenol gut microbiome," "phenolic microbial metabolites," "protocatechuic acid microbiome," "p-hydroxybenzoic acid microbiota," "polyphenol metabotype," "precision nutrition microbiome," "foodomics," "metabolomics," "short-chain fatty acids," and "bile acid microbiome."

The temporal focus was 2020–2026. Priority was given to randomized controlled trials, human clinical studies, systematic reviews, meta-analyses, scoping reviews, and recent high-quality narrative reviews. Mechanistically informative animal or experimental studies were included selectively where direct human evidence was unavailable, particularly for PCA and p-HBA. Experimental findings were explicitly separated from direct clinical evidence to avoid implying that activity of an isolated constituent or an animal model is equivalent to efficacy of the whole OPP mixture in humans.

The literature was synthesized through six main analytical themes: OPP composition and human evidence; phenolic bioavailability; microbial transformation; intestinal and systemic metabolic pathways; interindividual variability and metabotypes; and future precision-nutrition trial design. Evidence was compared for convergence, inconsistency, methodological limitations, and translational relevance. The analysis also considered intervention standardization and foodomics because the composition of a complex botanical preparation is itself a potential source of outcome heterogeneity.[10,24]

A key methodological principle was evidence separation. Findings observed directly after OPP supplementation in humans are treated as OPP-specific evidence. Results from PCA, p-HBA, berries, pomegranate, hydroxytyrosol, or other polyphenols are used to identify biologically plausible pathways and appropriate analytical methods, but not to claim that those mechanisms have been demonstrated for OPP. This distinction is particularly important because current clinical evidence for microbiota-derived polyphenol metabolites is expanding rapidly but remains heterogeneous across compounds and outcomes.[53,54]

RESULTS: THEMATIC FINDINGS

OPP has crossed an important translational threshold

The most important finding from the OPP-specific literature is that it has progressed from an exclusively experimental bioactive fraction to a compound mixture with controlled human evidence. The phase I trial reported by Muhammad Ismail Tadj et al.[4] demonstrated short-term tolerability in healthy participants and established a structured clinical basis for subsequent research. Safety is an essential translational milestone because nutraceutical candidates cannot be advanced responsibly on the basis of in vitro potency alone.

The 2025 hyperlipidaemia study extended the field by demonstrating changes in biological endpoints rather than tolerability alone. OPP supplementation increased measures of antioxidant capacity and reduced TNF-α, suggesting that OPP may influence inflammatory and redox-related pathways in people with an early cardiometabolic-risk phenotype.[5] Nevertheless, the study was relatively short and was not designed to identify microbial or metabolomic mediators.

Fairus et al.[6] further reported effects of encapsulated OPP across several doses in 97 healthy adults. The 250-mg/day group showed reductions in systolic and diastolic blood pressure after 60 days, while higher doses influenced aspects of antioxidant status. Lipid profiles did not show corresponding major improvement, illustrating that OPP responses may be pathway-specific rather than uniformly beneficial across conventional cardiometabolic biomarkers.

This pattern provides an important rationale for mechanistic research. If a botanical intervention changes TNF-α and blood pressure without producing equivalent changes in every lipid endpoint, then a generalized "antioxidant" explanation becomes less satisfactory. The next studies should determine whether vascular, immune, intestinal, or microbial pathways change before or in parallel with the clinical phenotype.

The OPP–microbiome hypothesis remains plausible but unproven

The second major finding is that there is currently a substantial mismatch between what is known about OPP clinical effects and what is known about their mechanism. Human OPP trials have not yet incorporated comprehensive microbiome sequencing or microbial metabolite profiling. Therefore, statements that OPP "works through the gut microbiome" would exceed the available evidence.

However, the wider polyphenol literature provides a strong rationale for testing this pathway. Dietary phenolics can reach the colon, undergo bacterial conversion, alter microbial functional activity, and generate metabolites capable of systemic absorption.[7,8,10,14] Recent clinical reviews show that specific microbiota-derived polyphenol metabolites have been associated with cardiometabolic, inflammatory, neurological, gastrointestinal, and other outcomes, although study methods remain heterogeneous.[53,54]

The strongest interpretation is therefore one of mechanistic opportunity rather than proof. OPP possesses appropriate chemical substrates, human biological activity has been demonstrated, and analogous polyphenol interventions can alter microbial or metabolomic outcomes. What is missing is a direct study connecting these three elements in the same OPP-treated participants.

