

From Palm-Mill Bioactives to Vascular Medicine: Oil Palm Phenolics as Emerging Cardiometabolic Nutraceuticals for Blood Pressure, Endothelial Function, Oxidative Stress, and Human Translation

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Abstract

Oil palm phenolics (OPP) are water-soluble bioactive compounds recovered from aqueous streams generated during oil palm fruit processing. Their development creates an unusual interface between circular bioeconomy, nutrition, vascular biology, and clinical nutraceutical science. Although OPP research was initially dominated by preclinical evidence, recent randomized human studies have extended investigation into safety, lipid metabolism, oxidative status, inflammation, and blood-pressure regulation. This qualitative literature review critically evaluates the emerging cardiometabolic evidence for OPP, emphasizing translation rather than antioxidant activity alone. Current findings indicate acceptable short-term tolerability of encapsulated OPP at doses up to 1,500 mg/day and suggest potentially favorable effects on antioxidant defense and inflammatory biomarkers.

A recent dose-ranging study additionally identified reductions in systolic and diastolic blood pressure at 250 mg/day in normotensive adults, whereas higher doses did not produce proportionally greater vascular responses. This pattern raises important questions concerning non-linear dose-response relationships, hormetic signaling, formulation, bioavailability, and interindividual metabolism. Human evidence nevertheless remains preliminary: trials are short, participant numbers are modest, clinically high-risk populations remain underrepresented, endothelial-function measurements are largely absent, pharmacokinetic data are insufficient, and no cardiovascular-outcome evidence exists. OPP should therefore be regarded as an investigational cardiometabolic nutraceutical rather than an established preventive or therapeutic intervention. Future development requires compositional standardization, metabolite profiling, controlled dose-ranging studies, ambulatory blood-pressure monitoring, direct vascular-function measurements, longer safety evaluation, and trials involving hypertensive, dyslipidemic, diabetic, and high-cardiovascular-risk populations.

Keywords: Oil Palm Phenolics, Cardiometabolic Health, Blood Pressure, Endothelial Function, Oxidative Stress, Phenolic Acids, Nutraceuticals, Nitric Oxide, Polyphenol Bioavailability, Circular Bioeconomy.

JEL Classification: I12; I18; O32; Q16; Q56

Introduction

Cardiometabolic diseases arise from interacting abnormalities in blood pressure, lipid metabolism, glucose regulation, vascular function, chronic inflammation, and oxidative homeostasis. Although pharmacological management of hypertension, dyslipidemia, diabetes, and established cardiovascular disease has substantially improved clinical outcomes, there remains considerable scientific interest in food-derived compounds that

could complement—not replace—evidence-based preventive approaches. Polyphenols have attracted particular attention because their biological actions extend beyond direct chemical antioxidant activity toward modulation of endothelial signaling, inflammatory pathways, transcriptional responses, lipid metabolism, and metabolic homeostasis [1-4].

Oil palm processing represents an especially distinctive setting

in which this biomedical interest intersects with resource recovery. During processing of *Elaeis guineensis* fruits, considerable quantities of aqueous material are generated. These streams contain water-soluble phytochemicals that differ fundamentally from the lipid-soluble carotenoids, tocopherols, tocotrienols, phytosterols, and other micronutrients normally associated with palm oil. Recovery of the phenolic fraction creates what is commonly described as oil palm phenolics or water-soluble palm fruit extract. OPP contains several phenolic acids and related compounds, including caffeoylshikimic-acid isomers, protocatechuic acid, and p-hydroxybenzoic acid, although composition varies according to raw material, recovery procedure, concentration, drying, storage, and formulation [5-8].

This origin gives OPP a conceptual advantage uncommon among nutraceutical candidates. Rather than requiring cultivation of an additional botanical resource solely for supplement production, OPP can potentially be recovered from an existing agro-industrial stream. Such recovery fits increasingly important circular-bioeconomy principles in which residual biomass and processing streams are treated as potential sources of higher-value chemicals, ingredients, biomaterials, fuels, and health-related products rather than merely as disposal problems. Recovery of polyphenols from palm-processing streams has therefore been studied alongside other approaches to valorizing oil palm biomass and palm oil mill effluent [9-12].

Environmental attractiveness, however, does not itself demonstrate biomedical value. One risk surrounding waste-derived or sustainably recovered bioactives is the development of a “green halo,” whereby environmental desirability implicitly increases perceived therapeutic credibility. A compound recovered through circular processing must satisfy the same evidentiary requirements as any conventional nutraceutical: reproducible chemical characterization, toxicological safety, appropriate dose determination, pharmacokinetic understanding, mechanistic plausibility, randomized human efficacy data, and ultimately clinically meaningful outcomes. Contemporary nutraceutical science increasingly emphasizes precisely these requirements because products marketed for cardiovascular or metabolic health frequently possess far stronger evidence for biomarker modification than for reduction of myocardial infarction, stroke, cardiovascular mortality, or other hard outcomes [13-15].

The scientific position of OPP has changed materially during the past several years. A 2020 cardiovascular review summarized extensive experimental evidence but also highlighted the relative scarcity of human studies [5]. Subsequent publications have expanded the clinical evidence base. A randomized phase-I study in healthy adults examined encapsulated OPP at 250, 1,000, and 1,500 mg/day for 60 days and reported no serious safety signals attributable to treatment [16]. A phase-II randomized study subsequently evaluated 250 mg/day in adults with hyperlipidemia, generating clinically relevant but not unequivocal lipid findings [17]. Further analysis of OPP supplementation in minor hyperlipidemia reported increases in measures of antioxidant defense and a reduction in tumor necrosis factor-alpha (TNF- α)

[18]. Most recently, analysis of the phase-I cohort demonstrated a blood-pressure signal at the 250 mg/day dose together with dose-dependent differences in antioxidant parameters [19].

These findings change the relevant research question. The issue is no longer whether OPP possesses antioxidant activity in chemical assays or whether experimental systems provide mechanistic plausibility. The more consequential question is whether the available translational evidence supports progression toward a clinically credible cardiometabolic nutraceutical. Such progression requires careful distinction between a change in total antioxidant capacity and prevention of cardiovascular disease; between within-group blood-pressure changes in normotensive participants and therapeutic antihypertensive effects; between short-term laboratory safety and long-term population safety; and between phenolic content measured before ingestion and biologically active metabolites reaching vascular tissues.

The present qualitative literature review therefore examines OPP through a translational cardiometabolic framework. It addresses four interconnected domains: first, the chemical and technological transformation of palm-mill aqueous bioactives into standardized preparations; second, biological mechanisms involving oxidative stress, endothelial nitric oxide, inflammation, lipid metabolism, and metabolic regulation; third, the emerging human evidence concerning safety, blood pressure, antioxidant defense, inflammation, and lipids; and fourth, the scientific requirements necessary to move from promising early-stage nutraceutical research toward clinically defensible use. Particular attention is paid to non-linear dose-response effects, formulation-dependent bioavailability, gut-microbial metabolism, trial-design limitations, and the difference between surrogate biomarkers and cardiovascular-risk reduction.

