Neurovascular–Metabolic Regulatory Mechanisms of Ginkgo biloba: Nutritional Pharmacology Insights into Mitochondrial, Endothelial, and Neurotransmitter Coupling Pathways

Clinical Evidence and Integrative Consensus of Ginkgo biloba in Menopausal Syndrome, PMS, and Neuro-Metabolic Dysregulation

Abstract

Background:

The convergence of Ginkgo biloba and soy isoflavones represents a novel paradigm in nutritional pharmacology, where two mechanistically distinct agents co-regulate the Neuro–Endocrine–Vascular–Metabolic (NEVM) system.

This study proposes and substantiates a four-axis integrative framework in which Ginkgo biloba acts as the executive synchronizer - modulating energy metabolism, endothelial dynamics, and neurotransmitter balance - while soy isoflavones function as the regulatory initiator, recalibrating endocrine rhythm through selective estrogen receptor-β (ER-β) and G-protein–coupled estrogen receptor (GPER1) signaling.

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Methods and Framework:

Through a synthesis of mechanistic literature, clinical trial data, and translational analyses, this paper integrates evidence from three key pathological contexts: menopausal syndrome, premenstrual dysphoric and metabolic-affective disorders (PMS/PMDD), and neuro-metabolic dysregulation.

Each condition was deconstructed into its primary axis imbalance - hormonal, neurochemical, vascular, or energetic - and then reconstructed through Ginkgo–Isoflavone–cofactor synergy (Vitex agnus-castus, magnesium, selenium, and vitamin E), forming a dynamic multi-nutrient network of systemic restoration.

Results and Mechanistic Insight:

Across all models, Ginkgo biloba activated AMPK–PGC-1α–Nrf2 and PI3K–AKT–eNOS pathways, enhancing mitochondrial biogenesis, nitric oxide bioavailability, and cerebral perfusion.

Soy isoflavones restored ER-β–mediated genomic signaling, improving serotonin synthesis (TPH2 upregulation), mitochondrial transcriptional control, and vascular remodeling.

The combined effect re-established bioenergetic and neurochemical coherence, converting endocrine modulation into vascular and cognitive stability.

Supporting cofactors extended these effects: magnesium reinforced AMPK–GABA coupling; selenium and vitamin E stabilized endothelial redox defense; Vitex agnus-castus normalized dopaminergic feedback.

Conclusions:

The findings establish a coherent systems framework in which nutrient synergy acts as network synchronization, not nutrient substitution.

The Ginkgo biloba–Isoflavone axis, supported by specific micronutrient partners, redefines complex chronic conditions such as menopausal transition, PMS/PMDD, and metabolic cognitive fatigue as disorders of system desynchronization, treatable through multi-axis coherence therapy.

This work positions Ginkgo biloba as the central synchronizer and soy isoflavones as the endocrine catalyst of the NEVM system - together forming a biological model of cross-axis harmony within the Keyora nutritional pharmacology paradigm.

Keywords:

Ginkgo biloba；Isoflavones；Phytoestrogens；Nutritional Pharmacology；Systems Biology；Neuro–Endocrine–Vascular–Metabolic Axis；AMP-Activated Protein Kinase (AMPK)；Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha (PGC-1α)；Nuclear Factor Erythroid 2–Related Factor 2 (Nrf2)；Phosphatidylinositol 3-Kinase (PI3K)–AKT–Endothelial Nitric Oxide Synthase (eNOS) Pathway；Mitochondrial Biogenesis；Cerebral Blood Flow；Endothelial Function；Neurotransmitter Modulation；Serotonin and Dopamine Homeostasis；Oxidative Stress；Energy Metabolism；Menopausal Syndrome；Premenstrual Syndrome (PMS)；Premenstrual Dysphoric Disorder (PMDD)；Neurodegenerative Disorders；Metabolic Syndrome；Homeostasis；Precision Nutrition；Network Synchronization.

Ginkgo biloba, one of the oldest surviving tree species on Earth, represents a unique botanical lineage that bridges traditional medicine and modern nutritional pharmacology. Extracts derived from its leaves (commonly standardized as EGb 761) are characterized by a precise composition of flavonol glycosides (24%) and terpenoid lactones (6%), primarily ginkgolides A, B, C and bilobalide, which together form a synergistic matrix of neuroprotective, vasodilatory, and antioxidant activities.

From a pharmacodynamic perspective, Ginkgo biloba exhibits multi-dimensional regulatory actions across the neurovascular–metabolic system, positioning it as a functional analogue to neurotrophic and endothelial-protective agents rather than a simple circulatory enhancer. Its mechanistic versatility encompasses enhancement of mitochondrial ATP generation, upregulation of nitric oxide (NO) bioavailability, stabilization of neurotransmitter dynamics (5-HT, dopamine, GABA), and modulation of oxidative and inflammatory signaling networks (Nrf2–NF-κB axis).

Within the context of functional nutrition, these properties translate into clinically relevant improvements in cognitive performance, mood regulation, sleep quality, vascular elasticity, and metabolic homeostasis, particularly under physiological stress or hormonal decline. Unlike pharmacologic monotherapies, Ginkgo biloba operates as a system-level modulator, restoring equilibrium through receptor-independent bioenergetic and redox pathways that complement endocrine-targeted nutrients such as soy isoflavones and Vitex agnus-castus.

In the Keyora framework, Ginkgo biloba is conceptualized as a “Neurovascular–Metabolic Axis Modulator”, whose actions converge on three interrelated targets:

- Mitochondrial Efficiency – enhancement of ATP synthesis and reduction of oxidative load;

- Endothelial Function – normalization of NO–eNOS signaling and microcirculatory perfusion;
- Neurotransmitter Coupling – modulation of 5-HT, GABA, and dopaminergic tone to stabilize emotional and cognitive rhythms.

Collectively, these features define Ginkgo biloba as a prototype of nutritional pharmacology for neurovascular-metabolic homeostasis, bridging ancient botanical medicine with modern systems physiology.

From Neuro–Endocrine–Metabolic to Neurovascular–Metabolic Integration

The human neuroendocrine system operates as a dynamic tri-axis network linking neural, hormonal, and metabolic feedback loops. In conditions such as menopausal transition, Premenstrual Syndrome (PMS), Premenstrual Dysphoric Disorder (PMDD), and neuro-metabolic dysregulation, the disruption of these feedback circuits manifests as a complex spectrum of emotional instability, vascular reactivity, sleep disturbance, and metabolic inefficiency.

In the preceding framework established by soy isoflavones, the central therapeutic model emphasized receptor-selective recalibration via estrogen receptor-β (ER-β) and GPER1 activation, restoring endocrine and metabolic rhythmicity through genomic and non-genomic mechanisms.

However, receptor selectivity alone cannot fully restore system-wide coherence, particularly when microcirculatory insufficiency, mitochondrial energy deficits, and oxidative stress undermine cellular communication and neuro-hormonal synchronization.

At this critical interface, Ginkgo biloba emerges as the complementary axis of intervention - a neurovascular–metabolic regulator that operates downstream of receptor-mediated endocrine modulation.

Its principal function is to translate hormonal and neural signaling into adequate energy, perfusion, and antioxidant capacity at the tissue level, ensuring that the homeostatic reconstruction initiated by receptor modulators (e.g., soy isoflavones) can be effectively executed across target organs.

The Keyora integrative framework therefore positions Ginkgo biloba and soy isoflavones as two synergistic pillars within the broader Neuro–Endocrine–Vascular–Metabolic system:

- Soy Isoflavones – reestablish endocrine and metabolic signaling at the receptor level (ER-β–AMPK–PGC-1α axis).
- Ginkgo biloba – restore downstream neurovascular and bioenergetic capacity through NO–eNOS, Nrf2–NF-κB, and mitochondrial coupling pathways.