PCA is a promising mechanistic bridge

PCA offers a particularly useful entry point for such research. It is relevant to OPP chemistry and is also recognized as a microbiota-derived phenolic metabolite within broader dietary polyphenol metabolism. This

makes PCA analytically valuable because it can connect the administered phytochemical mixture with microbial transformation and systemic host pathways.

Experimental research supports several candidate mechanisms. Dong et al.[25] found that PCA altered microbiome profiles in an adenoma-prone animal model while inhibiting adenoma development. Tan et al.[55] reported protective effects of PCA in metabolic dysfunction-associated steatotic liver disease associated with changes in microbial and metabolic pathways. These studies are preclinical and should not be translated directly into human OPP claims, but they indicate biological pathways suitable for prospective investigation.

Vascular research is particularly relevant. Chook et al.[26] demonstrated that physiologically relevant PCA concentrations protected vascular endothelial function under inflammatory conditions through Akt/eNOS-related signaling. More recently, Lee et al.[27] reported that gut-derived PCA attenuated endothelial dysfunction through GPER-mediated nitric-oxide signaling and inflammatory regulation. The relevance to OPP is clear: if the reported blood-pressure signal from OPP is reproduced, targeted measurement of PCA and related conjugates could test whether endothelial responses are associated with phenolic metabolite exposure.

p-HBA highlights a possible gut-barrier pathway

p-HBA provides another informative mechanistic example. Han et al.[28] demonstrated that p-HBA improved experimental colitis and mucosal-barrier characteristics in a microbiota-dependent manner. Antibiotic disruption reduced the benefit, supporting a role for the intestinal ecosystem rather than a purely direct chemical effect.

This mechanism is relevant because impaired intestinal barrier function may contribute to systemic low-grade inflammation through increased exposure to bacterial products. A polyphenol-rich diet has been reported to reduce serum zonulin in older adults, while MaPLE trial analyses linked dietary polyphenols, microbiota, metabolomic changes, and intestinal-barrier markers.[37,38]

The implication for OPP is not that it has been proven to repair intestinal permeability. Rather, future clinical trials should include barrier-related endpoints alongside circulating inflammatory markers. If OPP reduces TNF-α and simultaneously alters endotoxemia or barrier indices, the combination would provide a much more informative mechanistic signal than TNF-α alone.

Microbial metabolic outputs may matter more than taxonomic changes

Microbiome research often focuses on whether intervention increases or decreases the relative abundance of named bacterial taxa. Although taxonomic information is useful, microbial function may be more relevant to phenolic bioactivity. An OPP intervention could change microbial enzymatic activity without producing a large shift in community composition. Conversely, taxonomic differences might occur without clinically important metabolic consequences.

SCFAs illustrate this distinction. Meta-analysis suggests that polyphenol supplementation can increase total fecal SCFAs and butyrate in many interventions, but responses depend on health status, polyphenol class, duration, and analytical method.[46] Mao et al.[39] and González-Gómez et al.[45] similarly observed heterogeneity in obesity-related populations. It would therefore be inappropriate to assume that OPP will necessarily increase butyrate, but measuring SCFAs would help determine whether fermentation-related pathways are altered.

Bile-acid analysis should also be considered because microbial modification of bile acids affects signaling relevant to glucose and lipid homeostasis. Changes in bile-acid composition can reflect both host and microbial processes and may provide functional information not apparent from conventional microbiome sequencing.[17,19,36]

Aromatic microbial metabolites are another promising category. The MaPLE trial demonstrated that a polyphenol-rich dietary pattern increased indole-3-propionic acid in a subset of older adults and that response depended partly on renal function and microbiome characteristics.[40] Although indole-3-propionic acid is generated primarily from tryptophan rather than directly from OPP phenolics, this study illustrates an important principle: polyphenol-rich interventions may change microbial metabolism beyond the direct catabolism of the administered phenolic compounds.

