*Review Article* *Open Access*

**Journal of Biomedical Advancement Scientific Research**

**ISSN: 3069-0854**

**DOI:** doi.org/10.63721/26JBASR0172

# *From Palm-Mill Aqueous Streams to Precision Vascular Nutrition: Oil Palm Phenolics for Early Vascular Dysfunction and Hypertension—A Translational Qualitative Review*

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***Citation:*** *Loso Judijanto (2026) From Palm-Mill Aqueous Streams to Precision Vascular Nutrition: Oil Palm Phenolics for Early Vascular Dysfunction and Hypertension—A Translational Qualitative Review. J. of Bio Adv Sci Research, 2(5):01-19. WMJ/JBASR-172*

***Abstract***

*Oil palm phenolics (OPP) are water-soluble bioactive compounds recovered from aqueous streams generated during palm oil processing, creating an unusual intersection between cardiovascular science, nutraceutical development, and circular bioeconomy. This qualitative literature review critically evaluates contemporary evidence concerning OPP as a potential intervention for early vascular dysfunction and elevated blood pressure. The synthesis integrates OPP chemistry and processing, endothelial pathobiology, phenolic metabolism, mechanistic studies, broader polyphenol evidence, and emerging human trials. OPP contains phenolic constituents including protocatechuic acid, p-hydroxybenzoic acid, hydroxytyrosol, and caffeoylshikimic-acid derivatives. Mechanistically, these compounds may influence oxidative stress, inflammatory signaling, Akt/eNOS-dependent nitric-oxide bioavailability, vascular tone, and endothelial homeostasis. Human evidence has progressed from Phase I safety evaluation to Phase II cardiometabolic studies. Short-term supplementation has generally demonstrated acceptable tolerability, while emerging trials suggest effects on triglycerides in selected hyperlipidemic participants, antioxidant and inflammatory biomarkers, and office blood pressure. Nevertheless, evidence remains insufficient to classify OPP as an antihypertensive intervention. Major uncertainties involve pharmacokinetics, nonlinear dose-response relationships, ambulatory blood pressure, endothelial function, arterial stiffness, long-term safety, drug interactions, and responder heterogeneity. A precision-nutraceutical development framework is proposed integrating standardized chemical fingerprints, metabolomics, microbiome-related metabotypes, biomarker-guided dosing, and clinically meaningful vascular endpoints.*

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**Submitted:** 05.09.2026 **Accepted**: 15.09.2026 **Published**: 21.09.2026

**Keywords:** Oil Palm Phenolics, Hypertension, Endothelial Dysfunction, Nitric Oxide, Oxidative Stress, Inflammation, Polyphenols, Nutraceuticals, Precision Nutrition, Circular Bioeconomy

**JEL Classification Codes:** I12; I18; Q16; Q53; O32.

## Introduction

### Cardiovascular Prevention beyond Established Hypertension

Elevated blood pressure remains one of the most consequential modifiable determinants of cardiovascular morbidity and mortality. Contemporary hypertension guidelines increasingly conceptualize cardiovascular risk along a continuum rather than as a binary transition from "normal" to "hypertensive" blood pressure. The 2023 European Society of Hypertension guideline, the 2024 European Society of Cardiology guideline, and the 2025 AHA/ACC guideline all reinforce the importance of accurate diagnosis, lifestyle interventions, overall cardiovascular-risk assessment, and timely pharmacological treatment when indicated (Mancia et al., 2023; McEvoy et al., 2024; Jones et al., 2025). Earlier International Society of Hypertension guidance similarly emphasized population-wide prevention and standardized blood pressure assessment (Unger et al., 2020).

The vascular abnormalities that eventually support sustained hypertension can begin before overt clinical disease. Reduced endothelial nitric-oxide (NO) bioavailability, excessive reactive oxygen species (ROS), low-grade vascular inflammation, altered endothelin signaling, activation of the renin–angiotensin–aldosterone system (RAAS), abnormal vascular smooth-muscle behavior, glycocalyx degradation, and progressive arterial stiffening interact to impair vascular homeostasis (Touyz et al., 2020; Griendling et al., 2021; Wu et al., 2021; de Oliveira et al., 2022; Foote et al., 2022; Tomiyama, 2023). Endothelial dysfunction can therefore be viewed both as a marker of cumulative cardiovascular injury and as a potentially modifiable component of the pathway linking metabolic and inflammatory stress with future hypertension (Maruhashi et al., 2020; Behnoush et al., 2023; Caminiti et al., 2024; Auger et al., 2024).

This pathophysiological continuum creates interest in preventive approaches capable of acting before advanced vascular remodeling becomes established. Such interest should not be misunderstood as evidence that nutraceuticals can substitute for antihypertensive drugs. Contemporary pharmacological therapy is supported by extensive cardiovascular-outcome evidence, whereas most nutraceutical candidates remain supported primarily by mechanistic studies and intermediate outcomes. The more appropriate question is whether selected food-derived or plant-derived compounds could complement diet, exercise, weight control, sodium reduction, and clinically indicated pharmacotherapy by improving early vascular biology in defined populations (Liu et al., 2025).

### Why Oil Palm Phenolics are Scientifically Distinctive

Oil palm phenolics constitute an unusual candidate because they originate not principally from the oil fraction consumed as food, but from water-rich vegetation liquor and other aqueous streams generated during palm-fruit processing. During conventional milling, large quantities of biologically active water-soluble compounds can enter process-water streams. Technologies for recovering these compounds have created concentrated preparations generally described as oil palm phenolics or water-soluble palm-fruit extracts (Ibrahim et al., 2020; Gonzalez-Diaz et al., 2021; Dayoob et al., 2025). This distinction is essential because conclusions regarding palm oil fatty-acid composition cannot simply be applied to OPP, and vice versa.

OPP preparations contain several phenolic acids and related compounds, including protocatechuic acid (PCA), p-hydroxybenzoic acid, hydroxytyrosol and caffeoylshikimic-acid derivatives. The exact chemical profile depends on plant material, processing, concentration, drying, and formulation. Recent work comparing drying technologies demonstrates that processing choices can influence physical characteristics and preservation of phenolic constituents, illustrating why "OPP" should not be treated as a chemically invariant intervention (Dayoob et al., 2025). Broader palm-bioactive research likewise emphasizes extraction, concentration, fractionation and encapsulation as important determinants of stability and functional performance (Olivares-Tenorio et al., 2024).

The environmental origin of OPP adds a circular-bioeconomy dimension. Palm-oil processing creates substantial aqueous and solid by-products that require treatment, resource recovery or disposal. Recent reviews of palm-oil mill effluent (POME) technologies increasingly emphasize valorization and biorefinery concepts alongside pollution reduction (Cheng et al.,

2021; Ratnasari et al., 2022; Meena et al., 2023). Recovering a chemically standardized phenolic fraction could therefore generate value from a stream that would otherwise contribute principally to wastewater-management burdens. Importantly, however, environmental valorization and therapeutic efficacy are logically separate propositions. A material can be environmentally attractive without being clinically effective, and biomedical claims require independent validation.

