

Research Article

Open Access

Palm-Derived Tocotrienols in Polyendocrine Metabolic Ovarian Syndrome (Formerly PCOS): From Insulin Resistance and Adipose Inflammation to a Precision Translational Agenda a Critical Review

Loso Judijanto

IPOSS Jakarta, Indonesia

ABSTRACT

Polycystic ovary syndrome, recently renamed polyendocrine metabolic ovarian syndrome (PMOS), is increasingly recognised as a heterogeneous multisystem disorder in which insulin resistance, compensatory hyperinsulinaemia, androgen excess, adipose dysfunction, chronic inflammation, oxidative stress and metabolic comorbidity interact with reproductive dysfunction. Palm-derived tocotrienols represent a biologically interesting but clinically untested adjunct in this condition. This critical qualitative review evaluates the translational rationale for investigating tocotrienols in PMOS while explicitly distinguishing biological plausibility from established clinical efficacy. Contemporary evidence was interpreted across PMOS pathophysiology, tocotrienol pharmacology, vitamin E intervention studies and tocotrienol trials in related metabolic disorders. Tocotrienols show potentially relevant effects on insulin resistance, inflammatory and oxidative biomarkers, hepatic steatosis, adipokines and other cardiometabolic variables in non-PMOS populations. However, no robust tocotrienol-specific randomised clinical evidence currently establishes effects on androgen excess, sex-hormone-binding globulin, ovulation, menstrual regularity, fertility or patient-centred outcomes in PMOS. Evidence from alpha-tocopherol cannot be directly transferred because tocopherols and tocotrienols differ structurally and pharmacokinetically. Future research should prioritise standardised palm-derived preparations, pharmacokinetic verification, phenotype-enriched recruitment and integrated metabolic-reproductive endpoints. Tocotrienols should therefore be regarded as a precision translational hypothesis rather than an established PMOS therapy.

*Corresponding author

Loso Judijanto, IPOSS Jakarta, Indonesia.

Received: August 03, 2026; **Accepted:** September 08, 2026; **Published:** September 19, 2026

Keywords: Polyendocrine Metabolic Ovarian Syndrome, Polycystic Ovary Syndrome, Palm Tocotrienols, Tocotrienol-Rich Fraction, Insulin Resistance, Hyperandrogenism, Adipose Inflammation, Oxidative Stress, Metabolic Dysfunction, Precision Nutrition

JEL Classification: I10-Health General, I12-Health Behavior, I15-Health and Economic Development, I18-Government Policy, Regulation and Public Health, Q16-R&D, Agricultural Technology and Bio-based Innovation

Introduction

Polycystic ovary syndrome has traditionally been defined primarily through reproductive manifestations involving ovulatory dysfunction, clinical or biochemical hyperandrogenism and polycystic ovarian morphology. That framing has become increasingly inadequate because the syndrome encompasses substantial endocrine, metabolic, cardiovascular, hepatic and psychological morbidity across the life course. The 2023 International Evidence-based Guideline consequently emphasises metabolic risk assessment, healthy lifestyle, weight management, cardiovascular risk, diabetes prevention and broader patient-centred care alongside reproductive management [1]. A contemporary disease primer similarly characterises PCOS as a life-course endocrine-metabolic condition with important reproductive, metabolic and psychosocial consequences [2].

Recent prevalence syntheses further show that global estimates vary materially with diagnostic criteria, study quality, age and geographic context [3-4].

In 2026, a large international consensus process proposed changing the name from polycystic ovary syndrome to polyendocrine metabolic ovarian syndrome (PMOS). The new terminology was intended to remove the misleading implication that ovarian cysts define the condition and to better represent its multisystem endocrine, metabolic and ovarian physiology. The consensus involved extensive stakeholder engagement and recommended an evolutionary implementation period rather than abrupt abandonment of the established PCOS terminology [5]. For this reason, the present article uses PMOS as the emerging term while retaining PCOS where needed to connect with the existing literature.

The new name is particularly appropriate when metabolic pathophysiology is considered. Insulin resistance is common across PMOS/PCOS phenotypes, although its magnitude varies with adiposity, androgen status and diagnostic phenotype. Importantly, insulin resistance cannot be explained solely by obesity. Alterations in insulin signalling have been described in skeletal muscle, liver and adipose tissue, while compensatory hyperinsulinaemia itself contributes to reproductive and endocrine abnormalities [6-8]. Recent synthesis has therefore argued that

PCOS should be conceptualised explicitly as a metabolic as well as reproductive disease, because insulin resistance and compensatory hyperinsulinaemia are major determinants of both long-term metabolic risk and reproductive dysfunction [9].

A central pathogenic feature is the reciprocal relationship between insulin and androgen excess. Hyperinsulinaemia can promote ovarian androgen synthesis and decrease hepatic production of sex-hormone-binding globulin (SHBG), increasing biologically available androgen. Androgen excess can, in turn, worsen body-fat distribution, adipocyte function and insulin action, establishing a reinforcing metabolic–endocrine cycle [10–11]. This mechanism makes insulin sensitization relevant not only to glucose metabolism but potentially to reproductive manifestations.

Adipose tissue provides another important connection. Contemporary evidence indicates that women with PMOS/PCOS can exhibit abnormalities of adipogenesis, GLUT4 expression, lipolysis, nonesterified fatty-acid handling, cytokine secretion, adipokine physiology and mitochondrial function even when total adiposity is not markedly increased [12]. Reviews similarly emphasise adipose tissue as an active endocrine organ linking metabolic dysfunction, hyperandrogenism and chronic inflammation rather than as a passive energy-storage compartment [13].

Low-grade inflammation and oxidative stress further reinforce the metabolic phenotype. Meta-analytic evidence demonstrates higher circulating CRP in women with PCOS, including in analyses attempting to account for obesity, although causal direction remains uncertain [14]. Immune-cell abnormalities, altered cytokine networks and ovarian inflammatory signalling have likewise been proposed as contributors to follicular dysfunction and metabolic disease [15]. Oxidative-stress literature describes abnormalities involving reactive oxygen species, lipid peroxidation, nitric-oxide biology and antioxidant defenses that may affect insulin signalling as well as oocyte and granulosa-cell function [16–17].

Mitochondrial dysfunction may provide another biological bridge. Alterations in oxidative phosphorylation, mitochondrial DNA, reactive oxygen species generation, biogenesis and quality control have been reported in metabolic and reproductive tissues relevant to PMOS/PCOS. Although much of this evidence remains mechanistic or preclinical, mitochondrial impairment provides a plausible common denominator linking insulin resistance, oxidative stress and reproductive-cell dysfunction [18].

These interlocking abnormalities create interest in multitarget bioactive compounds. Palm-derived tocotrienols constitute one such candidate. Tocotrienols belong to the vitamin E family but differ from tocopherols because their side chain contains three unsaturated bonds. Palm oil contains substantial α -, γ - and δ -tocotrienols, which can be delivered in tocotrienol-rich fractions (TRFs). Contemporary reviews describe antioxidant, anti-inflammatory and metabolic actions that extend beyond classical α -tocopherol physiology [19–20].

However, the clinical evidence must be framed conservatively. Tocotrienol-specific randomised trials in PMOS/PCOS are essentially absent. Reviews of complementary insulin-sensitizing compounds have identified tocotrienols as theoretically interesting because of their antidiabetic, lipid-modulating and anti-inflammatory actions, but they have simultaneously highlighted the absence of direct clinical evidence in affected women [21].

This creates a classic translational situation in which biological plausibility exceeds disease-specific clinical validation. The purpose of this critical qualitative review is therefore not to recommend palm tocotrienols for PMOS/PCOS. It is to determine whether the mechanistic and cross-disease evidence is sufficiently coherent to justify targeted clinical investigation, to identify the most defensible candidate phenotypes, and to define the design of studies capable of determining whether metabolic improvements translate into endocrine or reproductive benefit.

Literature Review: Conceptual and Theoretical Foundations

Pmos/Pcos as a Heterogeneous Metabolic–Reproductive Syndrome
PMOS/PCOS cannot be regarded as a single metabolic phenotype. The Rotterdam framework produces combinations involving hyperandrogenism, ovulatory dysfunction and ovarian morphology, while metabolic severity varies substantially within and between phenotypes. Contemporary reviews consequently emphasise multifactorial interactions among genetics, environmental exposure, neuroendocrine dysfunction, insulin resistance, androgen excess, adiposity, inflammation and oxidative stress rather than a single causal pathway [22]. Genomic analyses further support biological heterogeneity and suggest that current phenotype-based classifications may not fully capture distinct causal architectures within the syndrome [23].