Figure 2. Proposed Bidirectional Interaction Between OPP and the Gut Microbiome

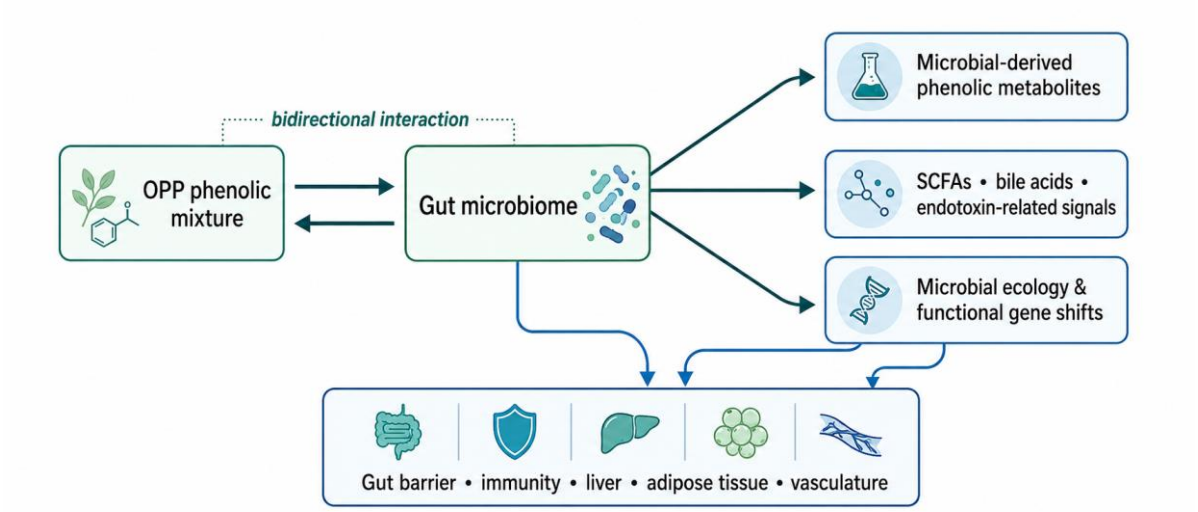

Figure 2 depicts the proposed bidirectional relationship between OPP and the intestinal microbiome. One arm represents microbial conversion of OPP-related phenolics into smaller phenolic metabolites. The second represents potential ecological or functional modification of the microbial community by OPP. These mechanisms converge on functional outputs including phenolic metabolites, SCFAs, bile-acid transformations, intestinal-barrier regulation, and inflammatory signaling.

The figure underscores why taxonomy alone cannot establish mechanism. A future OPP study should preferably integrate shotgun metagenomics or equivalent functional profiling with targeted and untargeted metabolomics. Demonstrating that OPP changes a microbial pathway, increases a defined circulating metabolite, and that this metabolite is associated with an endothelial or inflammatory outcome would represent a substantially stronger mechanistic chain than reporting a change in bacterial abundance alone.[14,24,53]

Interindividual variation may explain apparently inconsistent responses

The polyphenol literature repeatedly shows that individuals differ substantially in phenolic metabolism. Favari et al.[20] reviewed 153 human studies and found that gut microbiota, genetic characteristics, age, sex, ethnicity, body mass index, health status, and other variables contributed to interindividual differences in the absorption and metabolism of phenolic compounds.

This heterogeneity has direct implications for OPP. A trial reporting a modest average effect could contain a subset of strong responders and another subset producing little biological response. Conversely, an apparently positive population-average result could conceal participants for whom the intervention is ineffective. Traditional statistical analysis centered only on mean change does not necessarily reveal these patterns.

The concept of microbial metabotypes offers one approach. Well-established examples from other phenolics include different urolithin-producing phenotypes after ellagitannin exposure and equol producer status after isoflavone exposure. Espín et al.[47] argue that these phenotypes illustrate coevolution between host, diet, and microbiota and may provide a more functional basis for stratification than taxonomy alone. Perrone and D'Angelo[48] extend this argument toward precision nutrition but emphasize that clinical use remains premature.

No OPP-specific metabotype has yet been established. The appropriate near-term strategy would therefore be exploratory: classify participants according to observed OPP-derived metabolite profiles, identify associations with clinical response, and then test whether those patterns reproduce in an independent cohort. This would move the field gradually from biological heterogeneity toward validated stratification.

OPP fits naturally within a precision-nutrition research architecture

Precision nutrition is relevant to OPP for two reasons. First, the intervention is chemically complex and may vary across production batches. Second, host microbial processing of that intervention is likely to vary among participants. A rigorous OPP research program should therefore characterize both the input and the recipient.

The input side requires foodomics or equivalent analytical chemistry. Untargeted mass spectrometry can supplement targeted quantification of known OPP constituents and detect unexpected compounds or degradation products. The importance of this approach was emphasized by Keohane et al.,[24] who found that clinical polyphenol studies frequently under-characterize the intervention relative to the sophistication of biological sampling.