## Transition from Preclinical Promise to Human Investigation

Until relatively recently, the major weakness of the OPP cardiovascular literature was its reliance on animal models, cell experiments and indirect mechanistic evidence. The translational landscape changed when randomized human studies began to appear. A 2022 randomized, double-blind, placebo-controlled Phase I study assigned 100 healthy adults to placebo or 250, 1,000 or 1,500 mg/day of encapsulated OPP for 60 days. No serious adverse events or clinically important biochemical or hematological abnormalities were identified, supporting short-term tolerability up to 1,500 mg/day (Muhammad Ismail Tadj et al., 2022).

A subsequent Phase II trial randomized 50 adults with minor hyperlipidemia to placebo or 250 mg/day OPP for 60 days. The intervention did not produce broad improvements across all lipid variables, although triglycerides improved in male participants, and no serious safety signal was identified. This result is important precisely because it is not uniformly positive: it suggests that the biological effects of OPP may depend on phenotype, outcome selected, or subgroup characteristics rather than producing universal cardiometabolic improvement (Muhammad Ismail Tadj et al., 2023).

More recent evidence adds two additional dimensions. A 2025 randomized study in participants with minor hyperlipidemia reported improvement in antioxidant status and modulation of inflammatory biomarkers, including reduction in TNF-α, following OPP supplementation (Ibrahim et al., 2025). Another 2025 analysis of 97 healthy adults assigned to placebo or 250, 1,000 and 1,500 mg/day reported that 250 mg/day was associated with reductions in office systolic and diastolic blood pressure after 60 days, whereas higher doses produced stronger signals for selected antioxidant measures; lipid profiles were not significantly altered (Fairus et al., 2025).

These findings create a more interesting question than whether OPP "works." The emerging evidence raises the possibility that different biological outcomes have different dose-response relationships and that clinically relevant effects may not increase monotonically with total OPP exposure. This review therefore evaluates OPP through a Source–Exposure–Mechanism–Phenotype–Response–Translation framework, asking what is contained in an OPP preparation, what reaches biological targets, which vascular mechanisms are plausible, which individuals may respond, which outcomes have actually changed in humans, and what remains necessary before OPP could credibly become a precision cardiometabolic nutraceutical.

## Literature Review

### Early Vascular Dysfunction as a Therapeutic Target

The endothelium regulates vascular tone, thrombosis, inflammation, permeability and interactions between circulating cells and the vessel wall. Under physiological conditions, endothelial nitric-oxide synthase (eNOS) generates NO, which diffuses into vascular smooth muscle and promotes relaxation through cyclic-guanosine-monophosphate signaling. Hypertension and cardiometabolic disease disrupt this balance through reduced NO production, increased NO degradation and eNOS uncoupling (Wu et al., 2021; de Oliveira et al., 2022). Oxidative stress is not simply an excess of chemically reactive molecules; it represents dysregulated redox signaling in which ROS generation exceeds compensatory antioxidant and repair systems and begins altering vascular signaling, inflammation and structural remodeling (Touyz et al., 2020; Griendling et al., 2021).

Inflammation amplifies this process. Innate and adaptive immune mechanisms can increase vascular ROS, cytokine production and endothelial activation, while endothelial cells themselves increase adhesion molecules such as VCAM-1 and ICAM-1, facilitating recruitment of inflammatory cells. Macrophages, T lymphocytes and other immune populations contribute to the vascular and renal processes supporting elevated blood pressure (Zhang et al., 2023; Aboukhater et al., 2023). NF-κB is particularly important because it

integrates oxidative and inflammatory stimuli, whereas Nrf2-dependent signaling contributes to endogenous antioxidant and cytoprotective responses (Penna & Pagliaro, 2025).

The RAAS and endothelin system further connect inflammation and vascular tone with structural remodeling. Angiotensin II can promote vasoconstriction, oxidative stress and vascular smooth-muscle growth, while endothelin-1 contributes to increased vascular resistance and remodeling (Kostov, 2021). Chronic blood pressure elevation itself damages arteries, creating a bidirectional relationship between hypertension and arterial stiffness. Increased collagen deposition, elastin degradation, inflammation and endothelial dysfunction reduce arterial compliance; a stiffer arterial tree in turn increases systolic load and transmits pulsatile energy toward target organs (Kim, 2023; McNally et al., 2024).

This network explains why a nutraceutical that changes only an unspecific antioxidant assay cannot automatically be considered vasoprotective. A convincing vascular intervention should ultimately influence outcomes closer to vascular physiology, such as flow-mediated dilation (FMD), ambulatory blood pressure, pulse-wave velocity (PWV), endothelial inflammatory markers or other validated measures.

## Polyphenols as Vascular Signaling Molecules Rather than Simple Antioxidants

Polyphenol research has gradually shifted from a model based predominantly on chemical radical scavenging toward one emphasizing signaling, metabolism and host–microbiome interactions. Reviews of dietary polyphenols describe effects on eNOS, AMPK, Nrf2, NF-κB, SIRT1 and related pathways relevant to endothelial function and vascular inflammation (Grosso et al., 2022; Parsamanesh et al., 2021; Reis & Rocha, 2024). This broader framework is particularly important for OPP because physiologically achievable concentrations of phenolic compounds may be too low to account for human effects through stoichiometric antioxidant scavenging alone.

Clinical meta-analyses provide general support for modest vascular effects of some polyphenol-rich interventions while simultaneously revealing substantial heterogeneity. Kiyimba et al. (2023), analyzing randomized trials of polyphenol-rich foods and purified extracts, found improvements in several cardiometabolic markers and showed that effects were not identical across food-based and extract-based interventions. Wan et al. (2024), synthesizing hundreds of trials, similarly reported small but significant changes in multiple cardiometabolic risk factors for several polyphenol classes. These findings demonstrate biological plausibility but cannot be used as direct proof that OPP has the same magnitude of effect.

Specific subclasses also demonstrate clinically relevant vascular activity. Meta-analysis of proanthocyanidin trials reported reductions in systolic and diastolic blood pressure, with some analyses suggesting greater effects at lower doses, although evidence was based on relatively few studies (Ren et al., 2021). Catechin supplementation has been associated with improved FMD and reductions in PWV and augmentation index (Shafabakhsh et al., 2020). A 2024 dose-response meta-analysis found that citrus-flavonoid supplementation increased FMD, although heterogeneity remained substantial (Jalili et al., 2024). Most recently, a large meta-analysis of flavan-3-ol interventions reported reductions in office and ambulatory blood pressure and improvements in FMD, with larger BP effects among participants beginning with elevated or hypertensive blood pressure (Lagou et al., 2025).

That baseline-dependence is highly relevant to OPP. A phenolic preparation might show little effect in an individual whose endothelial function and blood pressure are already optimal but produce larger changes in participants with endothelial dysfunction, elevated BP, obesity or inflammatory metabolic phenotypes. This supports a precision-nutrition perspective rather than expecting identical effects across healthy and diseased populations.

## Phenolic Metabolites and Mechanistic Relevance to OPP

Protocatechuic acid deserves particular attention because it is present in OPP and is also generated as a metabolite of other dietary polyphenols. Experimental evidence at physiologically relevant concentrations indicates that PCA can preserve endothelial function during inflammatory stress. Chook et al. (2023) demonstrated that PCA improved endothelium-dependent relaxation and suppressed ROS, MCP-1, VCAM-1 and ICAM-1

while increasing Akt and eNOS phosphorylation in inflammatory endothelial models.