Literature Review: Conceptual and Theoretical Foundations **Oil Palm Phenolics as a Distinct Bioactive Fraction**

OPP should not be considered synonymous with palm oil. Conventional palm oil is predominantly a lipid matrix and contains fat-soluble minor constituents, whereas OPP is obtained from water-rich vegetation liquor generated during milling. The distinction is important scientifically and clinically because discussions concerning dietary saturated fat, palm-oil fatty-acid composition, or lipid-soluble palm tocotrienols cannot automatically be transferred to OPP. The latter is a predominantly hydrophilic phenolic preparation with different absorption pathways, metabolism, formulation requirements, and potential molecular targets [5-8].

Phenolic acids identified in oil-palm-derived aqueous fractions include protocatechuic acid, hydroxybenzoic-acid derivatives, and caffeoylshikimic-acid isomers. The biological effect of a complex phenolic mixture, however, cannot be inferred solely by adding together the known effects of isolated constituents. Extracts may exhibit additive, synergistic, antagonistic, or concentration-dependent interactions, and processing can alter the relative abundance and chemical state of constituents. Recent syntheses of polyphenol science further emphasize that chemical

structure, processing conditions, food matrix, gastrointestinal transformation, and host metabolism jointly shape bioavailability and bioactivity [20-23].

Studies of post-oil-extraction palm biomass have additionally demonstrated that palm-derived phytochemical fractions can retain strong antioxidant-related properties and possess predicted absorption profiles compatible with oral delivery [6]. Yet predicted absorption and ex vivo activity are not substitutes for human pharmacokinetic measurement. One of the most important remaining gaps in OPP research is therefore the absence of detailed profiles showing which parent compounds and metabolites appear in plasma, at what concentrations, after what time interval, and with what interindividual variation.

Recovery Technology, Circular Bioeconomy, and Product Standardization

Recovery of bioactive compounds from agro-industrial streams creates two value propositions: environmental burden reduction and generation of a higher-value ingredient. Palm-processing research has demonstrated several strategies for recovering or separating phenolic compounds, including membrane-related approaches, liquid-liquid systems, emulsion liquid membranes, adsorption, biological processing, and integrated biomass valorization [9-12]. Studies of microalgal and photodegradation processes further illustrate that phenolic constituents constitute an important chemical fraction in palm-mill aqueous systems, whether the objective is recovery or removal before discharge [11].

For nutraceutical development, however, the crucial challenge is not simply maximizing total phenolic recovery. The resulting product must have a reproducible chemical fingerprint, because two batches with similar total phenolic measurements can possess substantially different individual constituent profiles. Clinical translation therefore requires quantitative assays for major marker compounds, specification of impurities and degradation products, stability testing, microbiological standards, heavy-metal and contaminant limits, and predefined acceptance ranges for batch release. Recent work on botanical bioactives also shows that validated analytical methods, proficiency criteria, and authenticity testing are integral to reproducible quality control rather than optional manufacturing details [24, 25].

Processing itself may modify biological availability. Liquid preparations preserve a water-soluble matrix but face practical disadvantages involving volume, palatability, storage, microbial stability, and compliance. Spray drying and encapsulation improve logistical feasibility and may enhance stability, yet heating, carrier selection, wall materials, moisture content, particle properties, and dissolution can modify release and absorption. More broadly, human research on encapsulated polyphenols demonstrates that encapsulation does not universally improve systemic bioavailability; beneficial effects depend on the compound, delivery technology, formulation, and digestive context [26]. Consequently, an encapsulated OPP dose should not automatically be assumed bioequivalent to the same nominal mass

administered as liquid OPP.

Oxidative Stress and Redox Signaling

Oxidative stress is closely involved in hypertension, endothelial dysfunction, atherosclerosis, insulin resistance, and vascular aging. Reactive oxygen species can decrease nitric-oxide bioavailability, oxidize lipoproteins, activate inflammatory signaling, impair mitochondrial function, and contribute to endothelial nitric-oxide synthase uncoupling. However, the traditional concept that dietary polyphenols function primarily by directly scavenging circulating free radicals has become increasingly inadequate. Concentrations achieved in human tissues are often far below those used in chemical antioxidant assays, and many ingested compounds undergo rapid conjugation or microbial transformation [1-27].

Modern models emphasize redox-sensitive signaling. Polyphenols can influence transcription factors and enzymes governing endogenous antioxidant defenses, including Nrf2-associated pathways, glutathione metabolism, superoxide dismutase, and other cellular adaptive mechanisms. At the same time, excessive interpretation of antioxidant biomarkers is problematic. Total antioxidant capacity is influenced by numerous endogenous compounds, dietary variables, uric acid, metabolic state, and analytical method, and no single antioxidant-capacity measure can function as a comprehensive biomarker of disease protection[28].

This distinction is central to OPP interpretation. An increase in plasma total antioxidant capacity or preservation of antioxidant-enzyme activity provides evidence of biological interaction but does not establish that vascular oxidative injury has been reduced sufficiently to alter disease progression. Future OPP trials should therefore complement global antioxidant assays with more specific measures such as oxidized LDL, F2-isoprostanes, oxidative DNA products, glutathione redox balance, endothelial NO-related metabolites, and potentially redox-sensitive transcriptomic or metabolomic signatures.

Endothelial Function and the Nitric-Oxide Axis

The vascular endothelium regulates vasomotor tone, inflammation, platelet activity, thrombosis, vascular permeability, and smooth-muscle behavior. Reduced nitric-oxide availability is a central feature of endothelial dysfunction and hypertension. Endothelial nitric-oxide synthase produces NO from L-arginine under physiological conditions; NO then diffuses to vascular smooth muscle, activates soluble guanylate cyclase, increases cyclic GMP, and promotes relaxation. Oxidative stress can diminish this process through NO scavenging, tetrahydrobiopterin oxidation, and eNOS uncoupling [29-31].

Polyphenol research provides plausible mechanisms by which OPP might affect this axis. Resveratrol and several other phenolics have been reported to influence eNOS, AMPK, SIRT1, Nrf2, NF- κ B, and other pathways relevant to endothelial homeostasis[32]. Anthocyanin-rich products, flavan-3-ols, hydroxytyrosol, and other phenolic preparations have likewise been inves-

tigated for effects on vascular reactivity and endothelial function [33-35].

The broader evidence supports biological plausibility but should not be used as indirect proof of OPP efficacy. Different polyphenols possess different pharmacokinetics and target affinities. Thus, the most important unresolved question is whether OPP itself improves direct human endothelial-function measures. Flow-mediated dilation (FMD), peripheral arterial tonometry, pulse-wave velocity, augmentation index, endothelial microparticles, circulating adhesion molecules, and NO-related metabolites would provide substantially stronger mechanistic evidence than office blood pressure alone.

Inflammation, Lipid Oxidation, and Atherosclerotic Biology

Cardiovascular disease is driven by an interaction between lipid deposition, oxidative modification, endothelial activation, innate immunity, and chronic inflammation. Polyphenols may modulate macrophage cholesterol handling and reduce susceptibility of LDL to oxidative modification, although human effects vary considerably across compounds and study populations [36, 37]. Polyphenols have additionally been studied in relation to NF- κ B signaling, cytokine release, inflammasome activation, and related cardiometabolic pathways [38, 39].