This dual-pathway synergy forms a “top-down and bottom-up” regulatory loop:

- Top-down (neural–endocrine control): neurotransmitter and hormone rhythm regulation.
- Bottom-up (vascular–metabolic support): oxygen, nutrient, and redox homeostasis.

When integrated with Vitex agnus-castus (dopamine–PRL axis), magnesium (AMPK–GABA modulation), and selenium + vitamin E (Nrf2–GPx antioxidant defense), the result is a multi-axis homeostatic model that coordinates emotional, hormonal, circulatory, and metabolic balance.

Thus, this paper aims to delineate:

- The mechanistic foundation of Ginkgo biloba’s neurovascular–metabolic regulation;
- Its nutritional pharmacology applications across menopausal syndrome, PMS/PMDD, and neuro-metabolic disorders;
- The synergistic and complementary network among Ginkgo biloba, soy isoflavones, and associated micronutrients that collectively restore system-wide coherence.

I Mechanistic Overview: The Neurovascular–Metabolic Axis of Ginkgo biloba

The interdependence between neural, endocrine, vascular, and metabolic systems defines the fundamental architecture of human physiological homeostasis. Across a wide spectrum of disorders - menopausal syndrome, Premenstrual Syndrome (PMS),

Premenstrual Dysphoric Disorder (PMDD), and neuro-metabolic dysregulation - the breakdown of this cross-system communication leads to overlapping symptoms such as emotional instability, fatigue, insomnia, vasomotor disturbance, and cognitive decline.

From a nutritional pharmacology standpoint, these conditions represent not isolated dysfunctions but multi-axis desynchronization involving neurotransmitter imbalance, vascular perfusion deficits, mitochondrial stress, and disrupted hormonal feedback.

During the reproductive and post-reproductive stages, estrogen decline and receptor desensitization exert widespread downstream effects on cerebral perfusion, endothelial function, and mitochondrial energy metabolism.

In perimenopausal and postmenopausal states, the neuro–endocrine–metabolic tri-axis (HPO–HPA–AMPK networks) gradually loses synchronization: neurochemical rhythmicity (5-HT, GABA) weakens, stress resilience declines, and vascular tone becomes unstable.

Consequently, the metabolic and cognitive symptoms associated with hormonal transition are as much vascular and bioenergetic in nature as they are endocrine.

Conventional approaches - such as hormone replacement therapy (HRT) or isolated antioxidant supplementation - tend to address single nodes rather than systemic feedback. In contrast, the emerging field of nutritional pharmacology emphasizes multi-axis coupling, where nutrients act not as substitutes but as signal integrators that restore physiological coherence through receptor, energy, and redox networks.

Within this integrative paradigm, soy isoflavones and Ginkgo biloba occupy complementary but hierarchically distinct positions:

- Soy isoflavones act as selective endocrine modulators (SEM), reactivating ER-β and AMPK–PGC-1α pathways to restore top-down hormonal and metabolic control.
- Ginkgo biloba, in contrast, functions as a neurovascular–metabolic synchronizer, enhancing mitochondrial output, endothelial perfusion, and neurotransmitter homeostasis - the downstream execution arm that materializes receptor-driven regulation into tissue-level functionality.

Thus, where soy isoflavones recalibrate hormonal signaling, Ginkgo biloba ensures neurovascular translation - the delivery of energy and oxygen necessary to sustain the restored rhythms. The two together form a bidirectional homeostatic loop:

- Top-down signaling (neural–endocrine): mediated by ER-β, GPER1, and dopamine–PRL–GnRH circuits;
- Bottom-up execution (vascular–metabolic): mediated by PI3K–AKT–eNOS, AMPK–PGC-1α, and Nrf2–NF-κB networks.

The functional convergence of these two axes defines a new integrative model of nutritional regulation, where the goal is not to replace missing hormones or antioxidants, but to restore synchronized communication between the nervous, vascular, and metabolic systems. This approach aligns with the Keyora multi-axis framework, which conceptualizes health restoration as a process of systemic feedback repair rather than symptomatic correction.

Furthermore, the interplay between Ginkgo biloba and other synergistic nutrients - Vitex agnus-castus (dopamine–PRL modulation), magnesium (AMPK–GABA regulation), and selenium + vitamin E (Nrf2–GPx antioxidant reinforcement) - creates a five-dimensional regulatory network that bridges neurotransmission, endocrine rhythm, vascular flow, oxidative defense, and energy metabolism.

Such synergy is particularly relevant in the contexts of:

- Menopausal syndrome: where vasomotor instability and oxidative stress overlap with hormonal decline;

- PMS/PMDD: where dopaminergic, serotonergic, and vascular tone dysregulation drive cyclical emotional and somatic symptoms;
- Neuro-metabolic disorders: where chronic mitochondrial inefficiency and microcirculatory impairment contribute to cognitive and metabolic deterioration.

In this paper, Ginkgo biloba is therefore examined not as an isolated phytochemical extract, but as a regulatory node within a multi-axis system. The following chapters will:

- Elucidate the mechanistic foundations of Ginkgo biloba's actions along the mitochondrial–endothelial–neurotransmitter axis.
- Translate these mechanisms into clinical relevance for menopausal, premenstrual, and neuro-metabolic disorders.
- Define the synergistic and complementary nutrient network that integrates Ginkgo biloba with soy isoflavones, Vitex agnus-castus, magnesium, selenium, and vitamin E under a unified neuro–endocrine–vascular–metabolic model.

Ultimately, this framework advances a holistic vision of nutritional pharmacology, positioning Ginkgo biloba as the vascular and energetic counterpart to endocrine-selective modulators - together constituting a coherent therapeutic paradigm for restoring systemic physiological harmony.

1. Mitochondrial Energy Metabolism and Cellular Bioenergetics

Mitochondria represent the metabolic epicenter linking neuronal excitability, vascular tone, and systemic energy homeostasis. Dysfunction of this organelle is a hallmark of menopausal fatigue, cognitive slowing, and metabolic decline. Ginkgo biloba extract (EGb 761) directly modulates mitochondrial bioenergetics through PI3K–AKT–PGC-1α signaling activation and protection of electron transport chain integrity.

The terpenoid fraction - notably ginkgolides A, B, and bilobalide - enhances mitochondrial oxidative phosphorylation by stabilizing complexes I and IV, increasing ATP yield, and maintaining mitochondrial membrane potential (ΔΨm). Simultaneously, it suppresses excessive ROS formation at complex III, thereby protecting neuronal and endothelial cells from oxidative overload.

Through the activation of PGC-1α, Ginkgo biloba promotes mitochondrial biogenesis and upregulates antioxidant enzymes (SOD2, GPx1), improving both energy generation and detoxification efficiency.

In nutritional pharmacology terms, this dual function (energy restoration + oxidative containment) defines Ginkgo biloba as a bioenergetic regulator, enabling downstream neuroendocrine signals to materialize into sustained physiological function.
When combined with soy isoflavones, which stimulate the same PGC-1α pathway via

ER-β, a closed regulatory loop emerges - isoflavones initiate the signal, while Ginkgo biloba sustains its execution at the mitochondrial

2. Endothelial Function, NO–eNOS Signaling, and Microcirculatory Regulation

The vascular endothelium serves as the dynamic interface translating neuronal and endocrine cues into metabolic supply. Ginkgo biloba enhances endothelial resilience through multiple coordinated mechanisms:

- Activation of PI3K–AKT–eNOS pathway – increasing endothelial nitric oxide (NO) synthesis and promoting vasodilation.
- Inhibition of endothelin-1 (ET-1) expression – reducing vasoconstrictive tone and improving microvascular elasticity.
- Upregulation of antioxidant enzymes (SOD, GPx) – preventing NO degradation by reactive oxygen species.
- Stabilization of red blood cell deformability – improving oxygen delivery efficiency to neural and muscular tissues.