Festa et al. (2024) similarly reported that PCA and vanillic acid improved NO bioavailability under TNF-α-induced oxidative and inflammatory stress through Akt/eNOS-related mechanisms. Importantly, the compounds did not simply elevate NO indiscriminately in unstressed endothelial cells; their protective effects were more evident in an inflammatory environment. This observation is consistent with the possibility that phenolic efficacy depends on pathological context and may be difficult to detect in metabolically healthy populations (Festa et al., 2024).

Subsequent research showed that PCA and vanillic acid can attenuate monocyte adhesion to endothelial cells through pathways involving NF-κB and Nrf2, further connecting phenolic metabolism with early vascular inflammation (Festa et al., 2025). Experimental cardiovascular studies also associate PCA with attenuation of adrenergic cardiac hypertrophy, regulation of Nrf2/HO-1-related defenses and improved cardiometabolic parameters in animal models (Bai et al., 2021; Li et al., 2023; Li et al., 2020).

These studies do not establish that PCA is solely responsible for OPP effects. OPP is a mixture, and constituents may act additively, synergistically or independently. Furthermore, orally consumed compounds undergo absorption, conjugation, microbial catabolism and systemic metabolism before reaching vascular tissue. Nonetheless, the PCA literature provides an important mechanistic bridge between the chemical composition of OPP and clinically plausible endothelial pathways.

## Bioavailability and the Case for Precision Nutraceutical Development

A central limitation of traditional polyphenol research is the assumption that the administered dose closely reflects biologically active exposure. In reality, the parent compound measured in a capsule may represent only a fraction of the molecules encountered by endothelial tissue. Some polyphenols are absorbed in the small intestine, but substantial amounts can reach the colon, where microorganisms transform them into smaller phenolic metabolites that are subsequently absorbed and conjugated (Williamson, 2025). Processing and delivery technologies—including encapsulation, fermentation and nanoformulations—can further alter bioaccessibility and exposure (Polia et al., 2022).

Interindividual variation is especially important. Favari et al. (2024) reviewed 153 human studies and concluded that polyphenol ADME shows pronounced variability related particularly to gut-microbial composition and activity, with additional contributions from genetics, sex, age, ethnicity, BMI, physiological status, diet and physical activity. Individuals may behave as high or low metabolite producers, or may form qualitatively different metabolic profiles. Such differences provide a credible biological explanation for heterogeneous clinical responses to identical nutraceutical doses.

Cardiovascular studies increasingly link microbial metabolism with vascular outcomes. Human cohort evidence has connected the polyphenol metabolome and gut microbiome with cardiovascular health phenotypes (Li et al., 2023). Reviews focused on hypertension also describe gut-derived lipopolysaccharide/TLR4 signaling, altered barrier integrity and microbial metabolites as potential contributors to endothelial dysfunction and vascular inflammation (Grylls et al., 2021). Berry-polyphenol trials likewise illustrate the emerging intersection between microbial changes and blood pressure responses (Sweeney et al., 2022).

Accordingly, “250 mg OPP” should ultimately be regarded as an input, not a complete pharmacological description. Precision OPP research needs to establish which compounds and metabolites appear in plasma, at what concentrations, over what time course, and whether metabolic patterns identify responders.

## Method

### Review Design

This study was designed as a critical qualitative literature review, not as a systematic literature review or meta-analysis. Its purpose was interpretive and translational: to integrate evidence from OPP chemistry, palm-processing technology, molecular vascular biology, preclinical research, human clinical trials, polyphenol pharmacology, metabolomics and hypertension science into a coherent explanation of the current developmental status of OPP.

A qualitative approach was selected because the available evidence is heterogeneous in design and biological level. Direct OPP studies include chemical characterization, animal experiments, safety studies, randomized trials in healthy adults, and small trials in participants with cardiometabolic abnormalities. These cannot meaningfully be combined into a single pooled effect estimate. Evidence concerning PCA and other phenolic metabolites was included to evaluate mechanism rather than to estimate the clinical effect of OPP itself.

### Literature Identification

The review emphasized peer-reviewed literature published from January 2020 through September 2026. Searches were conceptually organized around PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect and major publisher databases. Search concepts included combinations of "oil palm phenolics," "water-soluble palm fruit extract," "oil palm aqueous by-products," "hypertension," "blood pressure," "endothelial dysfunction," "nitric oxide," "eNOS," "vascular inflammation," "arterial stiffness," "flow-mediated dilation," "protocatechuic acid," "polyphenol bioavailability," "microbiome," "metabotype," and "cardiometabolic nutraceutical."

The search was purposive rather than exhaustive. Priority was given to direct OPP clinical studies, contemporary hypertension guidelines, mechanistic studies using physiologically meaningful phenolic concentrations, meta-analyses of human polyphenol interventions, and recent studies relevant to OPP formulation and resource recovery. References were retained when they contributed directly to one or more thematic questions.

### Evidence Synthesis

Evidence was coded conceptually into seven interacting domains: source, exposure, mechanism, phenotype, response, heterogeneity, and translation. The source domain addressed chemical composition, extraction and formulation. Exposure included dose, absorption, metabolites and microbial transformation. Mechanistic themes included oxidative stress, inflammatory signaling, Akt/eNOS, NO, RAAS and vascular remodeling. Phenotype included healthy adults, minor hyperlipidemia, elevated BP and future hypertension populations. Response included BP, lipids, antioxidant and inflammatory markers and proposed vascular endpoints.

The analysis deliberately distinguished mechanistic plausibility from demonstrated clinical efficacy. Improvement in an antioxidant biomarker was not regarded as equivalent to improved endothelial function; changes in office BP were not regarded as evidence of cardiovascular-event prevention; subgroup findings were treated cautiously; and findings in healthy volunteers were not automatically generalized to patients with hypertension.

### Critical-Appraisal Principles

Several methodological issues were considered throughout the synthesis. First, the direct human OPP evidence remains numerically small and is concentrated within a relatively narrow research network. Second, studies generally used short intervention periods of approximately 60 days. Third, clinical trials have used intermediate outcomes rather than hard cardiovascular outcomes. Fourth, multiple endpoints and subgroup analyses increase the possibility of chance findings. Fifth, an intervention derived from palm-processing by-products carries potential commercial and institutional interests that should be transparently reported and independently replicated.

No PRISMA diagram was produced because the article does not claim systematic exhaustive retrieval. Similarly, no formal pooled meta-analysis was conducted. The objective was to generate a critical translational interpretation of a developing research field.

## Results: Thematic Findings

### Theme 1: OPP is a Chemically Distinct Palm-Derived Biomedical Resource

The first thematic finding is that OPP should be conceptualized as a water-soluble phenolic platform, not as conventional edible palm oil. Recent palm-processing literature demonstrates that palm-oil production generates chemically diverse by-products containing potentially recoverable bioactive compounds (Gonzalez-Diaz et al., 2021; Cheng et al., 2021; Ratnasari et al., 2022; Meena et al., 2023). The recovery of OPP therefore represents both a biochemical separation problem and a potential high-value application of circular processing.