The 2026 terminology change reinforces this multidimensional interpretation. PMOS explicitly recognizes that ovarian abnormalities coexist with endocrine and metabolic disturbances rather than constituting the entire syndrome [5]. This is relevant to tocotrienol research because a candidate metabolic adjunct should be tested according to the metabolic biology actually present in participants rather than according to a diagnostic label alone.

Insulin Resistance and the Insulin–Androgen Feedback Loop

Insulin resistance in PMOS/PCOS involves multiple tissues. Skeletal muscle may demonstrate impaired metabolic signalling and glucose uptake, hepatic insulin resistance contributes to metabolic dysregulation, and adipose tissue displays altered insulin-dependent glucose transport, lipolysis and lipid buffering. These abnormalities can coexist with selective preservation of signalling pathways in ovarian tissue, allowing high circulating insulin concentrations to continue facilitating steroidogenesis [7].

Insulin dynamics also involve secretion and clearance rather than sensitivity alone [8]. emphasise that hyperinsulinaemia can arise through interactions among reduced insulin sensitivity, altered β -cell secretion and hepatic insulin clearance. This broader view is important because HOMA-IR, although practical, cannot fully characterise the metabolic heterogeneity of PMOS/PCOS.

Hyperinsulinaemia promotes ovarian androgen synthesis and can reduce hepatic SHBG production, thereby increasing free androgen exposure. Conversely, androgen excess can promote central adiposity, alter muscle metabolism and compromise insulin action [10] characterise this as a self-reinforcing hyperinsulinaemia–hyperandrogenism cycle, while broader reviews similarly identify insulin resistance, inflammation and androgen excess as interdependent rather than isolated abnormalities [11].

This cycle provides the most compelling rationale for investigating metabolic interventions. If tocotrienols genuinely improve insulin sensitivity in a responsive PMOS/PCOS subgroup, downstream reductions in hyperinsulinaemia could theoretically influence androgen physiology. Yet this remains an inference: no tocotrienol

trial has demonstrated that improving HOMA-IR in PMOS/PCOS reduces testosterone, increases SHBG or restores ovulation.

Adipose Dysfunction Beyond Obesity

Adipose tissue is increasingly understood as a pathogenic organ in PMOS/PCOS [12]. identified impaired adipogenesis, altered storage capacity, hypoxia, abnormal glucose transport, excessive lipolysis, disrupted fatty-acid kinetics, adipokine abnormalities, inflammation and mitochondrial stress across adipose-tissue studies. Crucially, several abnormalities were not explained simply by higher BMI.

This distinction matters because BMI is an imprecise proxy for metabolic adipose dysfunction. Women with apparently “lean” PMOS/PCOS may retain visceral adiposity, ectopic-fat accumulation or cellular adipose abnormalities. Lemaitre [13]. similarly emphasise that hypertrophic adipocytes, inflammatory-cell recruitment and altered adipokine secretion contribute to both insulin resistance and reproductive dysfunction.

Adipokines may offer mechanistically informative biomarkers. Meta-analysis among non-obese women reported alterations

in several adipokines, illustrating that endocrine adipose abnormalities are not restricted to obesity [12]. Leptin evidence is heterogeneous: pooled analyses have shown higher concentrations in PCOS, but the association weakens when restricted to higher-quality studies, demonstrating the importance of methodological quality and adiposity control [25].

Metformin itself can modify adipose-related markers. A meta-analysis examining adiponectin after metformin therapy suggested that metabolic intervention can alter adipokine physiology in PCOS, although responses vary between studies [26]. This precedent supports including adiponectin and leptin in future tocotrienol trials, but not treating them as validated surrogate endpoints for reproductive benefit.

Figure 1 integrates the principal metabolic–reproductive feedback loops that could theoretically provide intervention points for palm tocotrienols. Insulin resistance, hyperandrogenism, adipose dysfunction, and oxidative–mitochondrial stress are represented as interacting components rather than independent targets.

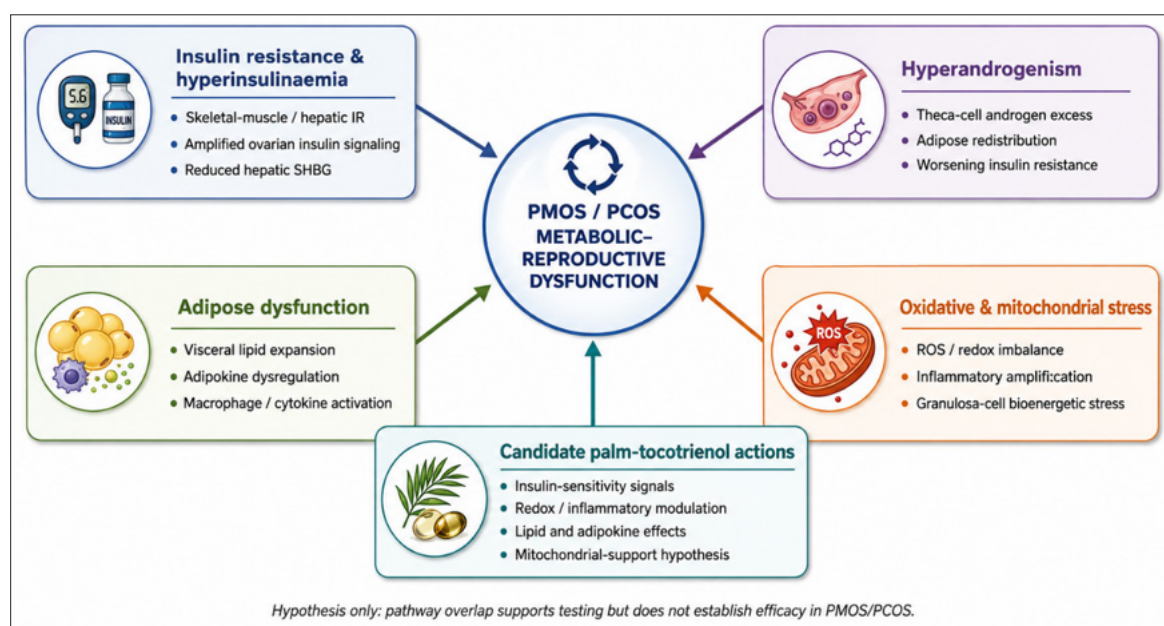


Figure 1: Metabolic-Reproductive Vicious Cycle in Pmos/Pcos and Candidate Tocotrienol Intervention Nodes. The Schematic Maps Interacting Insulin, Androgen, Adipose and Oxidative-Mitochondrial Pathways and Identifies Candidate Tocotrienol Actions; Arrows Indicate a Translational Hypothesis Rather than Demonstrated Clinical Efficacy

The figure should not be interpreted as evidence that tocotrienols interrupt all of these pathways in PMOS/PCOS. Instead, it illustrates the translational hypothesis: tocotrienol-related metabolic, inflammatory, and redox effects documented elsewhere overlap with biological pathways relevant to PMOS/PCOS. The missing element is direct demonstration that modifying these pathways with a palm-derived preparation changes disease-specific endocrine or reproductive outcomes.

Inflammation and Immune Dysfunction

Inflammation is a consistent but complex feature of PMOS/PCOS. Aboeldalyl [14] pooled 63 studies and found substantially higher CRP among women with PCOS. Importantly, elevations persisted in sensitivity analyses of non-obese groups, suggesting that adiposity alone may not explain the inflammatory phenotype.

Nevertheless, inflammation remains heterogeneous. Obesity, insulin resistance, androgen excess, dietary factors, sleep disturbance and hepatic steatosis can all influence systemic inflammatory markers [15]. describe abnormalities involving immune cells, chemokines and cytokines that may influence ovarian follicular function, but causal hierarchies remain incompletely resolved.

Gut dysbiosis has also been proposed as an upstream modifier of metabolic inflammation [27]. reviewed relationships among intestinal dysbiosis, permeability and inflammatory signalling, while [28]. reported systematic evidence of altered gut-microbiota composition

in PCOS. These findings broaden the metabolic ecosystem but also caution against attributing a single inflammatory biomarker to a single pathway.

Oxidative Stress and Reproductive Biology

Oxidative stress is attractive as a therapeutic target because it connects metabolic dysfunction with cellular injury, yet it is also prone to oversimplification [16]. describe mitochondrial mutations, altered oxidative phosphorylation, reactive oxygen species and antioxidant defences across PCOS pathophysiology. A 2024 clinical biomarker study likewise documented concurrent oxidative-stress and inflammatory abnormalities in women with PCOS, reinforcing the biological link while not establishing causality [29]. Oxidative stress can affect insulin signalling, endothelial biology and follicular cells, but reactive oxygen species also have physiological signalling functions.

[17] provide an especially relevant reproductive perspective. Nitric oxide, superoxide, hydrogen peroxide and related pathways participate in follicular development, oocyte maturation and ovulation. Excess or deficient signalling may therefore be problematic. An intervention should not simply be evaluated on the assumption that maximal ROS suppression is desirable.