The NLRP3 inflammasome is particularly relevant because metabolic stress, oxidized lipids, mitochondrial dysfunction, and danger-associated signals can promote its activation. Experimental evidence indicates that diverse polyphenols can attenuate elements of NLRP3 signaling, but direct clinical evidence remains far less developed than animal evidence [39]. Consequently, the reduced TNF- α reported in recent OPP supplementation research is encouraging but should be considered an initial inflammatory signal rather than comprehensive evidence of vascular anti-inflammatory action.

Polyphenol Bioavailability, Microbial Transformation, and Interindividual Response

A major conceptual shift in polyphenol research concerns the recognition that ingested parent compounds may not be the molecules producing systemic effects. Many polyphenols undergo intestinal and hepatic phase-II metabolism, whereas poorly absorbed fractions enter the colon and are transformed by microbial enzymes into smaller phenolic metabolites. These products may subsequently enter the circulation and influence host pathways. Interindividual microbiome composition can therefore generate distinct metabolite patterns or “metabotypes,” producing substantial differences in biological response to an apparently identical dose [40-42].

This framework is highly relevant to OPP because its phenolic-acid-rich composition is likely to undergo both host and microbial transformation. Without pharmacokinetic and metabolomic data, the active exposure remains poorly defined, and a nominal capsule dose such as 250 mg does not indicate what concentration of specific phenolics or metabolites reaches vascular tissues. Human studies of polyphenol metabolism show

substantial interindividual variability related to gut-microbiota composition, genetic polymorphisms, age, sex, body mass index, physiological status, and physical activity, reinforcing the need for OPP-specific metabolite profiling and responder analyses [40-43].

Method

This study was designed as a qualitative literature review (QLR), not a systematic literature review or meta-analysis. The objective was interpretive and translational synthesis rather than exhaustive enumeration of all records meeting predefined eligibility criteria. The review prioritized contemporary peer-reviewed publications from 2020–2026 addressing OPP, palm-derived aqueous phenolics, polyphenol vascular biology, endothelial dysfunction, oxidative stress, inflammation, lipid metabolism, phenolic bioavailability, gut-microbial metabolism, nutraceutical translation, formulation, and circular utilization of palm-processing streams.

Literature was considered through interconnected conceptual clusters: “oil palm phenolics,” “water-soluble palm fruit extract,” “oil palm vegetation liquor,” “blood pressure,” “endothelial function,” “nitric oxide,” “oxidative stress,” “antioxidant enzymes,” “inflammation,” “lipid profile,” “LDL oxidation,” “polyphenol bioavailability,” “gut microbiota,” “encapsulation,” and “nutraceutical.” Contemporary human trials were given the greatest evidentiary weight, followed by human mechanistic and meta-analytic literature, OPP-specific experimental studies summarized in recent peer-reviewed reviews, and broader polyphenol studies used for mechanistic context.

The synthesis intentionally distinguished four evidentiary levels: chemical or technological evidence; mechanistic evidence; surrogate human biomarker evidence; and clinically meaningful outcome evidence. This distinction was important because biochemical antioxidant effects and short-term changes in cardiovascular risk markers should not be interpreted as equivalent to prevention of cardiovascular events. The broader polyphenol evidence was used to contextualize plausible biological mechanisms but not as direct confirmation that OPP produces the same effects [44-46].

Particular attention was paid to potentially overlapping publications. The 2022 phase-I safety paper and the 2025 blood-pressure/antioxidant paper derive from the same registered parent clinical trial involving placebo and OPP doses of 250, 1,000, and 1,500 mg/day. They were therefore treated as separate analyses of one cohort rather than independent clinical replications [16-19]. Similarly, the strong similarity between the 2023 phase-II hyperlipidemia study and the 2025 antioxidant/inflammatory report—including participant number, dose, duration, and clinical context—requires caution regarding possible cohort overlap [17, 18]. This issue is important because counting secondary analyses as independent clinical trials can artificially inflate perceived evidence maturity.

No PRISMA flow diagram was employed because the methodol-

ogy was deliberately qualitative rather than systematic. The final thematic synthesis was organized around source and formulation, safety, blood pressure, endothelial biology, oxidative stress, inflammation, lipid effects, dose-response, bioavailability, and clinical translation.

Results: Thematic Findings

From Palm-Mill Aqueous Stream to Nutraceutical Ingredient
The first thematic finding is that the biomedical identity of OPP cannot be separated from its production technology. Oil palm generates a wide spectrum of residual biomass and aqueous outputs, and recent work increasingly frames such streams as sources of recoverable higher-value compounds [7-12]. Polyphenol extraction from palm mill effluent and sterilisation condensate

demonstrates that biologically interesting phenolic material can be recovered rather than destroyed during waste treatment [9]. At the same time, environmental treatment literature emphasizes that uncontrolled phenolic discharge can complicate wastewater management, further strengthening the rationale for upstream recovery [10, 11].

Figure 1 summarizes the proposed transformation pathway from oil palm milling to a medically credible nutraceutical. The central point is that recovery alone represents only the first step; translational development requires compositional characterisation, purification, stability control, standardized formulation, pharmacokinetic evaluation, and human clinical validation.