The participant side requires repeated dietary assessment, medication records, metabolic phenotyping, microbiome profiling, and metabolomics. Precision-nutrition models should not depend solely on microbiota because diet–microbiome interactions occur within a broader host context. Matusheski et al.[51] emphasize the combined roles of genes, nutrient status, microbiota, and technology in personalized nutrition, while Rouskas et al.[56] illustrate how digital and algorithmic tools are increasingly being integrated with dietary and microbiome information.

Fermentation models may also play a useful translational role. Zhang, Niu and Zhu[52] argue that multistage in vitro fermentation systems can model individual microbial responses to polyphenols under controlled conditions. Such models could be used before large trials to identify candidate OPP metabolites, optimize sampling times, and generate hypotheses regarding responder phenotypes.

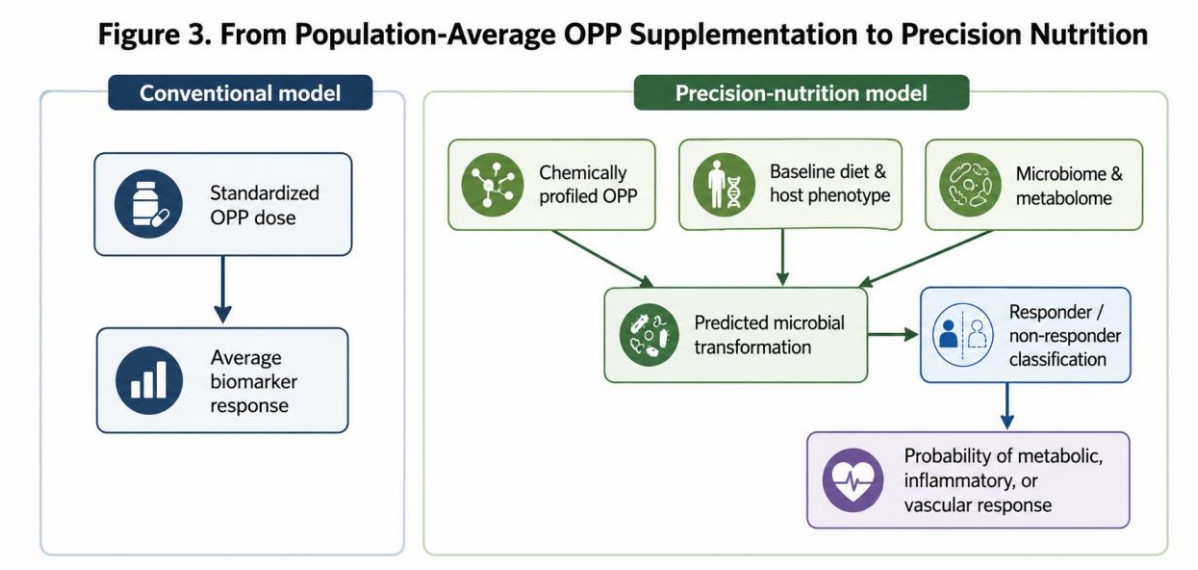

Figure 3 contrasts conventional OPP supplementation with a precision-nutrition approach. In the conventional model, a standardized external dose is related to the average biomarker response. In the proposed model, OPP is chemically profiled, participants are characterized by diet, host phenotype, microbiome, and metabolome, and the resulting information is used to investigate microbial transformation and classify biological response.

The purpose of this approach is not to replace randomized clinical trials. Randomization remains essential for estimating causal intervention effects. Precision analysis adds another layer by asking why effects differ within randomized groups and whether baseline biology predicts benefit. This distinction is important because current microbiome-guided nutrition remains scientifically promising but not sufficiently validated for routine individual prescription.[21,35,47]

DISCUSSION

Reframing OPP from antioxidant mixture to host–microbial substrate

The central argument of this review is that OPP should increasingly be investigated as a host–microbial substrate system rather than only as an antioxidant supplement. This reframing does not deny the antioxidant effects reported in human studies. Instead, it recognizes that measured antioxidant changes may represent downstream consequences of more complex biological processes.

The conventional model assumes that OPP phenolics are consumed, absorbed, circulate intact, scavenge reactive species, and thereby improve health. The contemporary model is more complex: some compounds are absorbed directly; others reach the colon; microorganisms transform them; the parent compounds and their metabolites may change microbial ecology; microbial products may influence the intestinal barrier and immune system; metabolites enter circulation; and downstream vascular or metabolic signaling occurs.