This nuance is crucial for tocotrienols. Their antioxidant properties provide biological rationale, but generic decreases in malondialdehyde or CRP cannot establish improved ovulatory physiology. Recent PCOS-focused reviews of dietary antioxidants reach similarly cautious conclusions: oxidative biomarkers often improve more consistently than hard reproductive outcomes, and intervention heterogeneity remains high [30].

Mitochondrial Dysfunction

Mitochondria regulate energy production, steroidogenesis, redox balance and apoptosis, making them relevant to both metabolic and reproductive aspects of PMOS/PCOS [18]. synthesize evidence concerning mitochondrial DNA, biogenesis, respiratory-chain function, organelle dynamics and oxidative stress in reproductive organs.

Mitochondrial dysfunction may also mediate the reciprocal relationship between hyperandrogenism and insulin resistance [10]. identify impaired electron transport and mitochondrial function as plausible contributors to both processes. This suggests that mitochondrial endpoints could be included in mechanistic tocotrienol studies, although direct human ovarian mitochondrial measurements are challenging.

Long-Term Metabolic Consequences

PMOS/PCOS carries consequences extending beyond reproductive years. Cardiovascular risk factors are common, and contemporary meta-analysis involving more than one million women found elevated odds for several clinical cardiovascular outcomes, although heterogeneity and certainty limitations remain important [31-32]. therefore, describe PCOS as a potential cardiovascular risk-enhancing condition while emphasizing the need for appropriate risk-factor management.

Hepatic metabolic disease is particularly relevant [33]. reported substantially higher odds of NAFLD among premenopausal women with PCOS [34]. estimated a high pooled NAFLD prevalence in PCOS, with HOMA-IR, waist circumference, hyperandrogenism and triglycerides among important correlates. A further meta-analysis similarly demonstrated increased NAFLD risk [35].

while a 2025 East Asian meta-analysis identified waist-to-hip ratio, HOMA-IR and testosterone as important pooled correlates of MASLD in women with PCOS [36].

MASLD therefore provides an unusually useful translational bridge for tocotrienol research because it combines insulin resistance, visceral adiposity, inflammation and ectopic lipid deposition-features frequently present in metabolically dysfunctional PMOS/PCOS. Its close association with hyperandrogenism and insulin resistance also makes hepatic fat a potentially informative phenotype-enrichment and response marker in future trials.

Tocotrienols are not Simply “Vitamin E”

Vitamin E comprises eight related compounds: four tocopherols and four tocotrienols. Tocotrienols have an unsaturated side chain, whereas tocopherols possess a saturated phytyl chain. These structural differences influence membrane behaviour, absorption, distribution and metabolism [19].

This distinction is methodologically critical for PMOS/PCOS. Trials described as “vitamin E supplementation” have generally administered α -tocopherol, often with omega-3 fatty acids or magnesium [37]. found improvements in several lipid and inflammatory outcomes in their meta-analysis but no consistent improvements across glycaemic indices, anthropometry and hormonal profiles. Those findings cannot be transferred directly to palm tocotrienols.

Tocotrienol pharmacokinetics vary further according to isomer and formulation [38]. demonstrated differences in bioavailability across preparations, while [39]. describes self-emulsifying delivery strategies intended to address limited and variable oral absorption. Two trials giving the same nominal dose may therefore not generate the same systemic exposure.

Methods

This study employed a critical qualitative literature review rather than a systematic literature review or meta-analysis. The objective was to integrate multiple evidence domains necessary to answer a translational question for which direct clinical trials are currently insufficient. The review therefore emphasises theoretical coherence, mechanistic triangulation, evidence boundaries and research-gap identification rather than exhaustive study enumeration.

Literature considered for the principal synthesis was published from 2020 through 2026. Priority was assigned to peer-reviewed articles from major biomedical journals and included the 2023 International Evidence-based PCOS Guideline, the 2026 PMOS terminology consensus, contemporary meta-analyses and mechanistic reviews, clinical studies of current metabolic treatments, and tocotrienol studies relevant to insulin resistance, inflammation, oxidative stress, metabolic syndrome and fatty liver disease.

Search concepts included combinations of polycystic ovary syndrome, polyendocrine metabolic ovarian syndrome, insulin resistance, hyperinsulinaemia, hyperandrogenism, adipose tissue, adipokines, inflammation, oxidative stress, mitochondria, NAFLD, MASLD, tocotrienol, tocotrienol-rich fraction, palm tocotrienol, vitamin E, tocopherol, metformin, GLP-1 receptor agonist and anti-obesity therapy. Citation chaining was used to identify closely related contemporary studies.

Selection was purposive because the scientific question required evidence from several populations. Direct PMOS/PCOS studies were prioritized for disease pathophysiology and established therapy, whereas tocotrienol studies from T2DM, prediabetes, metabolic syndrome and fatty liver disease were included specifically as translational evidence, not as direct PMOS/PCOS efficacy evidence. This distinction was maintained throughout the synthesis.

Evidence was organised into thematic categories encompassing PMOS/PCOS metabolic heterogeneity, insulin-androgen reciprocity, adipose dysfunction, inflammation and oxidative stress, mitochondrial dysfunction, tocotrienol pharmacology, cross-disease human evidence, alpha-tocopherol evidence, contemporary pharmacotherapy, candidate responder phenotypes and future clinical-trial requirements. This structure allowed mechanistic plausibility, human translational evidence and disease-specific uncertainty to be assessed separately before being integrated in the discussion.

An interpretive evidence hierarchy was applied. Disease-specific human randomised evidence was considered most relevant for clinical efficacy, followed by human trials in biologically related metabolic disorders. Meta-analyses were used to assess consistency. Mechanistic reviews and experimental studies were used to support plausibility but were not treated as evidence of clinical effectiveness.

The methodology intentionally does not claim systematic-review completeness. No PRISMA flow diagram, formal risk-of-bias table or pooled effect estimate was generated. The purpose is instead to answer a different question: whether the existing evidence is sufficiently coherent to justify a specific first-in-disease research program and how that program should be designed.

Results: Thematic Findings

Theme 1: PMOS/PCOS Metabolic Heterogeneity Argues Against Universal Supplementation

A major finding is that the PMOS/PCOS diagnosis is biologically heterogeneous. Insulin resistance is common but not uniformly severe, adiposity varies considerably, and hyperandrogenic phenotypes may have different cardiometabolic profiles from non-hyperandrogenic phenotypes. Contemporary guideline recommendations therefore favor individualized management rather than treating all affected women identically [1].

This has immediate implications for tocotrienol research. If benefit depends on elevated oxidative stress, pronounced insulin resistance or adipose inflammation, enrolling an unselected PMOS/PCOS population could dilute an otherwise meaningful treatment effect. Future studies should therefore characterise metabolic phenotype prospectively.

Theme 2: Insulin Resistance Provides the Strongest Human Translational Bridge

Human tocotrienol studies provide their clearest metabolic signal in glucose dysregulation. [40]. randomised individuals with T2DM to δ -tocotrienol or placebo and reported improvements in fasting glucose, insulin, HOMA-IR and HbA1c together with reductions in inflammatory and oxidative biomarkers.

Aggregate evidence is more restrained [41] found a modest reduction in HbA1c across randomised T2DM trials, with heterogeneity according to dose, treatment duration and disease

duration. Broader meta-analysis by [42]. found no consistent improvements across numerous metabolic and inflammatory outcomes. The contrast suggests that responsiveness may depend on formulation and phenotype rather than representing a universal tocotrienol effect.

Prediabetes provides another relevant model [43]. reported improved fasting glucose, insulin, HOMA-IR and HbA1c after δ -tocotrienol treatment. This finding is potentially important for PMOS/PCOS because metabolic dysfunction often begins before overt diabetes and might be more modifiable at an earlier disease stage.

Nevertheless, extrapolation must remain cautious. Insulin resistance in PMOS/PCOS has distinctive endocrine consequences because hyperinsulinaemia interacts directly with ovarian androgen production and SHBG. T2DM trials demonstrate that tocotrienols can affect metabolic endpoints in some populations; they do not demonstrate that such metabolic changes correct PMOS/PCOS reproductive physiology.

Theme 3: Adipose Dysfunction May be More Important Than Body Weight

Tocotrienol research has usually focused on glucose, lipids and systemic inflammatory markers rather than adipose-tissue function itself. Yet PMOS/PCOS pathophysiology suggests that adipose quality may be a more informative target than weight loss alone.