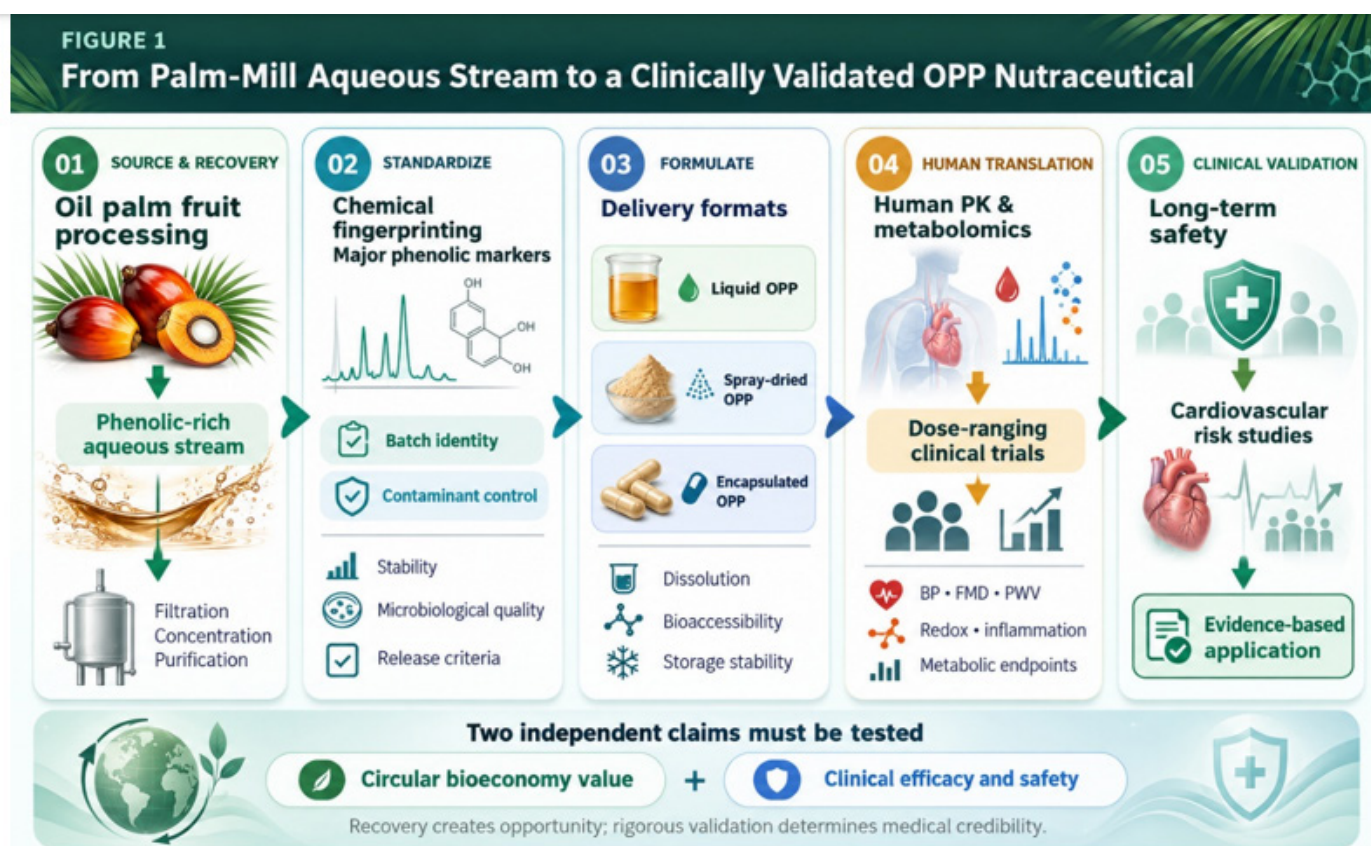


Figure 1: From Palm-Mill Aqueous Stream to a Clinically Validated OPP Nutraceutical

Figure 1 emphasizes why circular bioeconomy and clinical translation should be regarded as complementary but independent claims. Valorization can be successful from an environmental or industrial perspective even if clinical benefit is eventually modest. Conversely, demonstrating a physiological effect does not establish that large-scale recovery and standardization will be economically or environmentally optimal. A strong translational strategy therefore needs lifecycle and processing considerations alongside medical evidence.

Short-Term Safety Is the Most Mature Human Evidence

Among the different dimensions of OPP clinical development, short-term tolerability is currently the best characterized. In the randomized phase-I study, 100 healthy adults were allocated to

placebo or 250, 1,000, or 1,500 mg/day of encapsulated OPP over 60 days. Minor adverse events occurred across groups, with more events reported at higher exposure, but no serious treatment-related safety signal was identified, and hematological, renal, and liver parameters remained clinically acceptable [16].

The safety findings are important because many nutraceutical investigations move prematurely toward efficacy claims without adequate dose-escalation safety assessment. OPP development has at least established an early tolerability range for spray-dried encapsulated preparations. Nevertheless, the meaning of "safe" must be carefully constrained. Sixty-day tolerability in young or middle-aged healthy participants cannot demonstrate safety during years of use, in elderly populations, during pregnancy,

in chronic kidney or liver disease, or in combination with anti-hypertensive, anticoagulant, lipid-lowering, or glucose-lowering therapies.

The nutraceutical field illustrates why longer observation is required. Product safety depends not only on the active ingredient but on extract consistency, contaminants, adulteration, excipients, dose, duration, and interactions. Regulatory frameworks for nutraceuticals vary substantially, while international cardiovascular and metabolic guidelines generally demand stronger evidence before recommending nutraceuticals for disease management [13, 14]. Accordingly, OPP should currently be described as short-term well tolerated within studied doses, not as universally or indefinitely safe.

Blood Pressure: The Most Clinically Provocative New Signal

The 2025 publication from the phase-I cohort provides the most clinically intriguing OPP finding to date. Ninety-seven participants completed the study, and those allocated to 250 mg/day experienced statistically significant reductions in systolic and diastolic blood pressure relative to baseline at 60 days; the diastolic effect appeared earlier. Higher doses of 1,000 and 1,500 mg/day did not produce proportionally greater blood-pressure reductions [19].

This pattern is noteworthy for three reasons. First, blood pressure is more directly clinically interpretable than a chemical antioxidant assay. Second, the lowest active dose produced the clearest effect, raising the possibility of non-linear pharmacodynamics. Third, participants were healthy and normotensive, meaning that the finding may represent vascular modulation within physiological limits rather than antihypertensive treatment.

This distinction is essential. Within-group reduction from baseline does not necessarily imply superiority over placebo, particularly in a modest trial with repeated measurements, uncontrolled diet and activity, and normotensive participants. Blood pressure varies with sodium intake, sleep, stress, caffeine, physical activity, measurement setting, time of day, menstrual status, and regression to the mean. Larger placebo-adjusted trials using standardized measurement protocols are therefore required.

Nevertheless, the direction of the result is biologically plausible. Contemporary polyphenol evidence indicates that some polyphenol-rich foods and extracts can modestly reduce blood pressure, with response often larger in participants with elevated

baseline pressure [44-48]. Pomegranate meta-analysis, for example, supports a BP-modifying effect of phenolic-rich preparations, while clinical work involving roselle and standardized pomegranate extracts further demonstrates that botanical phenolic interventions can influence vascular endpoints [49-51].

The appropriate conclusion is therefore neither dismissal nor therapeutic endorsement. The finding is best viewed as a signal-generating observation requiring replication in prehypertension and hypertension, ideally using 24-hour ambulatory blood-pressure monitoring. Ambulatory monitoring would reduce white-coat and visit-to-visit effects and determine whether any OPP-associated changes persist during daytime activity and sleep.

Endothelial Function Is the Critical Missing Human Link

OPP's proposed blood-pressure mechanism is frequently linked to endothelial NO biology. This hypothesis is coherent with experimental OPP research summarized in recent reviews and with broader polyphenol literature showing modulation of endothelial signaling[5-8]. However, direct human evidence remains insufficient.

Endothelial dysfunction is both a mechanistic contributor to hypertension and an early feature of atherosclerotic cardiovascular disease. Reduced NO availability, excessive ROS generation, inflammation, and altered vasoactive mediator balance can increase vascular tone and arterial stiffness [29, 30]. Polyphenol interventions have demonstrated effects on endothelial function in several contexts, including flavan-3-ols, anthocyanins, resveratrol, citrus flavonoids, and hydroxytyrosol [32-52].

For OPP specifically, the absence of FMD measurement is therefore a major missed opportunity. A future study combining ambulatory BP with brachial-artery FMD, pulse-wave velocity, circulating nitrate/nitrite, cGMP, endothelin-1, and endothelial adhesion markers could test whether blood-pressure changes genuinely reflect improved endothelial signaling.

Figure 2 integrates the principal mechanistic pathways linking OPP exposure to possible vascular and metabolic outcomes while highlighting that several connections remain hypothetical in humans. It also separates upstream metabolism from downstream redox, endothelial, inflammatory, lipoprotein, and metabolic pathways so that the current evidentiary gaps are visually explicit.