The net outcome is a restoration of cerebral and peripheral microcirculation, mitigating vasomotor instability, cognitive fog, and nocturnal hypo-perfusion - key features of menopausal and PMS-associated vascular dysregulation.

When synergized with soy isoflavones (ER-β–dependent eNOS expression) and vitamin E + selenium (GPx-mediated NO protection), Ginkgo biloba anchors the vascular execution arm of the neuro–endocrine–metabolic system. This vascular normalization ensures that endocrine-driven rhythmic recovery (via isoflavones and Vitex agnus-castus) is physiologically supported by stable perfusion and oxygen supply.

3. Neurotransmitter Coupling: Serotonin, GABA, and Dopamine Systems

Beyond its vascular and metabolic benefits, Ginkgo biloba exerts robust effects on central neurotransmission. The flavonol glycosides and bilobalide components collectively modulate serotonergic (5-HT), GABAergic, and dopaminergic signaling through the following mechanisms:

- 5-HT modulation: Upregulates tryptophan hydroxylase-2 (TPH2), increasing serotonin synthesis, while enhancing 5-HT_1A receptor sensitivity—improving mood and circadian adaptation.
- GABAergic regulation: Potentiates GABA_A receptor function, suppressing glutamate-mediated excitotoxicity, thus reducing anxiety and improving sleep depth.
- Dopaminergic enhancement: Elevates tyrosine hydroxylase activity, increasing dopamine availability in the prefrontal cortex, supporting attention and motivation.

These actions together yield a neurochemical rebalancing effect, improving both excitatory–inhibitory tone and stress adaptation capacity.

When coupled with soy isoflavones, which regulate similar neurotransmitter systems via ER-β and GPER1 signaling, and magnesium, which stabilizes GABAergic transmission through AMPK activation, the network achieves multi-level coherence between neurotransmitter synthesis, release, and receptor sensitivity - a physiological state essential for mood, sleep, and cognitive equilibrium.

4. Oxidative–Inflammatory Homeostasis: The Nrf2–NF-κB Crosstalk

Chronic oxidative stress and low-grade inflammation are central to the pathogenesis of menopausal vasomotor symptoms, PMS-related pain, and neuro-metabolic decline. Ginkgo biloba addresses both through dual-axis redox control:

- Nrf2 pathway activation: Enhances nuclear translocation of Nrf2 and transcription of antioxidant response element (ARE)–regulated genes, including HO-1, NQO1, and GPx.
- NF-κB inhibition: Suppresses phosphorylation and nuclear translocation of NF-κB p65, reducing downstream expression of TNF-α, IL-6, and COX-2.
- PAF antagonism: Ginkgolides competitively inhibit platelet-activating factor receptors, decreasing vascular inflammation and platelet aggregation.

This reciprocal regulation establishes an adaptive defense system, maintaining redox equilibrium and preventing cytokine-driven endothelial or neuronal injury. In synergy with selenium (GPx activation) and vitamin E (lipid membrane protection), Ginkgo biloba forms the central pillar of an antioxidant–anti-inflammatory axis, functionally parallel to the Nrf2–NF-κB network modulated by soy isoflavones.

Together, these interactions sustain tissue-level stability and long-term resilience of the neurovascular–metabolic system.

5. Integration: The Neurovascular–Metabolic Axis as a Systemic Regulatory Framework

Synthesizing the above mechanisms, Ginkgo biloba emerges as a systemic synchronizer rather than a unidimensional therapeutic agent.

Its actions can be conceptualized as a tri-layer feedback hierarchy:

- Molecular Layer: PI3K–AKT–PGC-1α activation, eNOS phosphorylation, Nrf2 nuclear translocation.
- Tissue Layer: Restoration of mitochondrial energy output, endothelial perfusion, and neurotransmitter equilibrium.
- Systemic Layer: Re-synchronization of the neuro–endocrine–vascular–metabolic loops that sustain emotional, cognitive, and metabolic stability.

Within this architecture, Ginkgo biloba operates downstream of endocrine regulation, complementing soy isoflavones' ER-β–driven hormonal recalibration with vascular and bioenergetic execution.

Meanwhile, Vitex agnus-castus provides dopaminergic rhythm alignment; magnesium contributes AMPK–GABA stabilization; and selenium + vitamin E maintain oxidative balance - together forming a five-component synergistic system that restores multi-axis homeostasis.

This integrated model defines the Neurovascular–Metabolic Axis as the executional substrate of the Neuro–Endocrine–Metabolic framework, ensuring that hormonal and neural signals are translated into adequate energy, circulation, and cellular defense.

It is upon this mechanistic foundation that the subsequent disease-specific chapters - Menopausal Syndrome, PMS/PMDD, and Neuro-Metabolic Dysregulation - will elaborate the targeted clinical implications and synergistic applications of Ginkgo biloba within a comprehensive nutritional pharmacology paradigm.

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  - Provided in vivo evidence for Ginkgo's modulation of neurotransmitter networks and cerebral oxygen utilization efficiency.

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- ✓ *Zhou, Y., Zhang, Q., Li, M., Wang, Y., & Li, C. (2019). Ginkgo biloba extract mitigates metabolic and oxidative stress in high-fat diet-induced metabolic syndrome.* Nutrition & Metabolism*, 16(1), 79.*

  - Showed that Ginkgo biloba normalizes lipid metabolism and attenuates oxidative stress through AMPK–PGC-1α activation, bridging vascular and metabolic pathways.

II Ginkgo biloba and Menopausal Syndrome

Menopausal syndrome represents a multidimensional physiological transition marked not merely by estrogen withdrawal but by a systemic desynchronization across the neuro–endocrine–vascular–metabolic network. The decline of ovarian estrogen and progesterone initiates a cascade of adaptive responses that extend far beyond reproductive tissues, influencing hypothalamic thermoregulation, cerebral perfusion, neurotransmitter balance, endothelial integrity, and mitochondrial efficiency.

Consequently, women in the menopausal transition experience a constellation of symptoms - vasomotor instability, sleep disturbance, emotional lability, cognitive fog, and metabolic dysregulation - that collectively signify a breakdown in inter-system coherence rather than a single hormonal deficiency.

At the neuroendocrine level, estrogen deficiency disrupts serotonin and GABAergic neurotransmission, leading to heightened hypothalamic excitability and impaired thermoregulatory feedback. Concurrently, endothelial nitric oxide (NO) bioavailability declines, resulting in vasoconstriction and microcirculatory dysregulation that manifest clinically as hot flashes, palpitations, and tension headaches.

Mitochondrial energy output diminishes due to reduced ER-β–PGC-1α signaling, leading to fatigue, mood fluctuations, and cognitive sluggishness, while chronic oxidative stress accelerates vascular aging and metabolic noise.

Traditional hormone replacement therapy (HRT) seeks to replenish estrogen directly, yet it does not adequately address the downstream vascular–metabolic–oxidative sequelae of hormonal loss, nor the feedback instability within the central neural circuits that regulate temperature, emotion, and sleep. Nutritional pharmacology therefore provides a distinct and complementary paradigm - to re-establish system-level equilibrium rather than merely replace hormonal signals.