Evidence from fatty liver disease supports this possibility [44]. found that δ -tocotrienol improved HOMA-IR, hs-CRP, malondialdehyde and hepatic steatosis markers in NAFLD. In a subsequent active-controlled trial, δ -tocotrienol and α -tocopherol both improved insulin resistance and hepatic-steatosis measures, but δ -tocotrienol produced greater changes in body weight, IL-6, TNF- α , leptin and adiponectin [45].

The adipokine findings are particularly relevant because PMOS/PCOS itself exhibits adipokine disturbances [24-25]. However, a crucial research step remains missing: no trial has demonstrated that tocotrienol-induced adipokine changes occur in PMOS/PCOS or translate into altered androgen or ovulatory physiology.

Theme 4: Anti-Inflammatory and Antioxidant Activity Is Plausible but Inconsistent

Individual tocotrienol studies frequently report reductions in inflammatory or oxidative biomarkers [40]. observed improvements in hs-CRP, TNF- α , IL-6 and malondialdehyde, while [44]. reported reductions in inflammatory and oxidative markers in NAFLD.

However,[46]. found that pooled evidence for tocotrienol effects on inflammation and oxidative stress was substantially less consistent. CRP showed a favourable signal, but pooled IL-6, TNF- α and malondialdehyde findings were not uniformly significant [42]. similarly found heterogeneous cardiometabolic effects.

The implication is important for PMOS/PCOS. Because inflammation and oxidative stress are already heterogeneous within this condition, trials should not recruit solely on diagnostic status and expect a uniform anti-inflammatory response. Baseline inflammatory and redox phenotyping may be necessary.

A combination trial using δ -tocotrienol and resveratrol in metabolic syndrome reported improvements in several cardiometabolic and inflammatory biomarkers [47]. Yet the presence of two biologically

active compounds prevents attribution of the response specifically to tocotrienol. This exemplifies why future PMOS/PCOS studies should initially use a clearly defined single intervention.

Theme 5: MASLD is Probably the Most Relevant Cross-Disease Model

PMOS/PCOS and fatty liver disease share insulin resistance, visceral adiposity, dyslipidaemia, inflammation and hormonal-metabolic interactions. The high prevalence of NAFLD reported in PCOS meta-analyses therefore makes hepatic dysfunction an important phenotype rather than a peripheral comorbidity [33-35].

The δ -tocotrienol NAFLD trials consequently provide unusually relevant translational evidence. Improvements in HOMA-IR, inflammatory markers, hepatic-steatosis indicators and adipokines align with abnormalities present in metabolically dysfunctional PMOS/PCOS [44-45].

Future PMOS/PCOS studies could therefore specifically enroll women with coexisting MASLD. Magnetic-resonance-based liver-fat measurements, waist circumference, visceral fat, insulin resistance, adiponectin and androgen parameters could be assessed simultaneously to determine whether metabolic improvement occurs across related compartments.

Theme 6: Other Tocotrienol Clinical Signals Support Systemic Activity, Not Pmos Efficacy

Tocotrienols have shown biological activity across other clinical

domains [48]. reported renal-function signals in diabetic kidney disease, while [49]. identified improvements in selected nerve-conduction measures in T2DM. These trials demonstrate that tocotrienols can generate organ-specific physiological signals in humans.

A randomised study of tocotrienol-enriched oat supplementation also found improvements in selected metabolic-syndrome variables, although the oat food matrix prevents separation of tocotrienol-specific effect [50]. Similarly, preclinical diabetic research demonstrates broad metabolic and oxidative effects but cannot establish efficacy for palm TRF in human PMOS/PCOS [51].

A 2026 review synthesizing TRF evidence in diabetes and cardiovascular disease further underscores the expanding mechanistic and clinical literature while emphasizing the need for standardised formulations and larger outcome studies [52]. Collectively, this evidence supports systemic biological plausibility, not reproductive effectiveness.

Figure 2 represents the translational evidence bridge from established PMOS/PCOS biology through tocotrienol mechanisms and human evidence in related metabolic disorders to the major missing step: direct disease-specific randomised evidence. The visual separates what cross-disease evidence can reasonably support from claims that require direct PMOS/PCOS trials.

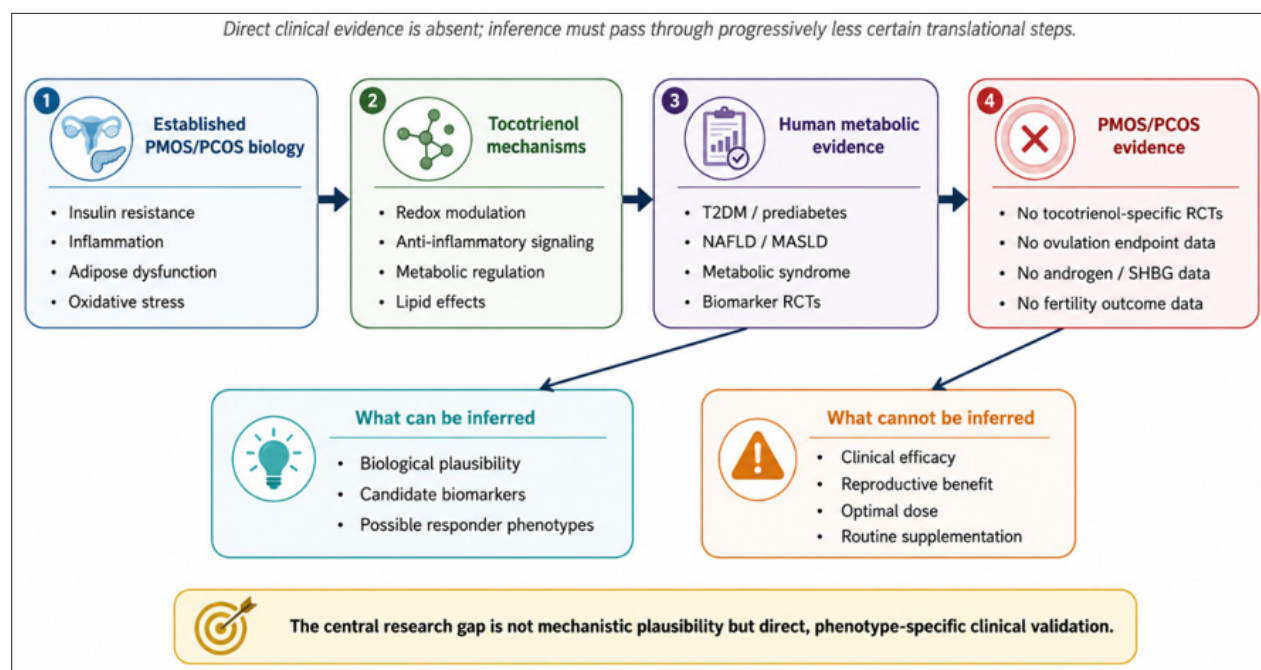


Figure 2: Translational Evidence Bridge for Palm Tocotrienols in Pmos/Pcos. Cross-Disease Metabolic Studies Support Biological Plausibility and Candidate Biomarkers, Whereas Direct Conclusions about Reproductive Efficacy, Optimal Dosing and Routine Supplementation Require Pmos/Pcos-Specific Trials.

Figure 2 illustrates that the direction of inference is intentionally asymmetric. Cross-disease evidence can help select doses, biomarkers and candidate phenotypes, but it cannot establish improved ovulation, androgen status or fertility. The nearer the inference moves toward PMOS/PCOS-specific clinical claims, the greater the need for direct evidence.

Theme 7: α -Tocopherol PCOS Studies are Informative but Cannot Fill the Tocotrienol Evidence Gap

[37] synthesized ten randomised PCOS trials of vitamin E alone or in combination with omega-3 or magnesium. Favorable effects were observed for several lipid parameters, hs-CRP, nitric oxide and hirsutism scores, but consistent improvements were not demonstrated for glycaemic indices, anthropometry or hormonal profiles.

These findings suggest that vitamin E-related interventions can influence selected PMOS/PCOS biomarkers, but they do not establish tocotrienol efficacy. Most interventions were α -tocopherol based, combination therapies confound attribution, and tocopherol and tocotrienol disposition differs materially [19-38].

The evidence gap should therefore be stated explicitly rather than obscured by class terminology: there is meaningful vitamin E literature in PMOS/PCOS, but essentially no disease-specific evidence base for palm-derived tocotrienols. Accordingly, alpha-tocopherol findings can inform hypothesis development but cannot be used as surrogate efficacy evidence for tocotrienol preparations.

Figure 3 highlights why α -tocopherol and tocotrienol evidence should remain analytically separate. Although both belong to the vitamin E family, structural, transport and pharmacokinetic differences mean that a positive α -tocopherol trial does not establish tocotrienol efficacy.