A therapeutically credible OPP product nevertheless

requires chemical consistency. Dayoob et al. (2025) confirmed that water-soluble palm-fruit extract contains PCA, p-hydroxybenzoic acid and three caffeoylshikimic-acid isomers and showed that freeze- and spray-drying influence product characteristics. Broader palm-bioactive literature likewise emphasizes that extraction and encapsulation technologies can modify stability and functional performance (Olivares-Tenorio et al., 2024). Consequently, future OPP trials should report not only milligrams of total extract but also quantitative marker-compound profiles.

Figure 1 summarizes the translational sequence through which an aqueous palm-processing stream must pass before it can become a reproducible biomedical intervention. The pathway highlights that recovery, standardization, formulation, human exposure, and vascular validation are sequential rather than interchangeable requirements.

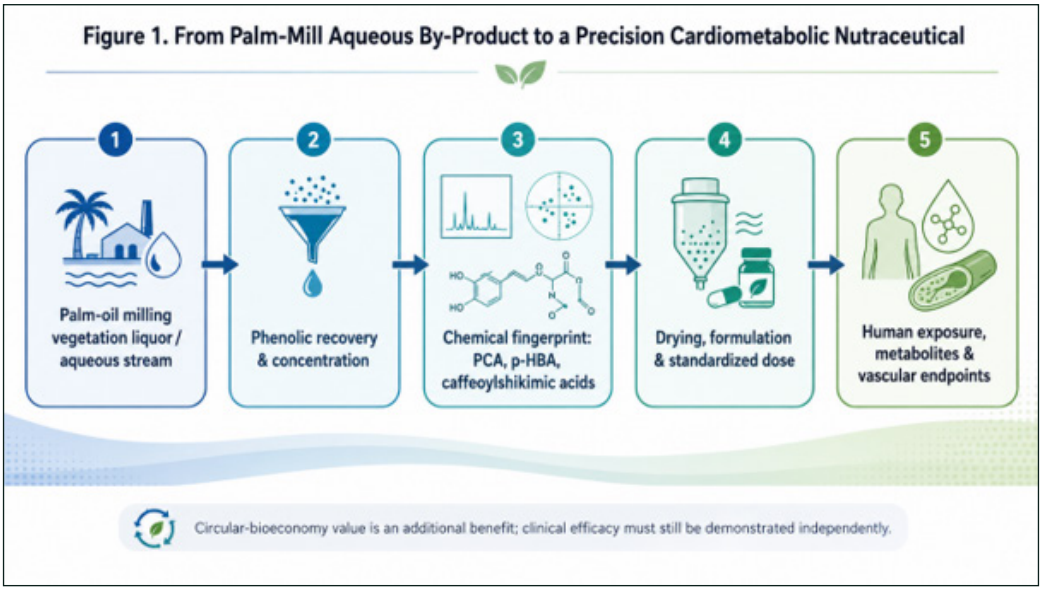


**Figure 1**: From Palm-Mill Aqueous By-Product to a Precision Cardiometabolic Nutraceutical

The figure emphasizes that circularity is only the starting point. Recovery must be followed by purification, chemical fingerprinting, stability control and standardized formulation before a meaningful biological dose can be defined. After ingestion, the administered extract is further transformed by human absorption, conjugation and microbial metabolism, and only then can vascular exposure and clinical outcomes be evaluated. The translational value of OPP therefore depends on connecting processing science with pharmacokinetics rather than assuming that identical extract mass necessarily represents identical biological exposure.

## Theme 2: OPP is Mechanistically Compatible with early Endothelial Protection

The second theme is that OPP is biologically plausible as a vascular-modifying intervention because several components and related metabolites intersect with pathways central to endothelial dysfunction. Hypertension-related vascular injury involves ROS accumulation, inflammation, eNOS dysfunction, altered NO bioavailability, endothelial activation, vascular smooth-muscle changes and arterial remodeling (Touyz et al., 2020; Griendling et al., 2021; Wu et al., 2021; de Oliveira et al., 2022; Aboukhater et al., 2023; Zhang et al., 2023).

PCA provides the clearest contemporary mechanistic bridge. At physiologically relevant concentrations, PCA improved endothelial relaxation and reduced inflammatory endothelial signaling while enhancing Akt/eNOS activation (Chook et al., 2023). Related phenolic-metabolite studies demonstrated improved NO availability during TNF-α-induced stress and reduced endothelial-monocyte adhesion through Nrf2/NF-κB-related pathways (Festa et al., 2024; Festa et al., 2025). These effects support a signaling-based interpretation of OPP rather than a simplistic chemical-antioxidant model.

Figure 2 illustrates how OPP-derived or OPP-related phenolic metabolites may intersect with multiple components of early vascular dysfunction. It also distinguishes upstream redox and inflammatory mechanisms from downstream vascular outcomes that still require direct clinical confirmation.

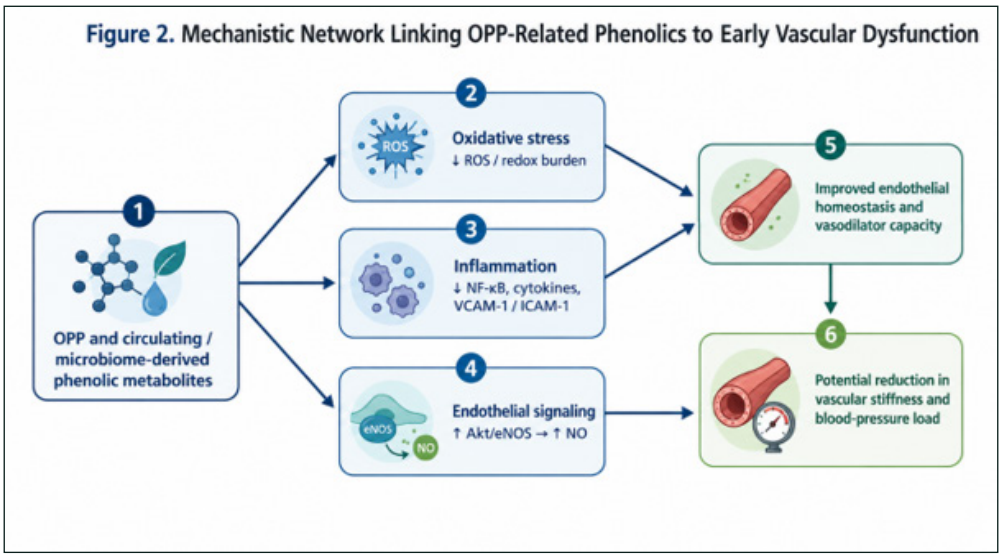


**Figure 2:** Mechanistic Network Linking OPP-Related Phenolics to Early Vascular Dysfunction

The model does not imply that every pathway has been directly demonstrated in humans receiving OPP. Instead, it distinguishes a plausible mechanistic network in which decreased oxidative burden and inflammatory signaling can preserve Akt/eNOS activity and NO bioavailability, thereby supporting endothelial vasodilator capacity. These proximal endothelial effects may eventually influence vascular resistance and arterial stiffness, but this downstream sequence remains to be directly demonstrated in controlled OPP trials using FMD, PWV and ambulatory BP measurements.