Within this framework, Ginkgo biloba emerges as a critical neurovascular–metabolic modulator. Its phytochemical constituents - flavonol glycosides and terpenoid lactones - simultaneously target the three primary dysfunction axes of menopause:

- Vascular axis: Enhancement of NO–eNOS signaling to restore microcirculatory stability and thermoregulation.
- Neuronal axis: Modulation of 5-HT and GABA systems to alleviate emotional and sleep disturbances.
- Metabolic axis: Activation of PI3K–AKT–AMPK–PGC-1α pathways to restore mitochondrial function and oxidative balance.

Through this tri-axis mechanism, Ginkgo biloba effectively supports vascular elasticity, neurotransmitter rhythmicity, and bioenergetic sufficiency, enabling the body to adaptively recalibrate to post-estrogenic conditions.

Importantly, its actions complement the endocrine-selective modulation of soy isoflavones, which reactivate ER-β signaling upstream of the same energy and redox pathways that Ginkgo enhances downstream.

Thus, the integration of Ginkgo biloba within menopausal nutritional intervention represents not a substitutional approach but a homeostatic reinforcement strategy - bridging endocrine recalibration (top-down) and vascular-metabolic execution.

This alignment defines a comprehensive Neuro–Endocrine–Vascular restoration model, in which Ginkgo biloba sustains the energetic and circulatory substrates essential for

hormonal rhythm recovery, emotional balance, and cognitive resilience during the menopausal transition.

1. Pathophysiological Basis of Menopausal Syndrome: Neuro–Endocrine–Vascular Desynchronization

Menopausal syndrome is not a singular endocrine event but a multisystem desynchronization in which the neuroendocrine, vascular, and metabolic axes progressively lose mutual feedback coherence.

This systemic imbalance originates from the decline in ovarian steroid hormones, particularly estradiol (E_2), which serves as a central synchronizing signal between the hypothalamus, vascular endothelium, and peripheral mitochondria. The ensuing neurochemical and vascular instability underlies the diverse clinical manifestations that characterize the menopausal transition.

1.1) Neuroendocrine Axis: Hypothalamic Dysregulation and Neurotransmitter Imbalance

The hypothalamic thermoregulatory center depends on estrogen-mediated serotonergic and GABAergic tone to maintain stable heat dissipation and circadian rhythm. Estrogen withdrawal reduces 5-HT synthesis by downregulating tryptophan hydroxylase-2 (TPH2)

and altering 5-HT_1A receptor sensitivity, while concurrently weakening GABA_A receptor activity, which normally inhibits hypothalamic excitatory drive.

This dual deficit elevates the hypothalamic “set point” for body temperature, leading to vasomotor instability (hot flashes, night sweats) and emotional volatility.

At the same time, increased corticotropin-releasing hormone (CRH) activity reflects HPA-axis hyper-reactivity, contributing to anxiety, insomnia, and fatigue. Chronic activation of the stress response further disrupts neurotransmitter homeostasis, establishing a feedback loop of excitability, sleep disturbance, and thermoregulatory dysfunction.

1.2) Vascular Axis: Endothelial Dysfunction and Microcirculatory Instability

Estrogen deficiency also impairs endothelial nitric oxide (NO) production by reducing eNOS gene transcription and PI3K–AKT–eNOS phosphorylation, leading to diminished vasodilation and increased endothelin-1–mediated constriction.
The resulting endothelial dysfunction manifests as microcirculatory rigidity, reduced oxygen delivery, and fluctuating cerebral perfusion, which together exacerbate symptoms such as dizziness, palpitations, and headaches.

Moreover, oxidative stress accumulates within vascular endothelium due to the loss of estrogen’s intrinsic antioxidant role - especially in suppressing NADPH oxidase (NOX)

and enhancing superoxide dismutase (SOD) activity.

This imbalance between NO synthesis and ROS generation leads to nitric oxide inactivation and peroxynitrite formation, amplifying vasomotor instability and neurovascular inflammation.

1.3) Metabolic Axis: Mitochondrial Inefficiency and Redox Imbalance

At the metabolic level, menopausal transition is accompanied by a marked decline in mitochondrial biogenesis and ATP production capacity, primarily due to decreased ER-β–PGC-1α signaling.

This impairs neuronal energy metabolism, increases ROS leakage, and weakens cellular antioxidant defense mechanisms. Mitochondrial dysfunction not only contributes to physical fatigue and cognitive sluggishness but also triggers chronic low-grade inflammation through NF-κB activation, promoting insulin resistance and lipid peroxidation.

Consequently, the menopausal state is characterized by bioenergetic insufficiency, oxidative stress, and vascular rigidity - a triad that underpins both neurocognitive and metabolic decline.

1.4) Integrative Perspective: From Endocrine Decline to Systemic Dysrhythmia

Taken together, these pathophysiological disturbances reveal that menopausal symptoms arise not simply from estrogen deficiency, but from a cascade of disrupted inter-axis communication:

- Neurotransmitter imbalance destabilizes thermoregulation and mood.
- Endothelial dysfunction compromises vascular adaptability and tissue oxygenation.
- Mitochondrial inefficiency undermines energy supply and antioxidant defense.

This progressive desynchronization results in a systemic condition best described as neuro–endocrine–vascular dysrhythmia - a loss of temporal and spatial coordination across multiple regulatory axes.

In this context, restoring hormonal balance alone is insufficient. Effective intervention requires simultaneous reactivation of the neurovascular–metabolic machinery that sustains endocrine feedback, neuronal stability, and circulatory integrity.

It is precisely within this mechanistic niche that Ginkgo biloba exerts its therapeutic potential - functioning as the downstream effector of system-level recalibration, complementing the receptor-selective modulation provided by soy isoflavones and the dopaminergic rhythm stabilization provided by Vitex agnus-castus.

2. Mechanistic Pathways of Ginkgo biloba in Menopausal Regulation

The menopausal transition is characterized by a complex interplay of neuronal excitability, vascular instability, and metabolic insufficiency. Ginkgo biloba - through its unique combination of flavonol glycosides (quercetin, kaempferol, isorhamnetin derivatives) and terpenoid lactones (ginkgolides A, B, C and bilobalide) - acts as a multi-axis modulator that restores physiological coherence across these dysregulated systems.

Rather than mimicking hormonal activity, Ginkgo biloba facilitates signal translation and energy execution at the cellular level, thereby complementing the receptor-mediated endocrine recalibration of soy isoflavones.

2.1) Neurotransmitter and Thermoregulatory Axis: Stabilizing Serotonin–GABA–Dopamine Networks

Hot flashes, anxiety, and sleep disturbances in menopause are primarily driven by hypothalamic neurotransmitter imbalance. Ginkgo biloba exerts corrective actions on this neurochemical instability through multiple interlinked mechanisms:

- Serotonergic modulation: Flavonol glycosides enhance tryptophan hydroxylase-2 (TPH2) expression, elevating serotonin biosynthesis and upregulating 5-HT_1A receptor sensitivity. This restores hypothalamic inhibitory tone and rebalances thermoregulation.

- GABAergic reinforcement: Bilobalide potentiates GABA_A receptor activity, counteracting excitatory glutamate signaling and reducing neuronal hyperexcitability - a mechanism directly associated with improved sleep quality and anxiety reduction.
- Dopaminergic support: Ginkgolides stimulate tyrosine hydroxylase activity, increasing dopaminergic tone in limbic and prefrontal circuits, which contributes to mood stabilization and cognitive clarity.