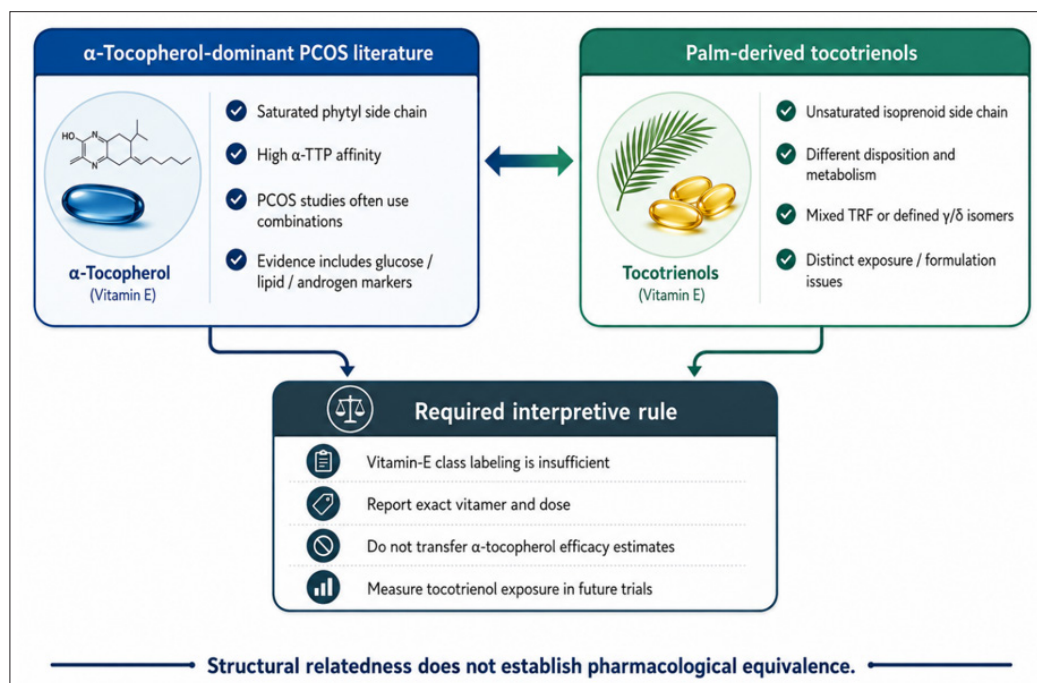


Figure 3: Why Alpha-Tocopherol Evidence Cannot Be Treated as Tocotrienol Evidence in Pmos/Pcos. Structural, Pharmacokinetic and Formulation Differences Require Exact Vitamer Identification and Prevent Direct Transfer of Alpha-Tocopherol Efficacy Estimates to Palm-Derived Tocotrienols.

Figure 3 illustrates that this distinction is particularly important in PMOS/PCOS because direct tocotrienol trials are absent. Treating all vitamin E evidence as interchangeable would create an artificial evidence base. Future studies should identify the precise palm-derived product, its tocotrienol isomer composition, tocopherol content, pharmaceutical formulation and achieved plasma exposure.

Theme 8: Current Metabolic Therapy Raises the Evidence Threshold

Metformin already targets insulin resistance and remains a central metabolic intervention. A contemporary meta-analysis demonstrated modest improvements in BMI, fasting glucose and HOMA-IR compared with placebo, supporting its use particularly in metabolically higher-risk patients [53].

Evidence for complementary compounds is more uncertain. Inositol is widely used, yet the systematic review undertaken for the 2023 guideline concluded that evidence for many clinical outcomes remains limited or inconclusive [54]. This history is instructive for tocotrienol research: widespread biological plausibility should not be allowed to outpace trial evidence.

GLP-1 receptor agonists further change the therapeutic context [55]. found limited but emerging evidence for anti-obesity drugs in PCOS, and [56]. subsequently reported reductions in weight, BMI and insulin resistance with GLP-1 receptor agonists across randomised trials. The 2026 analysis by Forslund et al. likewise found modest short-term weight reduction but emphasised that evidence concerning reproductive and broader metabolic outcomes remains uncertain.

For tocotrienols, the implication is twofold. First, future trials must determine whether tocotrienols add anything beyond effective metabolic treatments. Second, GLP-1-mediated weight loss may change inflammatory and metabolic phenotypes sufficiently to reduce the residual pathway available for tocotrienol intervention.

Discussion and Critical Analysis

Is the Tocotrienol PMOS Hypothesis Scientifically Credible?

The hypothesis is credible at the level of biological plausibility. PMOS/PCOS involves insulin resistance, adipose dysfunction, inflammatory activation, oxidative stress and ectopic metabolic disease. Tocotrienols have demonstrated actions relevant to these domains in experimental systems and selected human metabolic populations.

However, biological plausibility and clinical effectiveness occupy different evidentiary levels. The strongest tocotrienol studies involve T2DM, prediabetes or fatty liver disease rather than PMOS/PCOS. Consequently, any claim that palm tocotrienols “treat PCOS” would presently exceed the evidence.

The appropriate intermediate conclusion is that tocotrienols constitute a credible candidate for clinical testing. This is scientifically meaningful because many compounds fail even to reach that threshold. The existing evidence is sufficiently coherent to support carefully designed first-in-disease trials but insufficient to support clinical adoption.

Insulin Resistance Should be the Principal Initial Target

Among possible targets, insulin resistance provides the strongest translational rationale. It is central to PMOS/PCOS pathophysiology and is also one of the more consistently studied tocotrienol outcomes.

Nevertheless, HOMA-IR alone would be insufficient for a definitive trial. HOMA-IR is convenient but influenced by fasting insulin variability and does not distinguish hepatic from peripheral insulin resistance. A first trial could use HOMA-IR as a pragmatic primary metabolic endpoint while incorporating frequently sampled glucose testing or hyperinsulinaemic–euglycaemic clamp assessment in a mechanistic subset.

Continuous glucose monitoring could add another dimension. Many women with PMOS/PCOS do not have overt diabetes, so fasting glucose and HbA1c may show limited treatment responsiveness despite underlying metabolic dysfunction. Postprandial glucose excursions and glycaemic variability could potentially detect more subtle metabolic effects.

Metabolic Improvement Does Not Guarantee Reproductive Improvement

An especially important conceptual question is whether changing insulin resistance with tocotrienols would alter reproductive disease. The insulin–androgen model predicts that reduced hyperinsulinaemia could decrease ovarian androgen drive and increase hepatic SHBG. Yet the magnitude required to produce a meaningful reproductive effect is unknown.

Therefore, androgen outcomes should be prospectively integrated into clinical trials rather than inferred. Total testosterone, calculated free testosterone, SHBG and free androgen index should be measured using well-validated assays. Clinical hyperandrogenism measures such as hirsutism change more slowly and would require longer follow-up.

Ovulation should also be measured directly rather than inferred from self-reported cycle regularity. Progesterone confirmation, urinary hormonal monitoring or appropriately timed ultrasound could distinguish true ovulation from menstrual bleeding without ovulation. A treatment could thus succeed metabolically but fail reproductively, and that result would itself be scientifically informative. It would demonstrate that metabolic and ovarian pathways are not sufficiently coupled for the degree of metabolic modification achieved.

Adipose Phenotype May Identify Responders Better than BMI
BMI-based enrollment would probably be inadequate. Adipose-tissue research demonstrates dysfunction even among women without obesity, while visceral fat and ectopic lipid provide more direct indicators of metabolic risk [12].

Future studies should therefore measure waist circumference and preferably body composition. Imaging-based visceral adiposity could be incorporated into smaller mechanistic trials. Where PMOS/PCOS coexists with MASLD, quantitative liver-fat measurement could provide a second ectopic-fat endpoint.

Adiponectin and leptin are plausible mechanistic biomarkers because they link adipose tissue to insulin sensitivity and inflammation. However, their clinical interpretation remains uncertain, as meta-analyses demonstrate substantial heterogeneity [24-25]. They should therefore remain secondary mechanistic endpoints rather than primary claims of efficacy.

Inflammatory and Oxidative Phenotyping Could Increase Signal Detection

If tocotrienols exert much of their action through redox and inflammatory modulation, enrolling participants with little baseline inflammation creates a floor effect. A biomarker-enriched design could increase the chance of detecting a real pharmacological response.

Potential enrollment variables include elevated hs-CRP, defined oxidative-stress signatures or combinations of metabolic and inflammatory markers. The approach must remain cautious because no validated “tocotrienol-responsive” biomarker currently exists.

Similarly, malondialdehyde should not be used in isolation. Methodological variability in oxidative-stress assays can affect reproducibility. Panels incorporating lipid oxidation, antioxidant capacity and inflammatory mediators could provide more robust mechanistic evidence.