This framework provides a more plausible explanation for the apparent discrepancy between relatively low bioavailability of some parent polyphenols and measurable systemic outcomes. Williamson[10] emphasizes that microbial products can represent a substantial component of absorbed phenolic-derived material. Brown et al.[53] and Adorno Vita et al.[54] further show that clinical research increasingly links specific microbiota-derived metabolites with cardiometabolic and inflammatory phenotypes.

From antioxidant endpoints to mechanistic mediation

A major weakness of early nutraceutical trials is that they frequently measure only endpoints located far downstream of the intervention. For example, an improvement in blood pressure may be reported without determining what molecular or metabolic event preceded that improvement. Mechanistic mediation analysis can improve this situation.

Suppose a future randomized OPP trial demonstrates a reduction in systolic blood pressure. Researchers could simultaneously measure OPP-derived phenolic metabolites, endothelial nitric-oxide-related biomarkers, bile-acid profiles, SCFAs, inflammatory markers, and microbial functional pathways. If changes in a defined metabolite occur before blood-pressure improvement and statistically mediate a significant proportion of the intervention effect, this would create a stronger mechanistic hypothesis for subsequent validation.

PCA provides an obvious candidate. The vascular findings of Chook et al.[26] and Lee et al.[27] suggest that PCA-related exposure can affect endothelial nitric-oxide signaling. Future OPP trials should therefore determine whether participants with larger increases in PCA-related circulating metabolites also experience larger changes in blood pressure or endothelial function.

OPP and the metabolic–inflammatory interface

Metabolic syndrome, obesity, dyslipidaemia, prediabetes, hypertension, and metabolic liver disease share interconnected pathways involving inflammation, endothelial dysfunction, oxidative stress, and metabolic signaling. Gut microbiota can participate in these pathways through barrier integrity, microbial products, bile acids, and other metabolites.[34]

The reduction of TNF-α reported after OPP supplementation is therefore potentially important, but its interpretation should remain cautious.[5] TNF-α is a systemic inflammatory marker influenced by many pathways. Without microbial or metabolomic measurements, the finding cannot identify whether OPP acts through the intestine, through directly absorbed compounds, or through another mechanism.

The broader evidence nevertheless provides useful hypotheses. Polyphenol-rich interventions can reduce intestinal permeability in some contexts,[37] alter inflammatory or endotoxin-related biomarkers,[39,43] and generate microbiome-dependent metabolites associated with health outcomes.[53] OPP could reasonably be tested against this mechanistic background.

Implications for vascular health

The blood-pressure finding in the 2025 OPP trial may represent one of the most clinically relevant signals currently available. Hypertension is highly prevalent, and even modest sustained reductions in blood pressure could have population significance. However, the existing evidence is not sufficient to recommend OPP for hypertension treatment or prevention.

Future studies should use validated ambulatory or standardized clinic blood-pressure measurements, assess endothelial function, control background antihypertensive medication, and examine relevant metabolic mediators. Flow-mediated dilation, nitric-oxide-related measures, inflammatory biomarkers, PCA-related metabolites, and potentially vascular stiffness could provide complementary information.

Human trials of Aronia and blueberry polyphenols demonstrate feasible models in which vascular function is combined with microbiome and metabolite assessment.[41,42] OPP research can adopt similar integrated methods while preserving the distinct chemistry of the intervention.

Why multi-omics should become central to OPP research

The strongest methodological recommendation emerging from this review is the use of integrated multi-omics. Shotgun metagenomics can characterize microbial genes and functional pathways, offering greater mechanistic resolution than 16S rRNA sequencing alone. Metatranscriptomics can indicate which genes are actively expressed. Targeted metabolomics can quantify known OPP-derived phenolic metabolites, while untargeted metabolomics can identify unexpected metabolic products.

A comprehensive platform should also include intervention foodomics. It would be scientifically inconsistent to profile thousands of microbial genes and metabolites while describing the administered OPP simply by total phenolic content. The chemical identity of the intervention is part of the causal exposure and must therefore be characterized rigorously.[24]

Such designs can be strengthened by targeted panels of SCFAs, bile acids, phenolic acids, aromatic microbial metabolites, endotoxin-related biomarkers, and vascular markers. The objective is not to measure every possible analyte but to establish temporal and biological coherence between the intervention, microbial response, metabolite production, and host outcome.