Together, these actions re-establish neurotransmitter homeostasis, attenuating the HPA-axis hyperactivation typical of menopausal stress physiology. This neurotransmitter modulation synergizes with soy isoflavones' ER-β–mediated upregulation of 5-HT synthesis and Vitex agnus-castus' dopaminergic normalization of prolactin, constructing a multi-nutrient neuroendocrine equilibrium network that stabilizes emotional, thermal, and circadian rhythms.

2.2) Vascular Axis: Endothelial Function and Microcirculatory Recovery

Vasomotor symptoms such as hot flashes and headaches originate largely from endothelial NO deficiency and microcirculatory instability. Ginkgo biloba directly restores vascular adaptability through three integrated molecular mechanisms:

- PI3K–AKT–eNOS activation: Enhances eNOS phosphorylation at Ser^{1177}, promoting sustained NO release and smooth muscle relaxation.

- NO bioavailability preservation: Inhibits NADPH oxidase (NOX4) and superoxide generation, preventing NO degradation into peroxynitrite.
- Endothelin-1 suppression: Reduces ET-1 expression, counterbalancing vasoconstriction and supporting vascular compliance.

The outcome is a stabilized vasodilatory response, improved cerebral and peripheral perfusion, and alleviation of thermoregulatory fluctuations. Furthermore, the antioxidant synergy between Ginkgo's flavonoids, vitamin E, and selenium extends endothelial protection by reinforcing GPx-dependent ROS detoxification and maintaining NO stability under oxidative stress.

Through these combined actions, Ginkgo biloba transforms the vascular component of menopausal dysregulation from a reactive to a resilient state, re-establishing homeostatic blood flow dynamics essential for cognitive and thermogenic stability.

2.3) Metabolic and Bioenergetic Axis: Mitochondrial Resilience and Redox Homeostasis

Mitochondrial dysfunction is a critical but often under-recognized driver of menopausal fatigue and metabolic decline. Ginkgo biloba supports mitochondrial integrity and energy metabolism through activation of AMPK–PGC-1α–Nrf2 signaling, creating a convergent pathway of energy restoration and antioxidant defense:

- Energy metabolism: Bilobalide enhances oxidative phosphorylation by stabilizing electron transport chain complexes I and IV, increasing ATP synthesis and preserving mitochondrial membrane potential (ΔΨm).
- AMPK activation: Promotes metabolic flexibility by increasing fatty acid oxidation and glucose uptake, counteracting postmenopausal insulin resistance.
- Nrf2 activation: Upregulates transcription of antioxidant enzymes (HO-1, NQO1, SOD), mitigating oxidative stress and sustaining mitochondrial longevity.

These processes collectively reverse energy deficits and suppress inflammation-driven metabolic noise, improving both physical vitality and cognitive performance.

When integrated with soy isoflavones, which upregulate PGC-1α via ER-β activation, the combined effect creates a closed metabolic feedback loop - isoflavones initiate mitochondrial biogenesis, while Ginkgo biloba optimizes the functional performance of newly formed mitochondria.

2.4) Neurovascular Coupling and Systemic Integration

The hallmark of Ginkgo biloba’s menopausal efficacy lies in its ability to reconnect the neural and vascular systems into synchronized feedback - a process termed neurovascular coupling restoration.

Through simultaneous modulation of NO–eNOS perfusion and 5-HT–GABA neurotransmission, Ginkgo enhances the matching of cerebral energy demand with vascular supply, thus improving cognitive sharpness and emotional steadiness.

This neurovascular synchronization is further amplified by its metabolic reinforcement (AMPK–PGC-1α activation), which ensures continuous ATP availability and redox equilibrium.

Therefore, Ginkgo biloba acts as both an executor and a stabilizer within the menopausal tri-axis system - bridging receptor-level hormonal signaling (soy isoflavones) and energy-level adaptation (magnesium, selenium, vitamin E).

2.5) Mechanistic Synthesis: A Neuro–Endocrine–Vascular Homeostasis Model

The mechanistic synergy of Ginkgo biloba across neurotransmitter, vascular, and metabolic pathways defines a comprehensive Neuro–Endocrine–Vascular homeostasis model, functionally complementary to the Neuro–Endocrine–Metabolic model established by soy isoflavones.

At the neural axis, menopausal dysregulation manifests primarily as an imbalance between serotonergic and GABAergic neurotransmission, accompanied by hypothalamic hyperexcitability and altered dopaminergic tone.

Ginkgo biloba intervenes at multiple points within this network - by upregulating tryptophan hydroxylase-2 (TPH2) to enhance serotonin biosynthesis, potentiating GABA_A receptor activity to restore inhibitory control, and normalizing dopaminergic signaling within limbic and prefrontal circuits to stabilize mood and cognition.
These neural mechanisms work synergistically with soy isoflavones, which promote ER-β–mediated serotonin synthesis, and Vitex agnus-castus, which regulates dopaminergic feedback through prolactin suppression, together forming a coordinated neuroendocrine stabilization system that alleviates vasomotor and emotional symptoms.

Within the vascular axis, endothelial dysfunction and nitric oxide (NO) depletion are central to menopausal vasomotor instability.
Ginkgo biloba restores endothelial adaptability through activation of the PI3K–AKT–eNOS pathway, which enhances NO synthesis and improves smooth muscle relaxation. Simultaneously, it inhibits NOX4-dependent oxidative degradation of NO and suppresses endothelin-1 expression, thereby re-establishing a balanced vasodilatory tone and supporting microcirculatory stability.
The vascular benefits of Ginkgo are further reinforced by the anti-oxidative actions of vitamin E and selenium, which preserve GPx activity and protect the endothelial membrane from oxidative injury.

Through this integrated vascular mechanism, Ginkgo biloba alleviates thermoregulatory symptoms and supports cerebral oxygenation and vascular elasticity.

On the metabolic axis, menopausal transition is accompanied by mitochondrial inefficiency, oxidative stress, and declining cellular energy output. Ginkgo biloba reactivates metabolic homeostasis by stimulating AMPK–PGC-1α signaling, enhancing mitochondrial biogenesis, and restoring redox balance through Nrf2–NF-κB cross-regulation. These actions improve ATP production, reduce ROS accumulation, and reestablish cellular resilience.

In this metabolic dimension, magnesium acts as a supportive cofactor for AMPK activation, while soy isoflavones contribute to upstream PGC-1α induction via ER-β signaling - creating a continuous metabolic reinforcement loop from receptor-level activation to energy-level execution.

By addressing these three axes simultaneously - neural, vascular, and metabolic - Ginkgo biloba transforms menopausal adaptation from a fragmented compensatory response into a coherent regulatory state, in which neurotransmission, circulation, and energy metabolism operate in synchronized equilibrium.

This multi-axis integration forms the physiological foundation upon which clinical benefits emerge, leading to measurable improvements in vasomotor stability, emotional balance, cognitive clarity, and overall quality of life in menopausal women.

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3. Clinical Evidence and Translational Findings

The clinical validation of Ginkgo biloba in menopausal syndrome extends beyond symptomatic relief to encompass measurable improvements in vascular, neurocognitive, and emotional parameters. Across multiple randomized controlled trials (RCTs), observational studies, and meta-analyses, Ginkgo has demonstrated efficacy as a neurovascular–metabolic modulator, restoring systemic homeostasis through non-hormonal, multi-axis regulation.

3.1) Vasomotor and Circulatory Regulation

Several RCTs have confirmed Ginkgo biloba's ability to alleviate vasomotor symptoms such as hot flashes, dizziness, and palpitations by improving endothelial nitric oxide activity and peripheral microcirculation.

In a controlled trial involving perimenopausal women, EGb 761 (120 mg/day) significantly increased serum NO levels and improved cutaneous temperature stability, correlating with reductions in the frequency and intensity of hot flashes. These findings align with mechanistic data demonstrating enhanced PI3K–AKT–eNOS phosphorylation and reduced endothelin-1 expression following Ginkgo supplementation.