### Theme 3: Short-Term Human Tolerability is better Established than Vascular Efficacy

The 2022 Phase I randomized trial provides the strongest direct foundation for short-term safety. One hundred healthy volunteers received placebo or OPP doses of 250, 1,000 or 1,500 mg/day for 60 days. Minor adverse events occurred, particularly at higher exposure, but serious adverse events and clinically significant abnormalities in hematology, hepatic or renal parameters were not identified (Muhammad Ismail Tadj et al., 2022). This supports tolerability over two months but cannot establish long-term safety, safety during pregnancy, safety in older multimorbid populations or interactions with cardiovascular medications.

The 2023 Phase II study extended clinical investigation into adults with minor hyperlipidemia. Fifty participants were randomized to placebo or 250 mg/day OPP. Broad lipid improvement was not demonstrated, although triglycerides declined in male participants, and short-term safety findings were reassuring (Muhammad Ismail Tadj et al., 2023). This is a useful translational result because it demonstrates that an "optimal" dose identified in healthy participants does not automatically produce uniform efficacy when transferred to a target-risk population.

The subsequent 2025 Journal of Functional Foods study strengthened evidence for biological activity in minor hyperlipidemia by reporting increased antioxidant capacity and modulation of inflammatory parameters, including TNF-α (Ibrahim et al., 2025). These outcomes are mechanistically relevant but remain intermediate biomarkers. Reduction in TNF-α does not establish improvement in endothelial function, arterial stiffness or cardiovascular events.

Table 1 synthesizes the direct human OPP studies that currently anchor the translational argument. Taken together, these trials show a progression from short-term safety to selected cardiometabolic signals, while also demonstrating that efficacy remains outcome- and population-dependent.

**Table 1**: Direct Human Evidence for Oil Palm Phenolics, 2022-2025

| Study | Participants and intervention | Main findings | Translational interpretation |
|---|---|---|---|
| Muhammad Ismail Tadj et al. (2022) | 100 healthy adults; placebo or 250, 1,000, or 1,500 mg/day encapsulated OPP for 60 days. | No serious adverse events or clinically important hematologic, hepatic, or renal abnormalities were reported across the tested doses. | Supports short-term tolerability up to 1,500 mg/day but does not establish long-term or antihypertensive efficacy. |
| Muhammad Ismail Tadj et al. (2023) | 50 adults with minor hyperlipidemia; placebo or 250 mg/day OPP for 60 days. | No broad improvement across lipid variables; triglycerides declined in male participants, with reassuring short-term safety findings. | Suggests phenotype- or subgroup-dependent cardiometabolic effects that require larger confirmatory studies. |
| Ibrahim et al. (2025) | 50 adults with minor hyperlipidemia; placebo or 250 mg/day OPP for 60 days. | Total antioxidant capacity and several antioxidant parameters improved, and TNF-alpha was reduced by day 60. | Demonstrates biological activity in a risk population, but biomarkers remain intermediate rather than vascular efficacy outcomes. |
| Fairus et al. (2025) | 97 healthy adults completing the trial; placebo or 250, 1,000, or 1,500 mg/day OPP for 60 days. | The 250 mg/day group showed within-group reductions in office SBP and DBP; higher doses produced stronger signals for selected antioxidant measures. | Provides an early blood-pressure signal but requires confirmation with between-group effects, ABPM, and hypertensive populations. |

The table shows that the human evidence is still concentrated in short, small trials using intermediate outcomes. Accordingly, the strongest next-step evidence would come from prospectively powered trials using ambulatory blood pressure, endothelial function, arterial stiffness, and prespecified between-group comparisons.

### Theme 4: Blood-Pressure Effects are Promising but Remain Preliminary

The most directly relevant OPP finding for hypertension appeared in 2025. In a double-blind placebo-controlled study involving 97 healthy adults assigned to placebo, 250, 1,000 or 1,500 mg/day for 60 days, the 250 mg/day group showed significant within-group reductions in systolic and diastolic blood pressure by day 60. Higher OPP doses had greater effects on selected antioxidant measures, including preservation of glutathione-peroxidase activity and improvement in total antioxidant capacity, whereas lipid profiles were not significantly altered (Fairus et al., 2025).

This finding deserves interest but also methodological restraint. Participants were healthy rather than hypertensive; office blood pressure was used rather than 24-hour ambulatory monitoring; treatment lasted only 60 days; and the trial was not designed to demonstrate cardiovascular-event reduction. Moreover, a statistically significant within-group change does not necessarily provide the same causal evidence as a clearly significant treatment-

by-time difference against placebo. Future reports should prioritize prespecified between-group contrasts, confidence intervals and clinically interpretable effect sizes.

A further challenge is reproducibility. Contemporary guidelines increasingly recognize the importance of out-of-office BP because office measurements can be affected by white-coat responses, masked hypertension, measurement variability and regression to the mean (Cepeda et al., 2023; Cheng and Li, 2022). A future OPP study seeking to establish an antihypertensive effect should therefore use validated 24-hour ambulatory blood pressure monitoring as a central endpoint.

### Theme 5: OPP may Exhibit Nonlinear and Endpoint-Specific Dose-Response Behavior

Perhaps the most conceptually important human finding is the lack of a simple linear relationship between dose and all outcomes. The lowest studied dose, 250 mg/day, produced the clearest office-BP signal in the 2025 healthy-adult study, whereas higher doses generated stronger responses in some antioxidant markers (Fairus et al., 2025). If replicated, this pattern would argue against a simplistic assumption that more OPP necessarily produces greater vascular benefit.

Several explanations are plausible. First, endothelial signaling may exhibit threshold or biphasic responses. Second, higher doses may alter metabolic pathways or conjugation in ways that do not proportionally increase concentrations of the most biologically relevant metabolite. Third, baseline BP may modify effect size. Large-scale flavan-3-ol evidence indicates that blood pressure reductions are greater among individuals with higher baseline BP, suggesting that physiological room for improvement influences observed effects (Lagou et al., 2025). Fourth, small sample sizes and multiple endpoints can create apparent dose patterns through statistical variation.

Evidence from other polyphenols also demonstrates that dose-response assumptions can be misleading. Ren et al. (2021) reported meaningful BP reductions in analyses of lower-dose proanthocyanidin interventions, while different polyphenol classes show distinct effects across FMD, PWV, BP and metabolic markers (Shafabakhsh et al., 2020; Jalili et al., 2024; Wan et al., 2024). Thus, dose optimization for OPP should be outcome-specific and pharmacokinetically informed rather than based solely on maximal tolerated exposure.

### Theme 6: Antioxidant Improvement is not Equivalent to Vascular Efficacy

The OPP literature repeatedly reports antioxidant outcomes, but total antioxidant capacity, glutathione-related enzymes or other systemic oxidative markers should not be treated as validated surrogates for vascular benefit. Contemporary vascular biology understands ROS as signaling molecules with compartment-specific roles. Removing all ROS is neither achievable nor physiologically desirable; the relevant objective is restoration of abnormal redox signaling and preservation of NO-dependent vascular homeostasis (Touyz et al., 2020; Griendling et al., 2021).

A stronger translational program should therefore measure mechanistically proximal vascular outcomes. FMD is an established non-invasive measure of endothelium-dependent dilation, with contemporary work providing standardized reference approaches (Maruhashi et al., 2020). PWV provides information regarding large-artery stiffness and has prognostic relevance in hypertension (Kim, 2023; McNally et al., 2024). Biomarkers such as endocan may provide additional evidence of endothelial activation, although their clinical role remains under development (Behnoush et al., 2023).