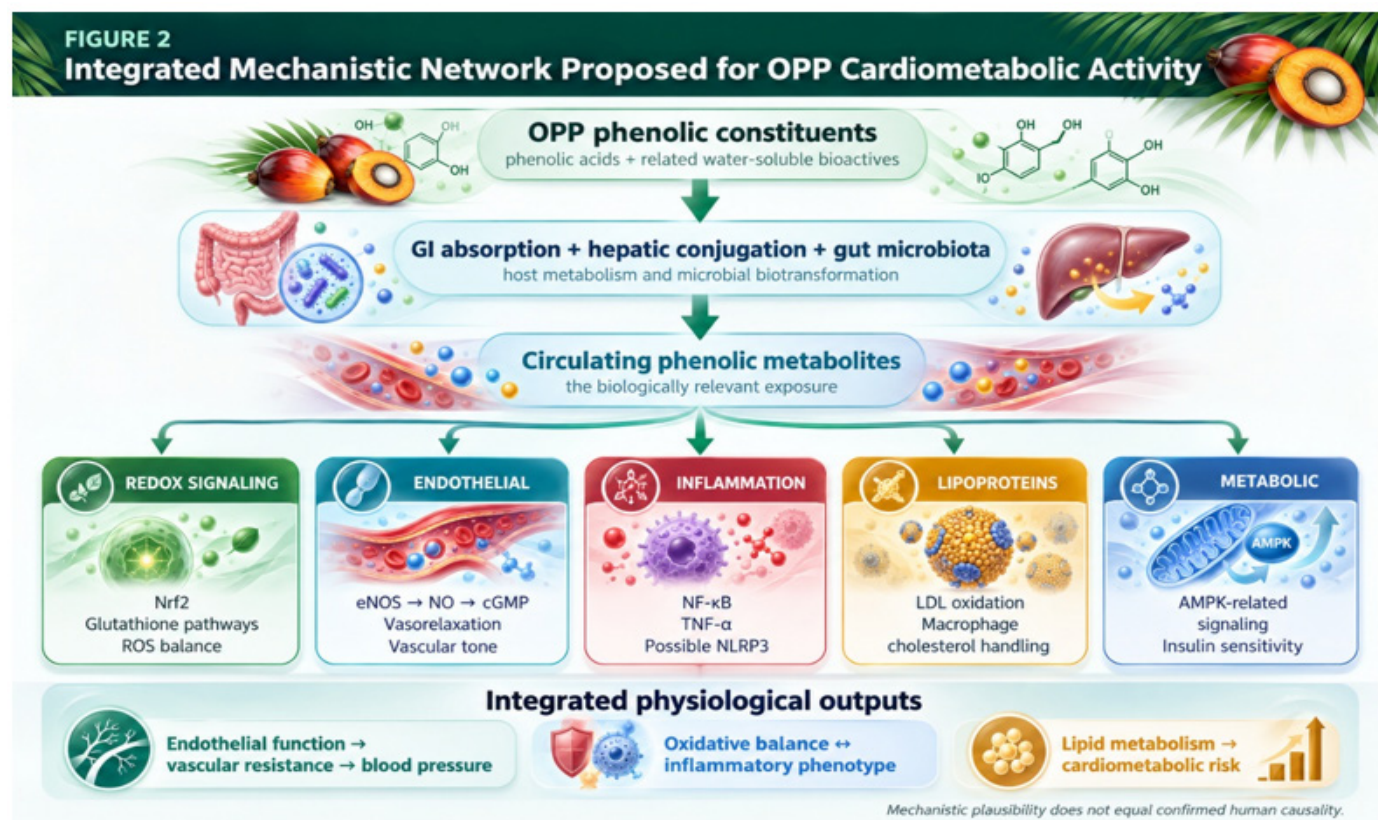


Figure 2: Integrated Mechanistic Network Proposed for OPP Cardiometabolic Activity

The mechanistic network in Figure 2 should be interpreted as a hierarchy of evidence rather than a proven causal pathway. OPP's effects on several branches are supported primarily by experimental evidence or analogy with other polyphenols. Direct human confirmation is strongest for selected antioxidant and inflammatory biomarkers and weakest for eNOS activity, vascular function, pharmacokinetics, and long-term atherosclerotic outcomes.

Antioxidant Status: Biological Activity Without Proof of Cardiovascular Protection

The 2025 phase-I analysis found complex antioxidant responses across OPP doses. The highest dose produced a significant increase in total antioxidant capacity at the intermediate assessment, while the higher-dose groups appeared to better preserve glutathione peroxidase relative to the decline observed in placebo and the 250 mg/day group. Total superoxide dismutase also appeared more stable in OPP groups. Importantly, however, glutathione reductase increased in placebo as well, making treatment specificity uncertain for that marker [19].

A second 2025 publication involving individuals with minor hyperlipidemia reported significantly improved total antioxidant capacity and changes in GSH-Px, glutathione reductase, and superoxide dismutase, together with lower TNF-α after 60 days of 250 mg/day OPP [18]. These findings strengthen evidence that OPP is biologically active in humans.

At the same time, antioxidant biomarkers must be interpreted conservatively. Plasma antioxidant-capacity assays integrate multiple endogenous and dietary influences and do not directly measure prevention of oxidative vascular injury. Indeed, the broader field has moved from simplistic antioxidant-scavenging narratives toward signaling, gene regulation, enzyme modulation, and metabolite-specific mechanisms [1-27]. Total antioxidant capacity is thus most useful when combined with disease-specific markers rather than interpreted as an independent surrogate of clinical benefit[28].

Inflammation: Promising but Undercharacterized

Reduction in TNF-α after OPP supplementation in minor hyperlipidemia provides an important translational bridge between preclinical anti-inflammatory observations and human biology [18]. TNF-α contributes to endothelial activation, insulin resistance, oxidative stress, and atherogenesis, meaning that sustained reductions could potentially have cardiometabolic relevance.

Yet a single inflammatory marker cannot define an anti-inflammatory phenotype. Future studies should incorporate high-sensitivity C-reactive protein, IL-6, MCP-1, soluble ICAM-1, VCAM-1, selectins, and—where feasible—markers related to NLRP3 inflammasome activity. The broader literature indicates that polyphenols can modulate inflammation but that effects vary considerably by compound, dose, population, and baseline inflammatory status [38, 39].

Lipid Effects Are Less Consistent Than Early Expectations

Earlier OPP research generated considerable interest in cholesterol metabolism and LDL oxidation. Mechanistically, phenolic compounds can influence intestinal cholesterol absorption, hepatic lipid pathways, macrophage cholesterol transport, and susceptibility of LDL to oxidative modification [36-53].

The clinical results are more complicated. In the phase-II hyperlipidemia trial, both placebo and OPP groups showed changes in total and LDL cholesterol, while HDL-C increased in the OPP group, making causal attribution to OPP uncertain [17]. In healthy participants, the subsequent dose-ranging analysis did not demonstrate a consistent lipid-lowering effect; some lipid variables increased within treatment groups while remaining in normal ranges [19].