Designing the next generation of OPP clinical trials

The ideal next trial would recruit participants with early cardiometabolic risk rather than individuals with advanced disease requiring therapeutic substitution. Potential groups include people with mild dyslipidaemia, prehypertension, prediabetes, central obesity, or early metabolic syndrome. These populations offer biologically relevant room for improvement while retaining a preventive rather than therapeutic framing.

Intervention duration should be longer than the short periods common in early-phase trials. Twelve to twenty-four weeks would provide a more meaningful window for persistent microbial adaptation and cardiometabolic outcomes. Multiple standardized doses could clarify whether OPP exhibits non-linear dose responses, particularly because the 2025 blood-pressure study suggested different biological effects across dose levels.[6]

Participants should undergo detailed baseline assessment. Habitual diet, medication use, recent antibiotics, probiotic use, metabolic phenotype, renal function, age, and body composition can all influence microbiome and metabolite measurements. Cortés-Martín et al.[43] demonstrated particularly clearly that medication can modify microbial responses to a polyphenol intervention, while Peron et al.[40] showed that renal function can modify microbial metabolite responses. Trial-design guidance from Nature Microbiology further recommends explicit measurement and reporting of habitual diet because background dietary exposure can modify both microbiome composition and the efficacy of microbiome-directed interventions.[57]

Repeated sampling is essential. A single baseline and endpoint stool sample may fail to distinguish stable intervention effects from natural temporal variation. Intermediate sampling would help identify whether changes in microbial function precede changes in clinical endpoints.

Responder analysis should be prespecified and adequately powered. Data-driven clusters discovered in small trials are vulnerable to overfitting. Candidate OPP metabotypes should therefore be identified in one cohort and prospectively validated in another before they are used for precision-nutrition recommendations.[20,48]

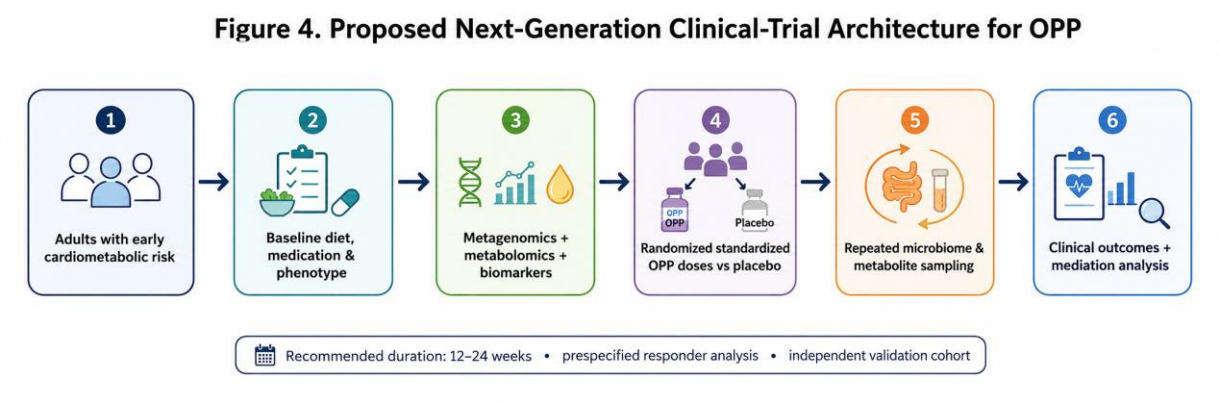

Figure 4 presents a proposed architecture for a next-generation OPP clinical trial. Participants with early cardiometabolic risk would receive standardized OPP or placebo after baseline dietary, phenotypic, microbiome, and metabolomic characterization. Repeated sampling would then enable temporal analysis of microbial, metabolite, inflammatory, and vascular responses.

The key analytical advance illustrated by Figure 4 is the combination of average treatment-effect estimation with mediation and responder analysis. The randomized design determines whether OPP produces an overall effect; mediation analysis investigates plausible mechanisms; and responder analysis evaluates whether baseline biological characteristics predict heterogeneity. Independent validation would then determine whether identified microbiome or metabolite signatures are reproducible.