Figure 3 positions the present OPP evidence according to the strength of translation from biological plausibility to clinically meaningful cardiovascular outcomes. The narrowing pyramid makes the principal evidence gap visible by contrasting a broad mechanistic base with limited direct evidence in elevated blood pressure and hypertension.

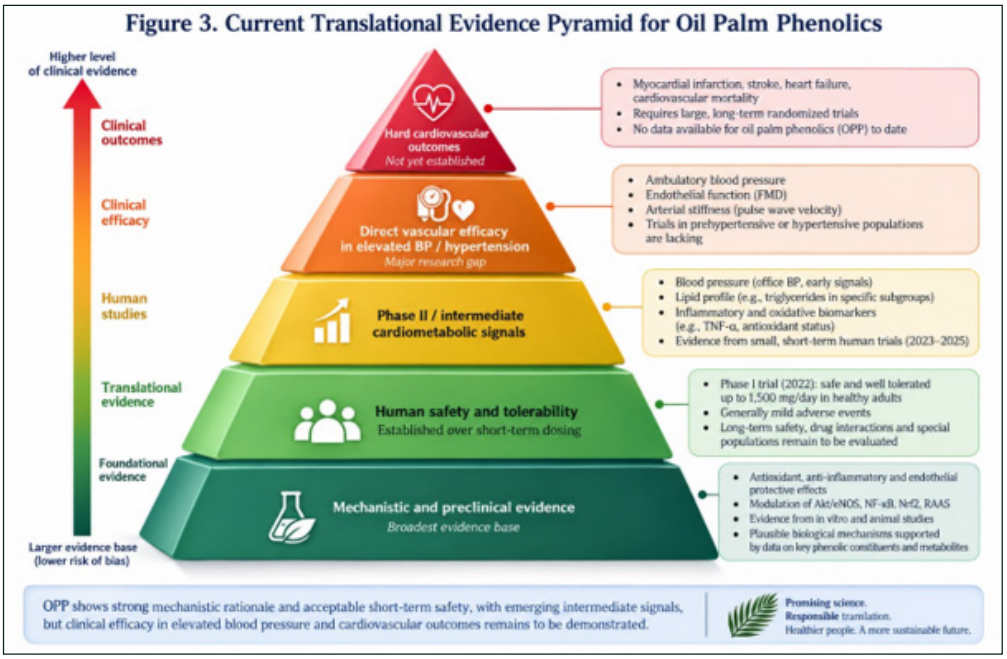


**Figure 3**: Current Translational Evidence Pyramid for Oil Palm Phenolics

The broad base consists of mechanistic and preclinical evidence. Human short-term safety occupies the next layer and is comparatively well supported. Intermediate cardiometabolic signals—including triglycerides in a subgroup, antioxidant and inflammatory biomarkers, and office BP—form a smaller layer. Direct demonstration of improved endothelial function, ambulatory BP or arterial stiffness in people with elevated BP remains largely absent, while evidence for reduced myocardial infarction, stroke, heart failure or cardiovascular mortality does not yet exist. The pyramid illustrates why OPP should currently be described as a promising candidate rather than an established cardiovascular therapy.

### Theme 7: Interindividual Metabolism Provides a Plausible Basis for Responder Heterogeneity

The final thematic finding is that OPP development should move toward precision phenotyping. Polyphenol metabolism varies widely between individuals, and the gut microbiome can determine both the identity and quantity of circulating metabolites (Favari et al., 2024; Williamson, 2025). Two individuals taking the same OPP capsule may therefore experience different endothelial exposure to PCA, hydroxybenzoic derivatives, caffeoylshikimic-acid metabolites or other products.

Potential modifiers include microbiome composition, age, sex, BMI, dietary background, baseline inflammation, baseline blood pressure, genetics and cardiometabolic status. The male-specific triglyceride signal in the 2023 Phase II study cannot establish a sex-dependent OPP effect, particularly because the trial was small, but it highlights the importance of prespecified stratification in future research (Muhammad Ismail Tadj et al., 2023).

Precision OPP development should consequently incorporate targeted or untargeted metabolomics and ideally microbiome profiling. These approaches could identify whether BP responders share a circulating-metabolite signature, whether low-dose and high-dose interventions generate qualitatively different profiles, and whether specific metabotypes predict efficacy.

## Discussion and Analysis

### What does the existing Evidence actually justify?

The accumulated evidence supports three conclusions of different strength. First, OPP is a chemically plausible bioactive material containing phenolic constituents with experimentally demonstrated vascular activities. Second,

short-term oral administration appears generally tolerable across the doses and populations studied. Third, preliminary human evidence suggests biological activity affecting antioxidant status, inflammatory markers, triglycerides in selected participants, and office blood pressure. These propositions are supported by direct human trials from 2022–2025 (Muhammad Ismail Tadj et al., 2022; Muhammad Ismail Tadj et al., 2023; Ibrahim et al., 2025; Fairus et al., 2025).

The evidence does not yet justify describing OPP as a treatment for hypertension. No adequately powered trial has demonstrated sustained ambulatory-BP reduction in a population selected for elevated BP or hypertension. No trial has established improvements in FMD or PWV attributable to OPP. Long-term medication interactions are unknown. Cardiovascular-event prevention has not been tested. These distinctions are essential to prevent nutraceutical enthusiasm from exceeding the evidence.

The appropriate developmental position is therefore between "biologically plausible supplement" and "candidate mechanism-based cardiometabolic nutraceutical." This is a stronger position than purely preclinical speculation but substantially weaker than evidence-based antihypertensive therapy.

## Reframing OPP beyond the Antioxidant Narrative

A generic antioxidant narrative risks obscuring the most interesting OPP biology. If antioxidant capacity alone determined vascular response, one might expect doses producing greater systemic antioxidant effects to produce proportionally greater BP reduction. The available human findings do not clearly show that relationship. This suggests that receptor-independent signaling thresholds, endothelial kinase pathways, phenolic metabolites or inflammatory context may be more important than bulk antioxidant capacity.

Mechanistic evidence for PCA supports this interpretation. Akt/eNOS phosphorylation, preservation of NO signaling and suppression of VCAM-1, ICAM-1 and MCP-1 provide more specific vascular mechanisms than measurements of total antioxidant capacity (Chook et al., 2023). Festa et al. (2024) further showed that phenolic metabolites enhanced NO-related responses particularly under inflammatory stress. Such context dependence could explain why effects vary according to baseline phenotype.

Resveratrol research provides an instructive comparison. Its endothelial effects involve SIRT1, AMPK, eNOS, Nrf2 and NF-κB rather than simply direct antioxidant scavenging (Parsamanesh et al., 2021). Broader polyphenol literature similarly supports signaling-centered explanations (Grosso et al., 2022; Auger et al., 2024; Reis & Rocha, 2024). OPP research should therefore measure relevant signaling and endothelial biomarkers whenever feasible.

## Interpreting the Low-Dose BP Signal

The observation that 250 mg/day showed a BP signal while higher doses more clearly affected antioxidant measures is scientifically provocative. At least four interpretations deserve simultaneous consideration.