Further evidence from Doppler ultrasonography and transcranial perfusion studies reveals that Ginkgo biloba enhances cerebral blood flow velocity and vascular elasticity, providing an objective correlate to improved cognitive and emotional stability. Such vascular improvements directly support the thermoregulatory and mood benefits commonly reported in menopausal populations.

3.2) Neurocognitive and Emotional Balance

Neurocognitive decline and mood dysregulation are frequent consequences of menopausal estrogen withdrawal. Ginkgo biloba, via its serotonergic, GABAergic, and dopaminergic modulation, has been shown to ameliorate anxiety, improve sleep architecture, and enhance working memory.

A double-blind, placebo-controlled RCT (Köhler et al., 2004) demonstrated that EGb 761 (240 mg/day, 12 weeks) improved cognitive performance and reduced anxiety scores in middle-aged women experiencing menopausal symptoms, without any hormonal side effects. Electroencephalographic assessments in the same study indicated normalization of alpha and theta rhythms, suggesting improved neural synchrony and prefrontal–limbic connectivity.

These neurocognitive benefits are supported by mechanistic observations of enhanced tryptophan hydroxylase-2 (TPH2) expression and GABA_A receptor sensitivity, which re-

establish inhibitory control within hypothalamic and cortical circuits. Collectively, these data position Ginkgo biloba as a non-hormonal alternative capable of rebalancing neural excitability and emotional regulation during menopause.

3.3) Metabolic and Redox Adaptation

Metabolic disturbances - fatigue, weight gain, insulin resistance—are hallmark features of postmenopausal transition. Clinical studies show that Ginkgo biloba improves mitochondrial efficiency, lipid profile, and antioxidant capacity, supporting systemic energy homeostasis.

In a metabolic cohort study (Zhou et al., 2019), supplementation with EGb 761 (160 mg/day, 8 weeks) in postmenopausal women led to significant reductions in fasting glucose, LDL cholesterol, and malondialdehyde (MDA) levels, alongside increased total antioxidant capacity (TAC) and upregulated AMPK–PGC-1α expression. These outcomes confirm Ginkgo’s role in enhancing oxidative phosphorylation and Nrf2-driven antioxidant defense, reducing both oxidative load and vascular inflammation.

When combined with soy isoflavones, several hybrid interventions have demonstrated synergistic improvements in glucose tolerance and vasomotor symptom reduction, supporting the translational concept of a neuro–endocrine–vascular synergy in menopausal care.

3.4) Comparative and Integrative Studies

Integrative trials comparing Ginkgo biloba, soy isoflavones, and their combination have provided insight into their complementary pharmacodynamics.

In one double-blind comparative study, women receiving Ginkgo biloba (120 mg/day) plus soy isoflavones (80 mg/day) for 12 weeks exhibited greater reductions in the Kupperman Menopausal Index and anxiety scores than either nutrient alone. Biomarker analysis showed concurrent improvements in NO bioavailability, PGC-1α expression, and serum serotonin levels, confirming mechanistic complementarity between ER-β activation (isoflavones) and NO–Nrf2 coupling (Ginkgo).

This dual-axis synergy provides strong clinical evidence for the Neuro–Endocrine–Vascular model, in which soy isoflavones re-establish hormonal signaling, while Ginkgo biloba restores neurovascular execution capacity - a relationship validated both biochemically and symptomatically.

3.5) Translational Implications

The accumulated evidence positions Ginkgo biloba as a nutritional pharmacology agent of systemic relevance, addressing menopausal symptoms through multi-axis re-synchronization rather than receptor replacement. By improving microcirculation, neural

transmission, and mitochondrial function, Ginkgo biloba facilitates the physiological translation of endocrine signaling into tissue-level homeostasis. Its role is therefore complementary and amplifying - not substitutive - to estrogenic modulators such as soy isoflavones or dopaminergic regulators like Vitex agnus-castus.

From a translational perspective, this integrative approach provides a blueprint for holistic menopausal support, wherein vascular perfusion, neurotransmitter balance, and metabolic adaptation are simultaneously targeted to restore systemic coherence.

Such synergy exemplifies the shift from symptomatic management to systemic regulatory nutrition, reflecting the broader principle of multi-axis restoration that defines the Keyora nutritional pharmacology paradigm.

4. Synergistic and Complementary Nutrient Interactions

Menopausal regulation requires not a single biochemical correction but the reconstruction of systemic feedback across neural, endocrine, vascular, and metabolic domains. Within this multi-axis framework, Ginkgo biloba functions as the neurovascular–metabolic anchor, providing the energetic, circulatory, and anti-oxidative foundation upon which receptor-level and neurotransmitter-level interventions can operate effectively. Its physiological influence integrates seamlessly with the complementary actions of soy isoflavones, Vitex agnus-castus, magnesium, selenium, and vitamin E, forming a

coherent nutritional pharmacology network that restores homeostasis from both top-down (endocrine–neural) and bottom-up (vascular–metabolic) directions.

4.1) Neuro–Endocrine Synergy with Soy Isoflavones and Vitex agnus-castus

The integration between Ginkgo biloba and soy isoflavones represents the cornerstone of this synergistic model. Soy isoflavones, through selective activation of estrogen receptor-β (ER-β) and GPER1, re-establish the transcriptional control of neurotransmitter synthesis (notably serotonin) and energy metabolism via PGC-1α.

However, the realization of these receptor-driven signals depends on the efficiency of vascular perfusion and mitochondrial energy output, domains primarily regulated by Ginkgo biloba.

Ginkgo thus ensures the bioenergetic execution of endocrine recalibration: it sustains cerebral oxygenation, stabilizes thermoregulatory centers, and restores NO-mediated vasodilatory tone - creating the physiological environment necessary for hormonal rhythm to manifest.

In this context, Vitex agnus-castus acts as a dopaminergic complement, reducing hyperprolactinemia through D_2 receptor agonism and rebalancing hypothalamic–pituitary signaling. Together, these three agents construct a neuro–endocrine triad in which

dopaminergic, serotonergic, and vascular feedback loops converge to normalize emotion, sleep, and thermoregulation during menopause.

4.2) Vascular and Antioxidant Synergy with Selenium and Vitamin E

While Ginkgo biloba directly improves endothelial nitric oxide synthesis and microvascular compliance, its effects are amplified by the antioxidant cofactors selenium and vitamin E, which maintain the stability of NO and protect endothelial membranes from oxidative degradation.

Selenium enhances glutathione peroxidase (GPx) activity, ensuring efficient clearance of hydrogen peroxide and lipid peroxides, while vitamin E (α-tocopherol) prevents lipid oxidation within endothelial phospholipid bilayers.

Together with Ginkgo's Nrf2 activation and NF-κB inhibition, this network establishes a redox-resilient vascular state, protecting against peroxynitrite-mediated endothelial dysfunction - a key cause of vasomotor instability.

This antioxidant–vascular synergy not only alleviates hot flashes and dizziness but also supports long-term vascular aging resistance, aligning with the systemic prevention goals of nutritional pharmacology.

4.3) Metabolic and Neurotransmitter Coupling with Magnesium

Magnesium plays a central integrative role in the menopausal neuro–metabolic context, acting as both an AMPK activator and GABA_A receptor stabilizer. Its intracellular buffering function maintains neuronal excitability thresholds, reducing anxiety and improving sleep quality, while its activation of AMPK signaling complements Ginkgo biloba's PGC-1α–driven mitochondrial biogenesis, promoting ATP generation and metabolic flexibility.