Pmos/Pcos with Masld May be the Highest-Value First Phenotype
The overlap between PMOS/PCOS and MASLD may offer the most efficient proof-of-concept population. Such participants have measurable metabolic dysfunction, often marked insulin resistance, visceral or ectopic adiposity, hepatic inflammation and elevated long-term metabolic risk.

The existing δ -tocotrienol NAFLD trials provide preliminary human information regarding dose, treatment duration and expected metabolic endpoints 44,45. This creates a more direct translational path than moving immediately from cell studies to a heterogeneous general PMOS/PCOS population.

A future trial could stratify participants by MRI-measured liver fat and assess whether tocotrienol-induced hepatic improvement tracks with HOMA-IR, inflammatory biomarkers, SHBG and testosterone. Such a design could test the broader question of whether improving ectopic metabolic disease modifies reproductive endocrinology.

Complementarity with Metformin

Metformin is an obvious background therapy because it improves insulin sensitivity and is recommended for metabolic management in appropriate PMOS/PCOS populations [1-,53]. This makes stable metformin exposure a logical design consideration for add-on tocotrienol trials, particularly when incremental metabolic benefit is the principal question.

Tocotrienols could theoretically complement metformin if their principal effects occur through redox, inflammatory, lipid or adipose pathways that remain incompletely modified by metformin. Alternatively, both treatments may converge sufficiently on insulin resistance that the marginal tocotrienol effect becomes small.

Future trials should therefore avoid uncontrolled variation in metformin exposure. Participants could either be treatment-naïve in a carefully selected early proof-of-concept trial or, more clinically relevantly, remain on stable metformin therapy and receive tocotrienol versus placebo as an add-on.

Complementarity with GLP-1-Based Therapy

GLP-1 receptor agonists may create an even greater challenge for detecting incremental benefit because they can produce substantial weight loss while improving insulin resistance and downstream inflammation. Recent PCOS syntheses show consistent anthropometric benefits, although reproductive evidence remains less certain [55-57].

A tocotrienol trial conducted during active GLP-1 dose escalation would be difficult to interpret because metabolic changes from the pharmacological therapy could overwhelm the nutraceutical signal. Participants receiving GLP-1-based therapy should therefore be stabilized before randomization.

Alternatively, initial tocotrienol trials could exclude GLP-1 users to determine biological efficacy under simpler conditions. Later pragmatic studies could evaluate additivity within modern metabolic therapy.

Formulation Standardisation is Mandatory

“Palm tocotrienol” is not a sufficiently precise intervention description. Palm TRF can vary in α -, γ - and δ -tocotrienol composition and in accompanying α -tocopherol. Purified δ -tocotrienol cannot automatically be considered equivalent to mixed palm TRF.

Pharmacokinetic variability further complicates comparisons [38]. demonstrate differences among tocotrienol preparations, while [39]. highlights formulation strategies capable of improving bioavailability. A negative clinical trial without exposure verification could therefore reflect inadequate pharmacokinetics rather than absence of biological activity.

Future trials should report batch composition, tocotrienol isomer concentrations, tocopherol concentration, excipients, formulation, meal conditions and product stability. Plasma tocotrienol concentrations should be measured in at least a pharmacokinetic subset.

A Proposed First-in-PMOS/PCOS Clinical Trial

A scientifically efficient first trial could enroll adults with confirmed PMOS/PCOS and objective insulin resistance, with enrichment for overweight/obesity or metabolic fatty liver disease. Participants should receive stable background lifestyle management, and use of metformin or other metabolic drugs should be standardised before randomization.

The intervention should be a well-characterised palm-derived TRF or defined palm-derived tocotrienol preparation. A matched placebo would allow double blinding, and a treatment period of approximately six months would be long enough to characterise metabolic and hormonal trajectories while remaining practical for proof-of-concept testing.

The primary metabolic endpoint could be change in insulin resistance, while co-primary or major secondary endocrine endpoints could include calculated free testosterone and SHBG. Additional endpoints should include fasting insulin, glucose, CGM variables, lipid profile, waist circumference, visceral fat, hepatic fat where relevant, hs-CRP, IL-6, TNF- α and validated redox biomarkers.

Reproductive outcomes should include menstrual-cycle tracking and objectively confirmed ovulation. AMH and ovarian morphology could be measured exploratorily, but changes in these markers should not be assumed to represent clinical benefit.

Safety should include adverse events, liver and renal biochemistry, bleeding-related events where relevant, treatment discontinuation and pregnancy surveillance. Women seeking immediate fertility treatment may need to be studied separately because letrozole and other ovulation-induction interventions would complicate attribution.

Figure 4 summarizes a trial architecture intended to resolve the principal weaknesses in the current evidence. Recruitment is based on metabolic phenotype, the product is standardised, and exposure is verified, while metabolic and reproductive outcomes are assessed simultaneously.

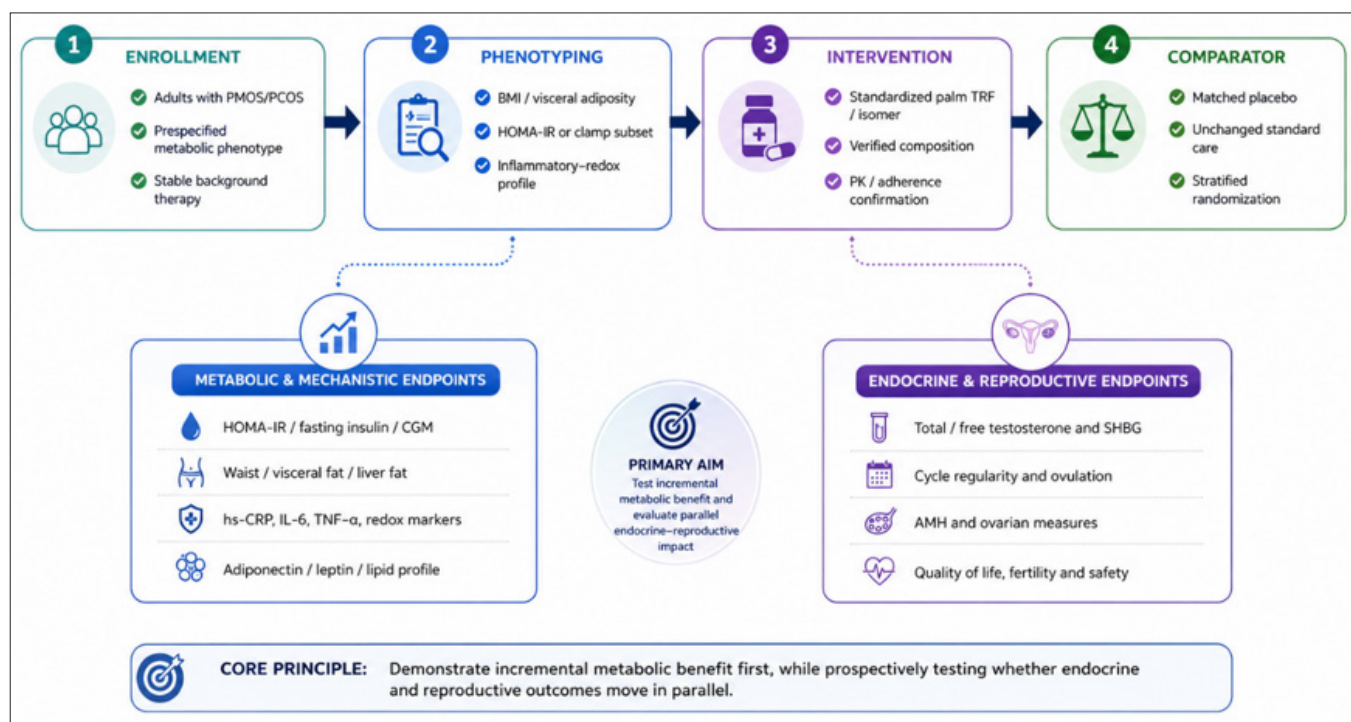


Figure 4: Proposed First-in-PMOS/PCOS Trial Architecture for Palm Tocotrienols. the Design Links Phenotype-Enriched Enrolment and Verified Intervention Exposure to Parallel Metabolic-Mechanistic and Endocrine-Reproductive Outcomes While Maintaining Stable Background Care.

Figure 4 shows that the design explicitly separates proof of biological exposure from proof of clinical benefit. A trial would first determine whether tocotrienols meaningfully modify insulin resistance and related pathways, and then whether endocrine and reproductive outcomes move in parallel. This avoids assuming that an antioxidant or inflammatory biomarker response constitutes successful treatment of PMOS/PCOS.

Why this Article Contributes Something Beyond Previous Nutraceutical Reviews

The principal novelty lies in moving beyond the generic question of whether antioxidants may be useful in PCOS. Existing nutritional reviews consider vitamin E, inositols, N-acetylcysteine, carnitine, resveratrol and other compounds, while recent antioxidant reviews continue to document plausible mechanisms [21,30].