Circular-bioeconomy implications

OPP also has a distinctive relevance beyond biomedical mechanisms because it originates from aqueous streams generated during palm-fruit processing. Recovering health-relevant molecules from these streams could increase value extraction from existing biomass and create additional product opportunities from material that historically has not been the primary commercial output of milling.[2,3] This valorization argument is consistent with broader palm-industry research showing that mill and refinery by-products can contain commercially relevant phytonutrients and can be incorporated into resource-recovery strategies, although environmental benefit depends on appropriate processing and pollution control.[58,59]

This opportunity is especially relevant to palm-producing countries. If chemically standardized OPP eventually demonstrates reproducible health benefits, value-added production could potentially be integrated with domestic food, nutraceutical, or pharmaceutical innovation. Such development could connect agricultural processing, biotechnology, clinical nutrition, and local manufacturing.

However, the circular-bioeconomy argument should not be overstated. Recovery of OPP does not by itself resolve wider sustainability issues associated with oil-palm cultivation, land use, biodiversity, or industrial wastewater management. Its defensible contribution is narrower: recovering valuable bioactives from existing

aqueous processing streams may improve resource efficiency and diversify product value. Comprehensive environmental claims require life-cycle and industrial assessments outside the scope of this review.

Public-health relevance and limitations of nutraceutical framing

The public-health significance of OPP depends on more than biological efficacy. A product that produces a small laboratory biomarker improvement but is expensive, inaccessible, poorly standardized, or marketed with exaggerated claims may have little population value. Public-health translation would therefore require evidence on safety, cost, formulation quality, adherence, accessibility, and real-world effectiveness.

Precision nutrition also creates equity concerns. Advanced microbiome sequencing, metabolomics, and algorithmic prediction remain expensive. If precision OPP research eventually identifies responder groups, translation should not depend indefinitely on high-cost individualized testing. One practical objective would be to identify simpler surrogate biomarkers or clinically recognizable phenotypes after complex discovery studies establish the underlying biology.

The article therefore does not advocate replacing established cardiometabolic prevention strategies with OPP. Dietary quality, physical activity, smoking cessation, blood-pressure treatment, lipid management, diabetes prevention, and evidence-based medical care remain foundational. OPP should be investigated as a potential adjunctive nutritional bioactive rather than as a substitute for proven interventions.

CRITICAL LIMITATIONS OF THE CURRENT EVIDENCE

The first limitation is the small OPP-specific clinical literature. Human trials now exist, but the total number of studies, participants, populations, intervention durations, and clinically relevant outcomes remains insufficient to support broad health claims. The current evidence should be viewed as an early translational signal rather than a mature clinical evidence base.[4–6]

Second, there is currently no direct human evidence demonstrating microbiome mediation of OPP effects. Much of the mechanistic framework developed in this review draws from broader polyphenol research. Such triangulation is valuable for generating hypotheses but must not be mistaken for OPP-specific causal evidence.

Third, OPP is a mixture. The biological relevance of PCA, p-HBA, caffeoylshikimic acids, hydroxytyrosol-related compounds, and unidentified minor constituents may differ, and interactions among compounds may matter. A whole-extract intervention cannot be reduced mechanistically to one constituent without direct evidence.

Fourth, experimental models may overestimate translation. PCA and p-HBA studies provide valuable evidence regarding endothelial signaling, metabolic regulation, microbiome changes, and intestinal barriers, but doses, exposure patterns, species physiology, and disease models differ from human OPP supplementation.[25,28,55]

Fifth, microbiome methods remain imperfect. Stool samples are convenient but do not fully represent mucosa-associated communities or microbial activity across different intestinal regions. Sequencing platforms, DNA extraction protocols, sequencing depth, reference databases, and bioinformatic pipelines can substantially affect reported outcomes.[35]

Sixth, metabolomics introduces its own uncertainty. Many microbial metabolites have multiple origins, including direct dietary intake, host metabolism, and bacterial metabolism. PCA itself illustrates this problem. Isotope-labeled interventions, controlled feeding, and carefully selected washout periods may be required to determine causal origin.