The first is a genuine nonlinear biological response. Nutraceutical compounds can exhibit hormetic or threshold behavior in which low or intermediate exposures stimulate adaptive pathways while higher exposures produce plateauing or qualitatively different effects. The second explanation is pharmacokinetic. Greater ingested dose does not guarantee proportional exposure to every metabolite because absorption, conjugation, microbial conversion and elimination can become pathway-dependent.

The third explanation involves baseline phenotype. The magnitude of BP reduction from dietary polyphenols is often greater when baseline BP is elevated. Lagou et al. (2025) found larger BP effects from flavan-3-ol interventions among elevated-BP and hypertensive populations, while the OPP BP study involved healthy adults. A future trial enrolling individuals with high-normal or mildly elevated BP may therefore generate a different dose-response pattern.

The fourth explanation is statistical uncertainty. Small studies with several intervention groups and numerous outcomes are vulnerable to random fluctuations, regression to the mean and multiplicity. The correct scientific response is not to choose the most attractive mechanism prematurely but to design a confirmatory study capable of distinguishing these alternatives.

## Comparison with Broader Human Polyphenol Evidence

The broader polyphenol evidence demonstrates both opportunity and caution. Kiyimba et al. (2023) found that whole polyphenol-rich foods, but not necessarily all purified extracts, reduced BP in pooled cardiometabolic-risk populations. Wan et al. (2024) found beneficial but generally modest changes across diverse polyphenol classes. Ren et al. (2021), Jalili et al. (2024) and Lagou et al. (2025) showed that specific subclasses can alter BP or endothelial function, but heterogeneity is common.

Individual randomized trials reinforce the possibility that phenolic preparations can influence prehypertension. For example, Marhuenda et al. (2021) investigated a polyphenolic Hibiscus sabdariffa–Lippia citriodora preparation in prehypertensive and grade-1 hypertensive adults and reported BP-related effects. Such studies provide useful design precedents for OPP, including enrollment based on baseline BP rather than healthy-volunteer status.

However, findings from cocoa, tea, citrus, berries, resveratrol or Hibiscus cannot be directly transferred to OPP. Polyphenol classes differ substantially in structure, bioavailability, metabolism and target exposure. OPP requires its own dose-ranging pharmacokinetic and efficacy program.

## Which Population should be Studied next?

The most informative next OPP vascular trial would probably not recruit completely healthy normotensive adults or high-risk patients requiring immediate medication adjustment. Instead, an appropriate proof-of-concept population could include adults **with elevated blood pressure or untreated low-risk stage-1 hypertension**, defined according to the relevant contemporary guideline and managed with appropriate ethical oversight (McEvoy et al., 2024; Jones et al., 2025).

This group offers several advantages. First, baseline vascular dysfunction and BP elevation create biological room for improvement. Second, short-duration mechanistic trials can be conducted before irreversible target-organ disease dominates outcomes. Third, ambulatory BP and FMD provide measurable intermediate endpoints. Fourth, participants can be stratified by age, sex, BMI, inflammatory state and metabolic phenotype.

A future trial might randomize participants to placebo, 250 mg/day, an intermediate dose and a higher dose for at least 12–16 weeks. The primary endpoint should be change in 24-hour ambulatory systolic BP or a prespecified vascular-function outcome rather than a large panel of exploratory biomarkers. Secondary endpoints could include daytime and nighttime BP, FMD, PWV, endothelial inflammatory markers, oxidative-redox markers, lipids and safety.

## Measurement Strategy: from Clinic bp to Vascular Phenotype

office bp remains clinically useful, but abpm would markedly strengthen causal inference. out-of-office monitoring distinguishes persistent bp changes from measurement artifacts and provides nighttime bp and circadian information with prognostic relevance (cepeda et al., 2023; cheng and li, 2022).

fmd would test whether opp improves an outcome directly linked to endothelial no-dependent vasodilation. maruhashi et al. (2020) provide contemporary diagnostic reference work for brachial-artery fmd and vascular smooth-muscle responses. pwv would address a different biological level—large-artery stiffness—and is especially important because hypertension and stiffness reinforce one another (kim, 2023).

biomarker selection should also become more mechanistic. instead of relying predominantly on total antioxidant capacity, future trials could evaluate no metabolites, endothelin-1, vcam-1, icam-1, endocan, crp, il-6, tnf-α and validated redox markers. endocan is of particular interest as an endothelial-derived biomarker associated with hypertension, although its incremental clinical utility requires further study (behnoush et al., 2023).

## Pharmacokinetics must Precede Claims of Optimal Dosing

One of the clearest gaps is the absence of a mature human OPP pharmacokinetic literature. The term “optimal dose” should be used cautiously until investigators know the systemic exposure produced by different doses and formulations. Contemporary polyphenol pharmacology shows that parent compounds can be

minor circulating species and that microbial products may dominate exposure (Williamson, 2025).

A dedicated pharmacokinetic study should quantify the major OPP phenolic compounds and their conjugated metabolites after single and repeated doses. Sampling should cover early absorption and later colonic-metabolism phases. Investigators should evaluate area under the concentration-time curve, peak concentrations, half-lives, urinary recovery and interindividual variability.

This design could reveal whether 250 mg/day generates a metabolite profile that differs qualitatively from 1,000 or 1,500 mg/day. If a metabolite strongly associated with endothelial signaling reaches a plateau at low doses, increasing total OPP might enhance unrelated antioxidant markers without producing additional vasodilation.

## The Microbiome and the Emergence of OPP Metabotypes

The gut microbiome provides a compelling route toward precision nutraceutical development. Favari et al. (2024) show that interindividual polyphenol metabolism can be classified according to high/low metabolite production or qualitatively distinct producer phenotypes. Such metabotypes can theoretically determine whether the same administered dose produces a biologically effective vascular exposure. Future OPP studies could collect fecal samples before supplementation and perform 16S rRNA sequencing or shotgun metagenomics alongside plasma and urine metabolomics. Statistical models could then assess whether specific microbial pathways predict production of PCA-related or other phenolic metabolites and whether those metabolites predict ABPM or FMD responses.

This concept also provides a way to interpret apparent nonresponders. Rather than concluding that OPP has no biological activity in a subgroup, investigators could test whether those participants failed to generate particular metabolites or already had near-normal vascular physiology.

## Safety, Drug Interactions and Long-Term Use

Short-term clinical studies have not generated major safety signals, but a two-month safety record cannot define chronic use. Individuals who would be most interested in a cardiometabolic supplement are frequently older and may take statins, ACE inhibitors, angiotensin-receptor blockers, calcium-channel blockers, diuretics, antiplatelet agents, anticoagulants or diabetes medications.

OPP could theoretically modify drug exposure through metabolic enzymes, transporters or gastrointestinal effects, although direct clinical evidence is currently inadequate. Future Phase II/III programs should therefore record concomitant medications, incorporate liver and renal function testing, assess bleeding or hypotension-related events where relevant, and include formal interaction studies when mechanistically justified.

Longer-term safety studies should also consider product-specific contaminants and degradation. Because OPP originates from an industrial processing stream, biomedical manufacturing requires strict specifications regarding microbiological quality, residual contaminants, oxidation, heavy metals, pesticides and batch consistency. “Natural” and “recovered from food processing” are not substitutes for pharmaceutical-quality assurance.