The present framework is more restrictive. It separates tocotrienols from tocopherols, maps the intervention specifically onto PMOS metabolic phenotypes, incorporates modern GLP-1 and metformin therapy, defines boundaries for cross-disease extrapolation and specifies what a first direct trial should measure.

This distinction is important because nutraceutical research frequently advances from mechanistic plausibility to clinical recommendation too rapidly. The PMOS/PCOS field has already encountered this problem with widely adopted complementary interventions for which high-quality evidence remains limited, as illustrated by the guideline-linked inositol review [54].

Palm tocotrienol research should avoid repeating that trajectory. Commercial availability should not precede scientific precision. The strongest contribution would come from standardised interventions, transparent product characterization, preregistered endpoints, meaningful comparators and replication.

Conclusion

The transition from PCOS to polyendocrine metabolic ovarian syndrome appropriately emphasises that the disorder extends beyond ovarian morphology and reproductive symptoms. Insulin resistance, hyperinsulinaemia, androgen excess, dysfunctional adipose tissue, chronic inflammation, oxidative stress, mitochondrial disturbances and ectopic metabolic disease interact in a heterogeneous and potentially self-reinforcing network.

Palm-derived tocotrienols are biologically relevant to several components of this network. Human evidence from related metabolic disorders suggests potential effects on insulin resistance, glycaemic control, inflammatory and oxidative biomarkers, hepatic steatosis and adipokine physiology. These findings are sufficient to justify disease-specific investigation. They are not sufficient to justify clinical treatment. No convincing direct evidence currently establishes that palm tocotrienols reduce androgen excess, increase SHBG, restore ovulation, normalize menstrual cycles, improve fertility, or alter long-term PMOS outcomes. Evidence from α -tocopherol studies cannot fill this gap because tocopherols and tocotrienols are not pharmacologically interchangeable.

The next research phase should therefore move from broad antioxidant narratives toward precision translation. Trials should enroll characterised PMOS phenotypes metabolically, use standardised palm-derived preparations, confirm systemic exposure and integrate metabolic, endocrine and reproductive endpoints. PMOS accompanied by marked insulin resistance, obesity or MASLD may provide particularly informative initial populations.

Palm-derived tocotrienols should consequently be regarded as a promising but unproven precision metabolic adjunct hypothesis. Their future role will depend not on accumulating additional evidence that they possess antioxidant activity, but on

demonstrating that a defined preparation, at a verified exposure, produces clinically meaningful incremental benefit in appropriately selected women with PMOS.

References

- Helena J Teede, Chau Thien Tay, Joop JE Laven, Anuja Dokras, Lisa J Moran, et al. (2023) Recommendations from the 2023 International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome. *Hum Reprod* 38: 1655-1679.
- Elisabet Stener Victorin, Helena Teede, Robert Norman J, Richard Legro, Mark Goodarzi O, et al. (2024) Polycystic ovary syndrome. *Nat. Rev. Dis. Primers* 10: 27.
- Amiri M, Hatoum S, Buyalos RP, Sheidaei A, Azziz R, et al. (2025) The influence of study quality, age, and geographic factors on PCOS prevalence a systematic review and meta-analysis. *J Clin Endocrinol Metab* 110: 2082-2103.
- Adriana Neven CH, Maria Forslund, Sanjeeva Ranasingha, Parneet Sethi, Raja Ram Dhungana, et al. (2026) Prevalence of polycystic ovary syndrome: A global and regional systematic review and meta-analysis. *Hum Reprod Update* 32: 277-312.
- Helena Teede J, Mahnaz Bahri Khomami, Rachel Mormanc, Joop Laven SE, Anju Joham E, et al. (2026) Polyendocrine metabolic ovarian syndrome, the new name for polycystic ovary syndrome: A multistep global consensus process. *Lancet* 407: 2329-2339.
- Moggetti P, Tosi F (2021) Insulin resistance and PCOS: Chicken or egg? *J. Endocrinol. Invest* 44: 233-244.
- Zhao H, Zhang J, Cheng X, Nie X, He B, et al. (2023) Insulin resistance in polycystic ovary syndrome across various tissues: An updated review of pathogenesis, evaluation, and treatment. *J Ovarian Res* 16: 9.
- Herman R, Sikonja J, Jensterle M, Janez A, Dolžan V, et al. (2023) Insulin metabolism in polycystic ovary syndrome: Secretion, signaling, and clearance. *J Mol. Sci* 24: 3140.
- Helvacı N, Yildiz BO (2025) Polycystic ovary syndrome as a metabolic disease. *Nat Rev Endocrinol* 21: 230-244.
- Jenifer Lizbet Hernández Jiménez, David Barrera, Emilio Espinoza Simón, James González, Rosario Ortiz Hernández, et al. (2022) Polycystic ovarian syndrome Signs and feedback effects of hyperandrogenism and insulin resistance. *Gynecol Endocrinol* 38: 2-9.
- Armanini D, Boscaro M, Bordin L, Sabbadin C (2022) Controversies in the pathogenesis, diagnosis and treatment of PCOS Focus on insulin resistance inflammation and hyperandrogenism. *J Mol Sci* 23: 4110.
- Fernando Bril, Uche Ezech, Mina Amiri, Sana Hatoum, Lauren Pace, et al. (2024) Adipose tissue dysfunction in polycystic ovary syndrome. *J Clin Endocrinol Metab* 109: 10-24.
- Lemaitre M, Christin Maitre S, Kerlan V (2023) Polycystic ovary syndrome and adipose tissue. *Ann Endocrinol* 84: 308-315.
- Aboeldalyl S, James C, Seyam E, Ibrahim EM, Shawki HED, et al. (2021) The role of chronic inflammation in polycystic ovarian syndrome a systematic review and meta-analysis. *J Mol Sci* 22: 2734.
- Shamsi M, Ghazavi A, Saeedifar AM, Mosayebi G, Khajeh Pour S, et al. (2022) The immune system's role in PCOS. *Mol Biol Rep* 49: 10689-10702.
- Zeber Lubecka N, Ciebiera M, Hennig EE (2023) Polycystic ovary syndrome and oxidative stress from bench to bedside. *J Mol Sci* 24: 14126.
- Awonuga AO, Camp OG, Abu Soud HMA (2023) review of nitric oxide and oxidative stress in typical ovulatory women and in the pathogenesis of ovulatory dysfunction in PCOS. *Reprod Biol Endocrinol* 21: 111.
- Siemers KM, Klein AK, Baack ML (2023) Mitochondrial dysfunction in PCOS Insights into reproductive organ pathophysiology. *J Mol Sci* 24: 13123.
- Szewczyk K, Chojnacka A, Górnicka M (2021) Tocopherols and tocotrienols bioactive dietary compounds what is certain what is doubt? *J Mol Sci* 22: 6222.
- Ranasinghe R, Mathai M, Zulli A (2022) Revisiting the therapeutic potential of tocotrienol. *Bio factors* 48: 813-856.
- Tabatha Petrillo, Elisa Semprini, Veronica Tomatis, Melania Arnesano, Fedora Ambrosetti, et al. (2022) Putative complementary compounds to counteract insulin-resistance in PCOS patients. *Bio medicines* 10: 1924.
- Hosna Mohammad Sadeghi, Ida Adeli, Daniela Calina, Anca Oana Docea, Taraneh Mousavi, et al. (2022) Polycystic ovary syndrome A comprehensive review of pathogenesis management and drug repurposing. *J Mol Sci* 23: 583.
- Dapas M, Dunaif A (2022) Deconstructing a syndrome: genomic insights into PCOS causal mechanisms and classification. *Endocr Rev* 43: 927-965.
- Lin K, Sun X, Wang X, Wang H, Chen X, et al. (2021) Circulating adipokine levels in nonobese women with polycystic ovary syndrome and in nonobese control women A systematic review and meta-analysis. *Endocrinol Lausanne* 11: 537809.
- Mahesh Kumar Seth, Sarthak Gulati, Shreya Gulati, Amit Kumar, Dimple Rawat, et al. (2021) Association of leptin with polycystic ovary syndrome A systematic review and meta-analysis. *J Obstet Gynaecol India* 71: 567-576.
- Duan X, Zhou M, Zhou G, Zhu Q, Li W, et al. (2021) Effect of metformin on adiponectin in PCOS A meta-analysis and a systematic review. *Eur J Obstet Gynecol Reprod Biol* 267: 61-67.
- Jim Parker, Claire Brien O, Jason Hawrelak (2022) A narrative review of the role of gastrointestinal dysbiosis in the pathogenesis of polycystic ovary syndrome. *Obstet Gynecol Sci* 65: 14-28.
- Pan Li, Ping Shuai, Sj Shen, Huimin Zheng, Ping Sun, et al. (2023) Perturbations in gut microbiota composition in patients with polycystic ovary syndrome A systematic review and meta-analysis. *BMC Med* 21: 302.
- Berra Sen, Senem Gonultas, Ceren Albayrak, Sevval Temur, Ilgar Acar, et al. (2024) Evaluation of oxidative stress and inflammation in patients with polycystic ovary syndrome. *Obstet Gynecol Sci* 67: 414-420.
- Nevin Adel Amer, Shatha Basheer Aldababseh, Doha Abdel Hady Abdel Gawad, Mostafa Abdelsadek M (2026) Oxidative stress and the therapeutic potential of dietary antioxidants in polycystic ovary syndrome A narrative review. *J Ovarian Res* 19: 171.
- Chau Thien Tay, Aya Mousa, Aadhya Vyas, Loyal Pattuwage, Fahimeh Ramezani Tehrani, et al. (2024) 2023 International Evidence-Based Polycystic Ovary Syndrome Guideline Update Insights from a systematic review and meta-analysis on elevated clinical cardiovascular disease in polycystic ovary syndrome. *J Am Heart Assoc* 13: e033572.
- Guan C, Zahid S, Minhas AS, Ouyang P, Vaught A, et al. (2022) Polycystic ovary syndrome A "risk-enhancing" factor for cardiovascular disease. *Fertil Steril* 117: 924-935.
- Mohamed Shengi, Tianyan Chen, Elena Guadagno, Agnihotram Ramanakumar V, Peter Ghali, et al. (2021) Nonalcoholic fatty liver disease in premenopausal women with polycystic ovary syndrome A systematic review and meta-analysis. *JGH Open* 5: 434-445.
- Ramiro Manzano Nunez, Marta Santana Dominguez, Jesus