These findings suggest that OPP should not presently be promoted as a lipid-lowering intervention. They also illustrate the importance of comparator-group analysis. A statistically significant change from baseline within an OPP arm does not demonstrate treatment efficacy if a similar change occurs with placebo. This principle is particularly important in nutritional trials where dietary behavior, regression to the mean, and participant awareness can affect lipid measurements.

More broadly, nutraceutical meta-analysis demonstrates that some agents can modify LDL-C, triglycerides, and other lipid endpoints, but effect magnitude and evidence quality vary substantially [15]. OPP will therefore require trials specifically designed around lipid endpoints, with dietary monitoring and adequate statistical power, before a lipid-lowering claim is defensible.

Discussion and Analysis

OPP Should Be Reclassified Conceptually: From “Antioxidant Extract” to Translational Nutraceutical Candidate

The most important conceptual conclusion of this review is that OPP has outgrown the narrow label of antioxidant extract. The relevant contemporary question concerns a multi-component phytochemical preparation moving through an early translational-development pathway. Such a pathway includes raw-material sourcing, extraction chemistry, quality assurance, dosage form, absorption, metabolism, biological targeting, clinical response, safety, and eventual regulation.

This interpretation is consistent with developments across polyphenol science. Dietary polyphenols are increasingly understood as signaling modulators with context-dependent effects, rather than molecules that simply circulate at high concentrations and neutralize radicals stoichiometrically [3-21]. Their cardiometabolic

effects may involve endothelial signaling, gene expression, lipid handling, inflammation, gut microbial transformations, and adaptation of endogenous antioxidant systems.

For OPP, this broader perspective helps reconcile apparently discordant findings. A dose that modifies blood pressure need not be the same dose that maximizes plasma antioxidant capacity. A preparation that produces no substantial LDL-C reduction might still influence vascular tone. A statistically favorable antioxidant assay does not guarantee clinical benefit. The important objective is therefore to identify the causal sequence from exposure to biologically active metabolites and from those metabolites to validated cardiovascular endpoints.

The Dose-Response Paradox May Be the Most Important Scientific Signal

A particularly interesting feature of the 2025 dose-ranging evidence is the absence of a conventional monotonic response. The 250 mg/day dose produced the clearest blood-pressure changes, whereas antioxidant effects appeared differently across the higher-dose groups [19]. If replicated, this observation could fundamentally influence OPP development.

Nutraceutical development often assumes that more active ingredient should produce greater benefit until adverse effects emerge. Polyphenols do not always behave in this manner. Biological effects can exhibit U-shaped, inverted-U-shaped, threshold, saturation, or biphasic patterns because different concentrations activate distinct signaling pathways. Absorption can saturate, microbial metabolism can shift, metabolites can compete for conjugation, and high concentrations may alter adaptive redox signaling.

Baseline physiological status may also change the response curve. A normotensive healthy individual has limited scope for beneficial blood-pressure reduction, whereas a hypertensive participant may show a different optimum; similarly, antioxidant enzymes in a metabolically healthy individual may not respond in the same manner as those in a person with diabetes, obesity, or chronic inflammation. Meta-analytic and umbrella-review evidence on dietary polyphenols likewise shows substantial heterogeneity across interventions, populations, and cardiometabolic outcomes, which cautions against assuming a uniform class effect [45-54].

Figure 3 proposes an endpoint-specific dose-response model rather than depicting efficacy as a straight ascending line. The diagram is intentionally conceptual and should be interpreted as a qualitative synthesis of reported response patterns, not as a plot of measured effect sizes.

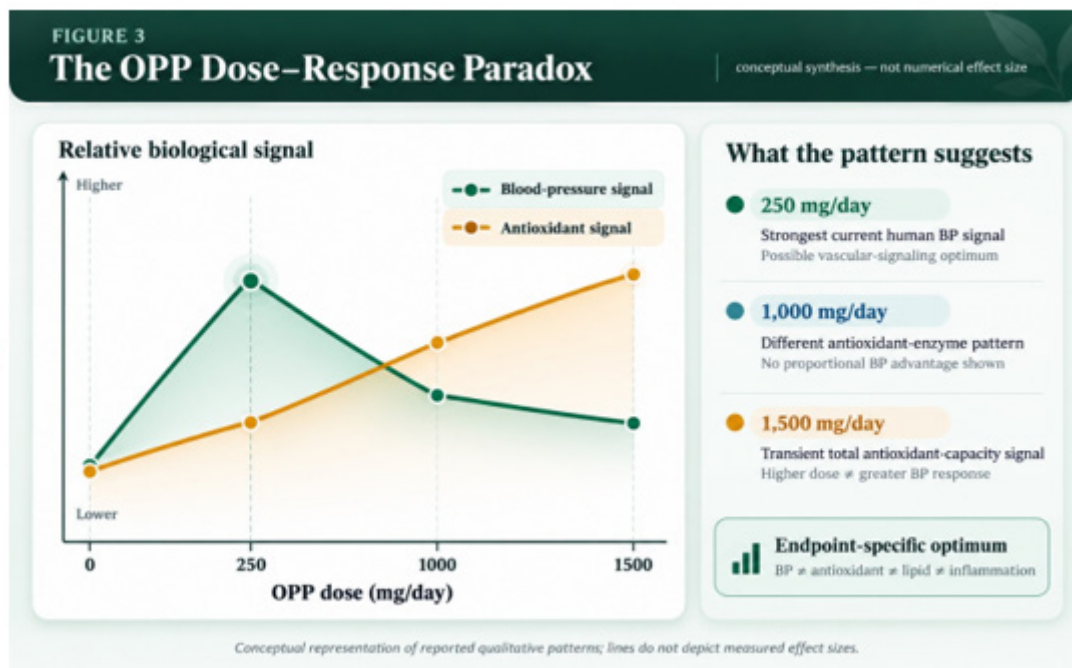


Figure 3: The OPP Dose–Response Paradox

Figure 3 illustrates why future trials should not choose a single high dose merely because it is well tolerated. Formal phase-II dose-ranging studies are needed, potentially testing doses below 250 mg/day and intermediate exposures between 250 and 1,000 mg/day. Pharmacokinetic sampling should occur simultaneously so that dose can be related to systemic metabolite exposure rather than capsule mass alone. The conceptual implication is that the dose associated with an optimal blood-pressure response may differ from doses that optimize antioxidant, lipid, or inflammatory endpoints.

Endothelial Function Should Become the Primary Mechanistic Endpoint

If OPP truly influences blood pressure through vascular relaxation, the next generation of human trials should make endothelial function central rather than peripheral. FMD is particularly attractive because it provides a validated physiological measure of conduit-artery endothelial function. Pulse-wave velocity would add information about arterial stiffness, while continuous or ambulatory BP monitoring would clarify whether vascular effects persist outside clinic visits.

Broader clinical polyphenol research supports this strategy. Dietary polyphenols and flavan-3-ols have been associated with improvements in vascular health, although findings differ by source, dose, and baseline cardiovascular status [34–44]. Meta-analysis of citrus flavonoids likewise suggests measurable endothelial effects in some populations [52]. Anthocyanin-focused evidence further connects polyphenol exposure with endothelial NO formation, oxidative balance, vascular aging, and endothelial senescence [35].