## The Circular-Bioeconomy Argument: Important but Secondary

OPP has a compelling sustainability narrative. Palm-processing effluents create substantial environmental-management challenges, while resource recovery can reduce waste and create new value chains (Cheng et al., 2021; Ratnasari et al., 2022; Meena et al., 2023). Recovering phenolics may diversify revenue and increase the value generated per unit of harvested biomass.

Yet the article's biomedical argument should remain logically independent of palm-sector sustainability claims. A successful circular product must satisfy at least four domains simultaneously: environmental advantage, chemical reproducibility, biological efficacy and economic feasibility. Weakness in any one domain can prevent successful translation.

The strongest narrative is therefore not that a “waste product cures hypertension,” which would be scientifically indefensible, but that a previously underutilized aqueous stream contains recoverable

molecules whose vascular potential has advanced sufficiently to justify rigorous clinical development. This framing keeps the circular-bioeconomy rationale subordinate to the evidentiary requirements of biomedical translation.

## Proposed Precision-Nutraceutical Development Pathway

A rational OPP development program can be organized into six sequential stages. Each stage addresses a distinct uncertainty that should be resolved before progressively stronger clinical or commercial claims are made.

First, **chemical standardization** should define concentrations and acceptable ranges for major marker compounds. Second, **human pharmacokinetics** should establish the relationship between ingested extract and circulating parent/metabolite exposure. Third, responder mapping should integrate baseline BP, sex, BMI, inflammatory phenotype, microbiome and metabolomics.

Fourth, **mechanistic Phase II trials** should investigate multiple doses using ABPM, FMD and PWV, ideally with a prespecified hierarchical endpoint structure. Fifth, **dose-optimization and interaction studies should determine whether the lowest biologically effective dose provides** the best efficacy–tolerability balance. Sixth, sufficiently positive results should lead to larger confirmatory trials and appropriately constrained evidence-based health claims.

Figure 4 presents the proposed precision-nutraceutical roadmap from standardized OPP chemistry to confirmatory vascular research. The sequence is intended to prevent premature efficacy claims by requiring exposure, responder, dose, safety, and endpoint validation before confirmatory trials.

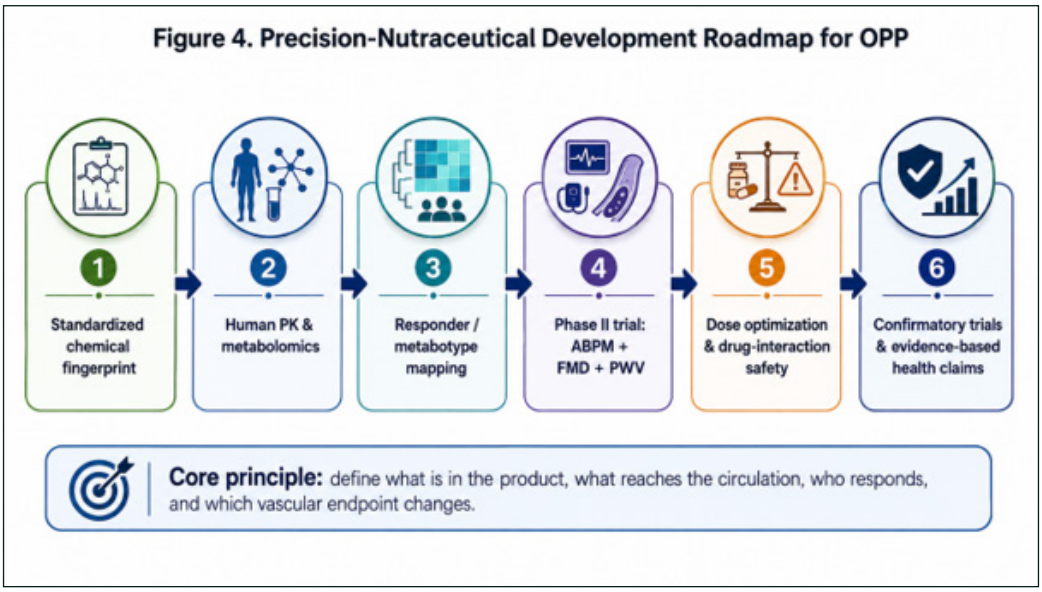


**Figure 4:** Precision-Nutraceutical Development Roadmap for OPP

The roadmap reverses the traditional supplement-development sequence in which a plant extract is marketed first and mechanistic clarification follows later. For OPP, the stronger approach is to define composition, exposure, response heterogeneity, and vascular efficacy before making broad claims. This pathway could also establish a model for other agricultural by-product-derived nutraceuticals.

## Limitations of the current evidence base

The current OPP literature has several limitations. Human studies are few, small and short. Healthy volunteers predominate in early trials. Cardiovascular outcomes are generally surrogate or intermediate markers. The existing

evidence has substantial institutional concentration, making replication by independent groups particularly important.

The phenolic composition of OPP may also vary between preparations. Even when the nominal dose is identical, drying and encapsulation could modify chemical stability and absorption. Direct comparisons of formulations are scarce.

Finally, much of the mechanistic rationale derives from individual phenolic compounds or broader polyphenol literature rather than direct mechanistic studies in people receiving OPP. These data are useful for hypothesis generation, but inferential boundaries should remain explicit.

## Conclusion

Oil palm phenolics occupy a distinctive position at the intersection of vascular biology, nutritional pharmacology and circular bioeconomy. Contemporary evidence has moved beyond purely experimental speculation. Randomized human studies indicate that encapsulated OPP can be administered for approximately 60 days without major safety signals across the doses examined, while emerging clinical studies report potentially favorable changes in triglycerides in selected hyperlipidemic participants, antioxidant and inflammatory biomarkers, and office blood pressure.Nevertheless, the evidence remains insufficient to describe OPP as an established antihypertensive intervention. The central scientific challenge is no longer merely demonstrating that OPP possesses antioxidant activity. It is determining **which OPP compounds and metabolites reach vascular targets, which biological pathways they modify, which individuals respond, and whether those changes produce reproducible improvements in validated vascular endpoints**. The apparent divergence between lower-dose blood pressure responses and higher-dose antioxidant responses is particularly important. If reproduced, it would undermine a simplistic "higher antioxidant dose equals greater cardiovascular benefit" model and support a signaling-, metabolism- and phenotype-based interpretation.

Future investigations should therefore prioritize standardized chemical fingerprints, human pharmacokinetics, ambulatory blood pressure monitoring, FMD, PWV, endothelial biomarkers, metabolomics and microbiome-informed responder analysis. Trials in adults with elevated blood pressure or early low-risk hypertension would provide greater translational value than further studies confined exclusively to normotensive healthy populations.

OPP's origin from an aqueous palm-processing stream creates an additional sustainability opportunity, but circularity should be viewed as complementary to—not proof of—clinical value. If rigorous independent research confirms vascular efficacy, standardized OPP could become a rare example of a bioeconomy-derived product progressing from industrial by-product recovery to precision cardiometabolic nutrition. Until such evidence exists, the scientifically appropriate position is one of **promising but conditional translation.**

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