- Rivera Esteban, Clara Sabiote, et al. (2023) non-alcoholic fatty liver disease in patients with polycystic ovary syndrome A systematic review meta-analysis and meta-regression. *J Clin Med* 12: 856.
35. Yao K, Zheng H, Peng H (2023) Association between polycystic ovary syndrome and risk of non-alcoholic fatty liver disease: A meta-analysis. *Endokrynol Pol* 74: 520-527.
36. Wu Z, Liang G, Zhang Y, Li R (2025) Risk factors for metabolic dysfunction-associated steatotic liver disease in patients with polycystic ovary syndrome in East Asia: a review and meta-analysis. *Endocr Pract* 31: 668-676.
37. Heidari H, Hajhashemy Z, Saneei, P (2022) A meta-analysis of effects of vitamin E supplementation alone and in combination with omega 3 or magnesium on polycystic ovary syndrome. *Sci Rep* 12: 19927.
38. Sharif M, Khan DA, Farhat K, Noor M, Khan MA, et al. (2023) Pharmacokinetics and bioavailability of tocotrienols in healthy human volunteers A systematic review. *J Pak Med Assoc* 73: 603-610.
39. Mohamad NV (2023) Strategies to enhance the solubility and bioavailability of tocotrienols using self-emulsifying drug delivery system. *Pharmaceuticals Basel* 16: 1403.
40. Mahjabeen W, Khan DA, Mirza SA, Pervez MA (2021) Effects of delta-tocotrienol supplementation on glycemic control oxidative stress inflammatory biomarkers and miRNA expression in type 2 diabetes mellitus A randomized control trial. *Phytother Res* 35: 3968-3976.
41. Phang SCW, Ahmad B, Abdul Kadir K, Palanisamy UDM (2023) Effects of tocotrienol-rich fraction supplementation in patients with type 2 diabetes A systematic review and meta-analysis of randomized controlled trials. *Adv Nutr* 14, 1159-1169.
42. Li F, Xu B, Soltanieh S, Zanghelini F, Abu Zaid A, et al. (2022) The effects of tocotrienols intake on obesity blood pressure inflammation liver and glucose biomarkers A meta-analysis of randomized controlled trials. *Food Sci Nutr* 62: 7154-7167.
43. Suleman F, Khan DA, Pervez MA, Aamir M (2022) Effects of delta-tocotrienol supplementation on glycaemic control in individuals with prediabetes A randomized controlled study. *J Pak Med Assoc* 72: 4-7.
44. Pervez MA, Khan DA, Slehria AUR, Ijaz A (2020) Delta-tocotrienol supplementation improves biochemical markers of hepatocellular injury and steatosis in patients with nonalcoholic fatty liver disease A randomized placebo-controlled trial. *Complement Ther Med* 52: 102494.
45. Muhammad Amjad Pervez, Dilshad Ahmed Khan, Shakeel Ahmed Mirza, Atiq Ur Rehman Slehria, Uzma Nisar, et al. (2022) Comparison of delta tocotrienol and alpha tocopherol effects on hepatic steatosis and inflammatory biomarkers in patients with non-alcoholic fatty liver disease A randomized double blind active controlled trial. *Complement Ther Med* 70: 102866.
46. Ban Hock Khor, Hui Ci Tiong, Shing Cheng Tan, Sok Kuan Wong, Kok Yong Chin, et al. (2021) Effects of tocotrienols supplementation on markers of inflammation and oxidative stress A systematic review and meta-analysis of randomized controlled trials. *PLoS ONE* 16: e0255205.
47. Fatima S, Khan DA, Aamir M, Pervez MA, Fatima F, et al. (2023) δ -Tocotrienol in combination with resveratrol improves the cardiometabolic risk factors and biomarkers in patients with metabolic syndrome A randomized controlled trial. *Syndr Relat Disord* 21: 25-34.
48. Yan Yi Koay, Gerald Chen Jie Tan, Sonia Chew Wen Phang, J Ian Ho, Pei Fen Chuar, et al. (2021) A Phase IIb randomized controlled trial investigating the effects of tocotrienol rich vitamin E on diabetic kidney disease. *Nutrients* 13: 258.
49. Pei Fen Chuar, Yeek Tat Ng, Sonia Chew Wen Phang, Yan Yi Koay, J Ian Ho, et al. (2021) Tocotrienol rich vitamin E (Tocovid) improved nerve conduction velocity in type 2 diabetes mellitus patients in a Phase II double-blind randomized controlled clinical trial. *Nutrients* 13: 3770.
50. Norazman CW, Sopian MM, Lee LK (2025) Effects of tocotrienol-enriched oat supplementation on metabolic profile nutritional status and health related quality of life among patients with metabolic syndrome. *Food Funct* 16: 1847-1863.
51. Gustav Dallner, Magnus Bentinger, Shafaat Hussain, Indranil Sinha, Jiangning Yang, et al. (2021) Dehydro tocotrienol- β counteracts oxidative-stress-induced diabetes complications in db/db mice. *Antioxidants* 10: 1070.
52. Ali M, Sheikh Abdul Kadir SH, Ibrahim E, Albaraikan A (2026) Tocotrienol-rich fraction of vitamin E in diabetes and cardiovascular disease from molecular mechanisms to clinical application. *J Cardiol Cardiovasc Risk Prev* 30: 200686.
53. Johanna Melin, Maria Forslund, Simon Alesi, Terhi Piltonen, Daniela Romualdi, et al. (2023) The impact of metformin with or without lifestyle modification versus placebo on polycystic ovary syndrome A systematic review and meta-analysis of randomized controlled trials. *Eur J Endocrinol* 189: S37-S63.
54. Victoria Fitz, Sandro Graca, Shruthi Mahalingaiah, Jing Liu, Lily Lai, et al. (2024) Inositol for polycystic ovary syndrome A systematic review and meta-analysis to inform the 2023 update of the international evidence-based PCOS guidelines. *J Clin Endocrinol Metab* 109: 1630-1655.
55. Alyse Goldberg, Sandro Graca, Jing Liu, Vibhuti Rao, Selma Feldman Witchel, et al. (2024) Anti-obesity pharmacological agents for polycystic ovary syndrome A systematic review and meta-analysis to inform the 2023 international evidence-based guideline. *Obes Rev* 25: e13704.
56. Shike Lin, Yan Deng, Jing Huang, Meiyang Li, Suren Rao Soorann, et al. (2025) Efficacy and safety of GLP-1 receptor agonists on weight management and metabolic parameters in PCOS women A meta-analysis of randomized controlled trials. *Sci Rep* 15: 16512.
57. Maria Forslund, Per Wändell, Lisa Forsberg, Marie Österberg, Jessica Dagerhamn, et al. (2026) GLP-1 receptor agonist treatment in women with polycystic ovary syndrome a systematic review and meta-analysis. *Eur J Endocrinol* 194: S25-S45.

Copyright: ©2026 Loso Judijanto. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.