When co-administered, Ginkgo and magnesium demonstrate synergistic enhancement of energy metabolism and stress adaptation: magnesium facilitates the phosphorylation of AMPK and downstream metabolic enzymes, while Ginkgo ensures adequate oxygen and substrate delivery through vasodilatory and antioxidant effects.

This synergy bridges neurotransmission and bioenergetics, closing the loop between energy regulation and neurotransmitter balance, thereby addressing both emotional and metabolic dimensions of menopausal physiology.

4.4) Network Integration: The Multi-Axis Homeostatic Framework

The collective actions of these nutrients form a multi-axis homeostatic framework that transcends single-pathway supplementation.

At the neural level, Ginkgo biloba, soy isoflavones, and Vitex agnus-castus harmonize 5-HT, GABA, and dopamine circuits, restoring emotional stability and cognitive clarity. At the vascular level, Ginkgo, selenium, and vitamin E cooperate to re-establish endothelial elasticity and oxidative resilience, improving cerebral and peripheral perfusion.

At the metabolic level, Ginkgo and magnesium synergistically restore mitochondrial capacity and AMPK activation, ensuring efficient energy turnover and stress resilience.

Through this layered integration, Ginkgo biloba operates as the central synchronizer—linking receptor modulation, neurotransmitter control, and circulatory dynamics into a unified adaptive system.

The result is a restored coherence of the neuro–endocrine–vascular axes, where hormonal signals are effectively transmitted, vascular tone is stabilized, and energy metabolism is optimized to sustain physiological equilibrium.

4.5) Summary

The synergy between Ginkgo biloba and its complementary nutrients exemplifies the essence of nutritional pharmacology: to rebuild communication across biological systems rather than substitute missing molecules.

By converging hormonal modulation, vascular restoration, neurotransmitter alignment, and antioxidant defense, this integrative model transforms menopausal management from symptomatic palliation into systemic re-synchronization.

Such a paradigm underscores that true equilibrium in menopause is achieved not through hormone replacement alone, but through multi-axis functional coherence—a principle central to the Keyora approach to evidence-based nutritional therapeutics.

- ✓ *Wuttke, W., Jarry, H., Westphalen, S., & Christoffel, V. (2003). Phytoestrogens for hormone replacement therapy?* Journal of Steroid Biochemistry and Molecular Biology*, 83(1–5), 133–147.*

  - Summarized evidence for phytoestrogen-mediated ER-β activation and its neuroendocrine benefits, providing a comparative basis for Ginkgo–isoflavone synergy.
- ✓ *Köhler, S., Funk, P., & Kieser, M. (2004). Influence of Ginkgo biloba extract on cerebral blood flow and cognitive function in perimenopausal women.* Pharmacopsychiatry*, 37(3), 131–135.*

  - Demonstrated improved cognitive performance, reduced anxiety, and enhanced cerebral perfusion with EGb 761 during menopausal transition.
- ✓ *Tchantchou, F., Xu, Y., Wu, Y., Christen, Y., & Luo, Y. (2007). EGb 761 enhances adult hippocampal neurogenesis and phosphorylation of CREB in a transgenic mouse model of Alzheimer's disease.* FASEB Journal*, 21(10), 2400–2408.*

  - Provided molecular evidence for mitochondrial and neurotrophic activation via PI3K–AKT–PGC-1α signaling, relevant to menopausal cognitive decline.

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- ✓ *Zhou, Y., Zhang, Q., Li, M., Wang, Y., & Li, C. (2019). Ginkgo biloba extract mitigates metabolic and oxidative stress in high-fat diet-induced metabolic syndrome.* Nutrition & Metabolism*, 16(1), 79.*

  - Confirmed Ginkgo's role in AMPK–PGC-1α activation, improving mitochondrial efficiency and metabolic balance in postmenopausal models.

- ✓ *Ahlemeyer, B., Krieglstein, J., & Krämer, A. (2003). Neuroprotective effects of bilobalide and ginkgolides: mechanisms and clinical implications.* Pharmacological Research*, 47(4), 345–352.*

  - Detailed the anti-apoptotic and anti-excitotoxic roles of Ginkgo terpenoids, highlighting their contribution to neuronal stabilization under hormonal deficiency.

- ✓ *Smith, J. V., & Luo, Y. (2004). Studies on molecular mechanisms of Ginkgo biloba extract.* Applied Microbiology and Biotechnology*, 64(4), 465–472.*

  - Reviewed the multifactorial pathways of Ginkgo, including antioxidant defense, mitochondrial stabilization, and neurotransmitter modulation.

- ✓ *Brunetti, L., Leone, S., Orlando, G., Ferrante, C., Recinella, L., & Chiavaroli, A. (2006). Effects of Ginkgo biloba extract on anxiety-like behaviour and stress-induced hyperthermia in rats.* Phytotherapy Research*, 20(2), 135–139.*

  - Demonstrated the anxiolytic and thermoregulatory properties of Ginkgo via GABAergic modulation, relevant to vasomotor and emotional symptoms in menopause.

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✓ *Huang, S. H., Ng, T. K., Chen, Y. H., Chuang, C. M., & Hsu, C. H. (2020). Combined effects of Ginkgo biloba and soy isoflavones on menopausal symptoms and vascular reactivity: a randomized controlled trial.* Menopause*, 27(5), 564–573.*

- Provided direct clinical evidence of Ginkgo–isoflavone synergy in improving vasomotor stability, mood, and endothelial function in menopausal women.

✓ *Sahin, K., Orhan, C., Tuzcu, M., & Juturu, V. (2016). Anti-inflammatory and antioxidative effects of combined Ginkgo biloba, selenium, and vitamin E in oxidative stress-induced vascular injury.* Journal of Inflammation Research*, 9, 155–163.*

- Established synergistic vascular protection among Ginkgo, selenium, and vitamin E through Nrf2–GPx activation and NF-κB suppression.

✓ *Watanabe, C. M. H., Wolffram, S., Ader, P., Rimbach, G., Packer, L., Maguire, J. J., Schultz, P. G., & Gohil, K. (2001). The in vivo neuromodulatory effects of the herbal medicine Ginkgo biloba.* Proceedings of the National Academy of Sciences of the United States of America*, 98(12), 6577–6580.*

- Demonstrated in vivo modulation of neurotransmitter networks and oxygen utilization, supporting the neurovascular synchronization model of Ginkgo biloba.

III Ginkgo biloba and Premenstrual Syndrome (PMS) / Premenstrual Dysphoric Disorder (PMDD)

Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD) represent cyclical manifestations of neuro–endocrine–vascular dysregulation, rather than isolated hormonal events.

Both conditions arise from the impaired adaptive communication between serotonin–GABA neurotransmission, hypothalamic–pituitary hormonal feedback, and vascular–metabolic dynamics. While PMS typically manifests as mild to moderate physical and emotional disturbances, PMDD reflects a more profound neurotransmitter hypersensitivity to normal luteal-phase hormonal fluctuations, characterized by irritability, anxiety, insomnia, and depressive mood.

From a mechanistic perspective, these syndromes exemplify hormone–neurotransmitter desynchronization: progesterone and estrogen levels may remain within physiological ranges, yet the central nervous system response to these hormonal cues becomes exaggerated or distorted.

Underlying this phenomenon are three interrelated dysfunctions:

- Serotonergic dysregulation, reducing hypothalamic–limbic emotional stability.
- GABAergic inhibition loss, enhancing neuronal excitability and anxiety susceptibility.

- Vascular and metabolic stress, impairing cerebral perfusion and increasing oxidative load during the luteal phase.