Seventh, the broader polyphenol literature is heterogeneous. Different compounds cannot be assumed to produce equivalent microbiome effects. Meta-analyses demonstrate substantial variation by intervention type, dose, health status, and duration.[39,45,46]

Finally, microbial metabotypes remain research tools rather than routine clinical diagnostics. Although the concept is well supported for several phenolic classes, standardization and replication are required before it can support everyday precision-nutrition prescriptions.[20,47,48]

FUTURE RESEARCH AGENDA

Future OPP research should first standardize intervention chemistry. Each clinical batch should be characterized using validated quantitative methods for principal compounds, supplemented where feasible by untargeted chemical profiling. Reporting should include concentration, stability, formulation, excipients, processing history, batch variation, and relevant contaminants. Such information is necessary for reproducibility and meaningful comparison across studies.[24,30]

Second, the microbiome should become a prespecified endpoint rather than an exploratory afterthought. Shotgun metagenomics is preferable where feasible because it can identify functional genes rather than only approximate taxonomy. Relevant pathways could include enzymes involved in phenolic degradation, aromatic metabolism, bile-acid transformation, and SCFA production.

Third, metabolomics should be used as the biochemical bridge between microbiome and host. Targeted analysis should include PCA and related conjugates, p-HBA-related compounds, relevant phenolic acids, SCFAs, bile acids, and selected microbial co-metabolites. Untargeted analysis should be retained for discovery because important OPP-derived metabolites may not yet be known.[53,54]

Fourth, future trials should measure intestinal-barrier and systemic inflammatory endpoints simultaneously. This would help determine whether observed anti-inflammatory effects are associated with changes in gut permeability or endotoxemia rather than occurring independently.

Fifth, clinical vascular phenotyping should be strengthened. Blood pressure should be complemented with endothelial-function or arterial-stiffness measures where possible, especially because PCA-related mechanisms provide a plausible link with nitric-oxide signaling.[26,27]

Sixth, studies should evaluate dose–response relationships and formulation effects. Higher OPP doses do not necessarily produce larger benefits, and encapsulation may alter pharmacokinetics and microbial exposure. The findings of Fairus et al.[6] underline the need to avoid assuming a simple linear relationship between dose and effect.

Seventh, trials should incorporate background diet quantitatively. Dietary polyphenols from coffee, tea, fruits, vegetables, cocoa, and other foods can contribute to the same metabolites being attributed to OPP. Repeated dietary records, controlled feeding periods, or biomarker-supported dietary assessment may therefore be required.

Eighth, responder and metabotype analyses should be replicated. Discovery cohorts could identify metabolite patterns associated with OPP response, but independent prospective validation should precede clinical use.
Ninth, longer safety studies are needed. Short phase I tolerability does not establish safety under long-term intake, particularly when concentrated phenolic preparations are used. High-dose botanical extracts cannot automatically be assumed safe because their constituents originate from foods.[10,33]

Tenth, research in palm-producing countries should examine population-specific microbial and dietary contexts. Much microbiome evidence derives from populations in high-income countries, yet habitual diet, antibiotic exposure, environment, and microbial composition can differ substantially by geography. An OPP intervention developed from a tropical agricultural system should ultimately be tested in populations where it is most likely to be produced and consumed.

CONCLUSION

Oil palm phenolics constitute a scientifically distinct palm-derived bioactive fraction that has moved beyond purely experimental research into early controlled human investigation. Short-term clinical studies indicate tolerability and provide preliminary evidence concerning antioxidant status, inflammation, and blood pressure. These findings justify further investigation but are not sufficient to establish OPP as a treatment for cardiovascular, metabolic, or inflammatory disease.

The most important conceptual advance proposed in this review is the shift from viewing OPP simply as an antioxidant supplement toward understanding it as a complex substrate entering a host–microbiome metabolic system. Phenolic compounds may be absorbed directly, transformed by intestinal bacteria, converted into microbial and host co-metabolites, and potentially influence microbial function, intestinal integrity, inflammation, and vascular signaling. PCA and p-HBA provide particularly useful mechanistic candidates, although evidence from isolated compounds cannot substitute for direct OPP clinical studies.

The next phase of OPP research should therefore be mechanistically ambitious. Chemically standardized interventions should be combined with metagenomics, targeted and untargeted metabolomics, foodomics, intestinal-barrier biomarkers, inflammatory and vascular phenotyping, detailed dietary assessment, and adequately powered responder analysis. These methods can determine whether OPP-associated biological effects are actually mediated by specific microbial transformations and whether interindividual microbial metabotypes explain heterogeneous responses.

Such evidence could ultimately position OPP at the intersection of functional-food science, microbiome-informed precision nutrition, preventive public health, and value addition from palm-processing streams. Until that evidence is generated, OPP should be regarded as a promising translational research candidate rather than a proven therapeutic. Its greatest scientific value at present lies not in making stronger health claims, but in asking more precise mechanistic questions.

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