The scientific advantage of direct vascular measurements is that they can separate competing explanations. If OPP reduces office

BP but does not alter ambulatory BP, FMD, arterial stiffness, or NO-related biomarkers, the vascular interpretation would weaken. Conversely, concordant improvements across these measures would substantially strengthen causal plausibility.

Bioavailability Is a Bottleneck, Not a Technical Footnote

OPP studies typically report dose in milligrams of extract, yet extract mass is not equivalent to bioactive exposure. Each preparation contains multiple compounds; each compound can undergo different absorption, conjugation, degradation, and microbial transformation. Human polyphenol metabolism therefore produces a dynamic mixture of parent molecules and metabolites rather than a single pharmacological species.

Gut microbiota add another layer of complexity. Bacterial enzymatic capacity can transform poorly absorbed polyphenols into smaller metabolites with altered bioactivity, while differences between individuals can generate substantially different circulating metabolite profiles from identical dietary exposure [40–42].

Encapsulation should likewise be treated empirically. Although it may protect polyphenols during storage or digestion, human studies indicate that encapsulation can improve, fail to alter, or even reduce bioavailability depending on the compound and technology used [26]. Thus, future OPP formulations require head-to-head pharmacokinetic evaluation of liquid, spray-dried, and encapsulated preparations.

An ideal pharmacokinetic study would obtain serial blood and urine samples after a standardized dose; quantify major OPP phenolics and conjugates by LC-MS/MS; use untargeted metabolomics to detect previously unrecognized products; assess fecal microbiota; and relate metabolite area-under-the-curve values to BP, FMD, and antioxidant/inflammatory responses. Such studies

could identify responder phenotypes and ultimately support precision-nutrition approaches.

Oxidative Stress Should Be Measured Through a Network, Not a Single Score

Current OPP trials have appropriately explored glutathione-related enzymes, SOD, and total antioxidant capacity. The next stage should move toward a systems-level redox phenotype. This is necessary because antioxidant enzymes can increase in response to beneficial adaptive signaling but also in response to greater oxidative challenge. Similarly, unchanged enzyme activity may represent either absence of effect or successful prevention of oxidative stimulation.

Contemporary antioxidant science discourages interpretation of a single global assay as proof of antioxidant protection [28]. A more informative OPP panel would combine total antioxidant capacity with glutathione redox status, lipid peroxidation products, oxidized LDL, protein oxidation, urinary F2-isoprostanes, and markers of NO oxidation. Transcriptomic measures of Nrf2-regulated genes could further indicate whether OPP alters endogenous defense pathways. This approach is particularly important because reduction in oxidative stress should ultimately be linked to vascular or metabolic consequences. Oxidative biomarkers become more clinically informative when changes correlate with improved FMD, arterial stiffness, insulin sensitivity, or inflammatory status.

OPP and LDL Biology: Oxidation May Matter More Than Concentration

The absence of consistent LDL-C lowering does not eliminate potential relevance to atherosclerotic biology. LDL particle oxidation contributes to macrophage uptake and inflammatory plaque development, and polyphenols can modify susceptibility to oxidative processes in experimental settings [37-53].

This suggests that future OPP lipid research should move beyond the conventional four-component lipid panel. ApoB, non-HDL cholesterol, oxidized LDL, LDL particle number, particle size, and lipidomic profiles may offer more mechanistic information. Yet such measures should complement—not substitute for—standard risk factors, because no evidence currently demonstrates that OPP reduces atherosclerotic events.

Distinguishing Biomarker Improvement from Clinical Cardiovascular Prevention

A recurring problem in nutraceutical research is the escalation of language from “biomarker changed” to “cardioprotective.” These are not equivalent claims. A product can increase an antioxidant enzyme without preventing hypertension; lower TNF- α without changing cardiovascular risk; or improve an experimental vascular marker without reducing clinical events.

The evidentiary hierarchy progresses from biological activity to validated mechanistic effects, then to intermediate clinical endpoints, disease-risk modification, and finally hard cardiovascular outcomes. Movement from one level to the next requires pro-

gressively stronger causal, reproducibility, and clinical evidence.

OPP currently occupies the first two levels and has begun to enter the third. It has demonstrated biological activity, short-term tolerability, selected antioxidant and inflammatory effects, and an early blood-pressure signal. It has not established sustained antihypertensive efficacy, prevention of dyslipidemia, reduction of diabetes risk, prevention of myocardial infarction or stroke, or cardiovascular mortality benefit.

The same caution is reflected in international nutraceutical assessments. Even relatively well-studied nutraceutical products often lack evidence for hard cardiovascular endpoints, which limits their role in major clinical guidelines[14]. OPP should therefore not be positioned as an alternative to statins, antihypertensive drugs, diabetes medications, smoking cessation, weight management, exercise, or established dietary interventions.

Standardization Is Part of Clinical Causality

Standardization is sometimes treated as an industrial quality-control issue separate from efficacy. For complex botanical extracts, this separation is artificial. If two batches contain materially different concentrations of active constituents, they are functionally different interventions. Reproducibility of clinical effect therefore depends directly on reproducibility of chemical composition.

Future OPP publications should report at minimum total phenolic content, concentrations of major marker phenolics, moisture, carrier materials, batch number, storage conditions, stability period, contaminant testing, and dissolution or release characteristics. Ideally, chromatographic fingerprints should be deposited as supplementary data.

This requirement becomes even more important if different studies use “250 mg OPP” from preparations manufactured at different times or using modified processing. Without compositional equivalence, nominally identical doses may represent different biological exposures.

Circular Bioeconomy Benefits Should Be Evaluated Independently of Medical Claims

OPP development is attractive because it links resource recovery and health-product innovation. Yet circularity should be quantified rather than presumed. Extraction requires energy, water, filtration materials, drying, encapsulation, packaging, and transport. A complete sustainability assessment should therefore compare the environmental cost of recovery with avoided wastewater-treatment burden, displaced conventional ingredient production, product value, and potential co-products.

Nevertheless, the principle is compelling. Contemporary oil-palm biomass research demonstrates considerable potential for converting processing residues into chemicals, fuels, fibers, nanomaterials, and phenolic ingredients [7-12]. OPP adds a biomedical dimension to this portfolio and could increase value capture from existing production without requiring additional

plantation expansion specifically for phenolic extraction.

Proposed Clinical-Translation Roadmap

The first translational priority is compositional standardization, supported by human pharmacokinetic characterization. Manufacturing specifications should define major phenolic constituents, impurities, stability, dissolution, and inter-batch variability, while liquid, spray-dried, and encapsulated OPP should be compared using targeted and untargeted metabolomics to characterize circulating and urinary metabolites.

The second priority is formal dose-ranging followed by mechanistic vascular testing. Randomized trials should examine doses below and above 250 mg/day rather than assuming that the highest tolerated dose is optimal, and they should incorporate FMD, pulse-wave velocity, ambulatory blood pressure, nitrate/nitrite, cGMP, endothelial inflammatory markers, and oxidative biomarkers.

The third priority is evaluation in metabolically at-risk popu-

lations together with longer-term safety assessment. Prehypertension, established hypertension, dyslipidemia, metabolic syndrome, type 2 diabetes, and older age should be studied as distinct clinical contexts, while six- to twelve-month trials should evaluate sustained responses, adherence, adverse effects, medication interactions, and metabolic outcomes.

Only after these earlier stages demonstrate reproducibility should event-oriented clinical research be considered. Larger studies would then be justified to determine whether OPP-associated biomarker or vascular changes translate into durable reductions in clinically meaningful cardiovascular risk.

Figure 4 summarizes this evidence-maturity pathway and identifies the current location of OPP development. The roadmap distinguishes established chemical and preclinical foundations from emerging human biomarker signals and the major gaps in pharmacokinetics, high-risk populations, direct vascular efficacy, and long-term cardiovascular outcomes.

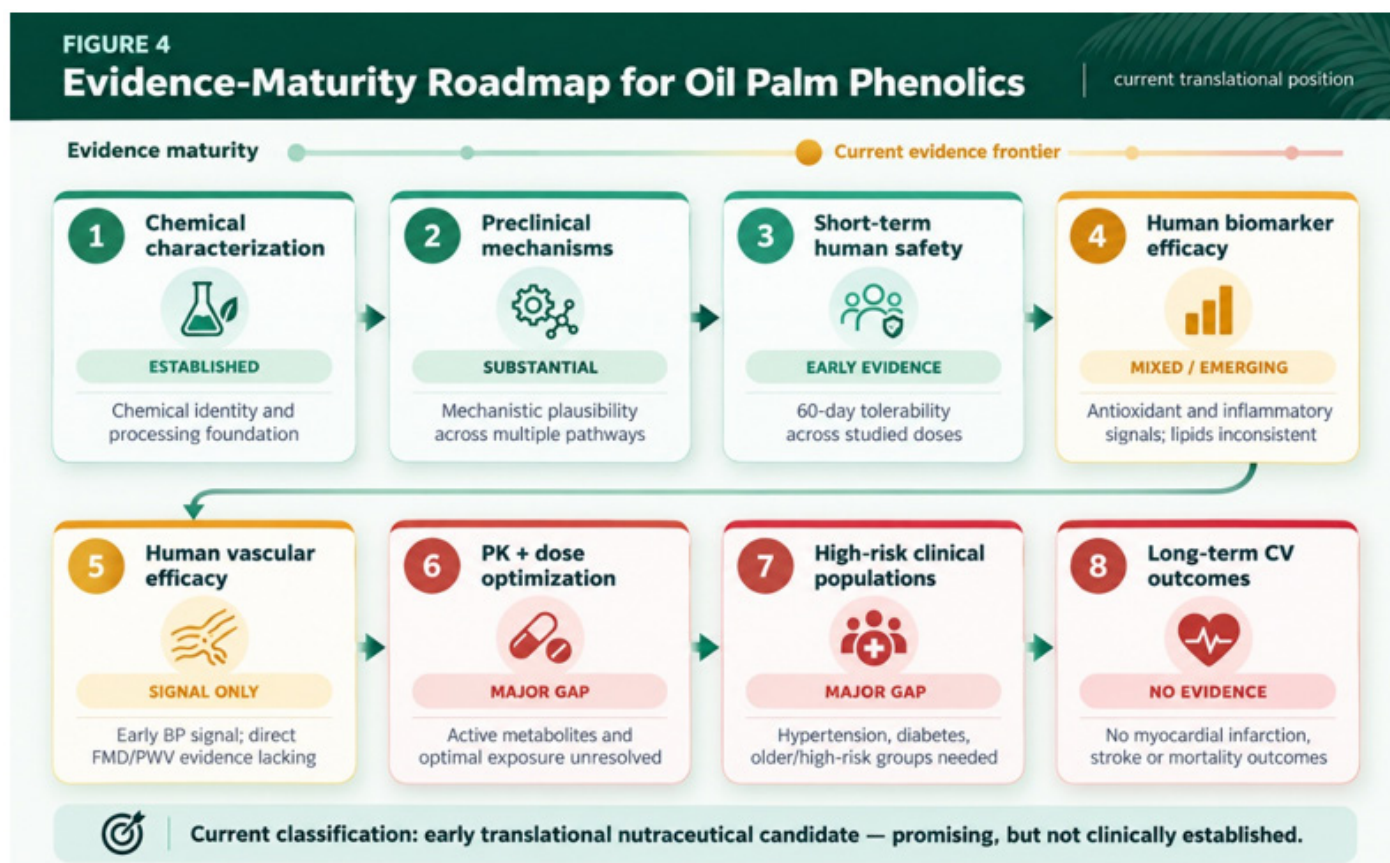


Figure 4 : Evidence-Maturity Roadmap for Oil Palm Phenolics

Figure 4 indicates that OPP should presently be regarded as an early translational nutraceutical candidate rather than a clinically established cardiovascular intervention. The strongest advancement has occurred in short-term safety and biomarker research, while the most important gaps lie in pharmacokinetics, direct vascular testing, clinical-risk populations, long-term exposure,

and cardiovascular outcomes.

Conclusion and Future Directions

Oil palm phenolics represent an unusually compelling intersection between resource recovery, nutritional biochemistry, vascular biology, and nutraceutical innovation. Recovery of water-sol-

uble phenolics from palm-processing streams demonstrates that an agro-industrial output can potentially be transformed into a standardized health-related ingredient. Human research has now advanced sufficiently beyond preclinical experimentation to justify serious translational evaluation.

The existing evidence nevertheless supports caution rather than clinical endorsement. Short-term encapsulated OPP has demonstrated acceptable tolerability across studied doses, while randomized studies have produced signals involving antioxidant defense, inflammatory status, lipid-related parameters, and blood pressure. The recent observation that 250 mg/day was associated with greater blood-pressure modulation than higher doses is particularly important because it challenges a conventional linear dose-response model and raises the possibility of endpoint-specific optimal exposure.

Several decisive gaps remain. The active circulating metabolites of OPP are insufficiently characterized; direct measurements of human endothelial function are lacking; ambulatory blood-pressure evidence is unavailable; lipid effects are inconsistent; follow-up periods remain short; high-risk cardiometabolic populations are inadequately studied; and no evidence demonstrates prevention of cardiovascular events. Furthermore, formulation, chemical standardization, and batch consistency require integration into clinical-trial design rather than treatment as separate manufacturing concerns.

Future OPP research should therefore prioritize pharmacokinetic and metabolomic profiling, formal dose-ranging studies, direct vascular measurements, standardized dietary and lifestyle control, longer exposure, and trials involving hypertensive, dyslipidemic, diabetic, and older populations. Only after reproducibility across these stages should outcome-oriented clinical development be considered.

OPP should accordingly be viewed not as a proven natural antihypertensive or lipid-lowering therapy, but as a promising investigational cardiometabolic nutraceutical whose strongest scientific value currently lies in connecting circular bioresource utilization with rigorously designed human translational medicine. Clinical recommendations should await replicated efficacy, standardized exposure characterization, and longer-term safety and outcome evidence.

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