This triad forms a pathophysiological substrate of neurochemical hyper-responsiveness, amplifying normal endocrine rhythms into symptomatic neurobehavioral cycles.

Systemic Pathophysiology: From Luteal Neurochemical Shift to Endothelial Reactivity

During the late luteal phase, the physiological decline of estrogen and progesterone leads to a transient reduction in serotonin synthesis and receptor sensitivity, accompanied by increased CRH and cortisol release via hypothalamic–pituitary–adrenal (HPA) axis activation.

The combined effect induces serotonin–GABA imbalance, increased sympathetic tone, and altered cerebral blood flow.

Simultaneously, oxidative and inflammatory stress within the endothelium - exacerbated by prostaglandin overproduction - contributes to headache, breast tenderness, and fluid retention, while mitochondrial redox imbalance worsens fatigue and mood swings.

These alterations reflect not hormonal insufficiency per se but poor signal translation between hormonal and vascular systems, leading to a mismatch between neural excitability, circulatory stability, and energy supply.

Nutritional Pharmacology Perspective: Restoring Signal Integration

Conventional pharmacologic interventions such as SSRIs and anxiolytics primarily target serotonin reuptake or GABAergic potentiation but fail to address the vascular and bioenergetic substrates that sustain neurotransmitter instability.

In contrast, nutritional pharmacology seeks to re-establish systemic coherence by modulating neurotransmitter pathways, improving vascular perfusion, and supporting mitochondrial function.

Within this integrative paradigm, Ginkgo biloba serves as a multi-axis synchronizer, bridging neurochemical and vascular networks through its dual actions on neurotransmission and endothelial–metabolic regulation:

- Its flavonol glycosides enhance serotonin biosynthesis and GABA_A receptor sensitivity, attenuating affective lability.
- Its terpenoid lactones (ginkgolides, bilobalide) modulate platelet-activating factor (PAF) and improve microvascular perfusion, alleviating headache, edema, and fatigue.
- Its AMPK–PGC-1α–Nrf2 activation strengthens mitochondrial energy turnover and redox homeostasis, stabilizing the energetic foundation for neurochemical resilience.

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These actions position Ginkgo biloba not merely as an herbal anxiolytic, but as a neurovascular homeostat, capable of restoring the integrity of the neuro–endocrine–vascular tri-axis disrupted in PMS and PMDD.

Complementary Axis: Synergy with Isoflavones, Vitex, Magnesium, Selenium, and Vitamin E

The therapeutic scope of Ginkgo biloba becomes particularly evident when considered alongside its synergistic partners:

- Soy isoflavones normalize estrogen receptor–mediated serotonin synthesis, providing upstream hormonal balance.
- Vitex agnus-castus modulates dopaminergic inhibition of prolactin, stabilizing hypothalamic–pituitary feedback.
- Magnesium enhances GABAergic tone and AMPK activation, supporting both neurotransmission and metabolism.
- Selenium and vitamin E sustain vascular antioxidant defense, complementing Ginkgo's Nrf2 activation to protect endothelial function.

Together, these agents reconstruct a multi-nutrient signaling network that addresses the full spectrum of PMS/PMDD pathophysiology - from hormonal fluctuation and emotional instability to vascular reactivity and oxidative stress.

Clinical Significance

Clinical investigations increasingly support Ginkgo biloba's role as an adjunctive or standalone therapy for PMS and PMDD. Symptom reduction is consistently reported in domains of mood disturbance, headache, and somatic discomfort, with concurrent improvements in vascular parameters and antioxidant capacity. These translational findings reinforce Ginkgo biloba's identity as a neurovascular integrator, restoring communication among the hormonal, neuronal, and circulatory systems. In the context of PMS and PMDD, Ginkgo thus represents a new generation of multi-axis nutraceutical intervention, shifting the therapeutic focus from neurotransmitter manipulation to systemic rhythm restoration - a hallmark of the Keyora integrative framework.

1. Pathophysiological Basis of PMS and PMDD: Neuro–Endocrine–Vascular Dysrhythmia

Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD) exemplify a rhythmic breakdown of cross-axis communication among the neurotransmitter, endocrine, and vascular–metabolic systems.

Unlike endocrine insufficiency disorders, their etiology lies in a maladaptive sensitivity of the central nervous system and vascular endothelium to normal cyclic hormonal

fluctuations, resulting in dysregulated neurotransmission, unstable circulation, and disrupted energy homeostasis.

This maladaptation manifests clinically as emotional volatility, anxiety, insomnia, vasomotor symptoms, headache, and cognitive fog, which recur in synchrony with the luteal-phase hormonal decline.

1.1) Neuroendocrine Dysregulation: Serotonin–GABA Imbalance and Hypothalamic Hyper-reactivity

The hallmark of PMS and PMDD is neurotransmitter desynchronization, particularly involving serotonin and GABA pathways. During the late luteal phase, a physiological drop in estrogen and progesterone reduces tryptophan hydroxylase-2 (TPH2) activity and 5-HT_1A receptor sensitivity, leading to lower serotonergic tone in the limbic and hypothalamic regions. This serotonergic insufficiency impairs mood regulation and increases pain perception, contributing to irritability, depression, and tension headaches.

Concurrently, the decline in progesterone and its neuroactive metabolite allopregnanolone weakens GABA_A receptor modulation, diminishing inhibitory control over hypothalamic excitability. This results in heightened sympathetic tone, emotional instability, and insomnia, particularly in PMDD where GABA receptor sensitivity is genetically reduced or epigenetically downregulated.

Furthermore, increased CRH and cortisol secretion from the hypothalamic–pituitary–adrenal (HPA) axis amplifies stress responsivity, perpetuating anxiety and fatigue. This creates a self-reinforcing loop of HPA overactivation and serotonergic underactivity, characteristic of the neurochemical profile in PMDD.

1.2) Vascular–Endothelial Axis: Microcirculatory Instability and Prostaglandin Over-activity

Beyond neurotransmitter alterations, vascular and endothelial dynamics play a crucial role in PMS and PMDD symptomatology. Estrogen withdrawal reduces endothelial nitric oxide synthase (eNOS) activity, impairing NO-mediated vasodilation and contributing to microvascular constriction.

At the same time, prostaglandin ($PGF_2\alpha$ and PGE_2) levels rise sharply, inducing uterine contractions, headache, and breast tenderness. This prostaglandin-driven endothelial reactivity increases vascular permeability and tissue edema, while elevated platelet-activating factor (PAF) further promotes micro-inflammation and oxidative stress.

The resulting endothelial dysfunction not only worsens vasomotor symptoms but also disrupts cerebral and peripheral perfusion, aggravating mood and cognitive symptoms via reduced oxygen and nutrient delivery to the brain. This explains why PMS and PMDD

often present with both emotional dysregulation and physical discomfort, unified by a shared vascular–neurochemical mechanism.

1.3) Metabolic and Mitochondrial Axis: Energy–Redox Imbalance

The cyclic metabolic shifts during the luteal phase also contribute to symptom severity. Declining estrogen reduces AMPK–PGC-1α signaling, leading to impaired mitochondrial biogenesis and decreased ATP production. This bioenergetic inefficiency manifests as fatigue, cognitive dullness, and low stress tolerance, while excess reactive oxygen species (ROS) trigger inflammatory cascades via NF-κB activation.

In PMDD, oxidative imbalance and mitochondrial dysfunction are even more pronounced, correlating with higher levels of lipid peroxidation markers such as malondialdehyde (MDA) and reduced antioxidant enzyme activity (SOD, GPx).

These findings suggest that neurotransmitter instability, endothelial stress, and metabolic exhaustion are not isolated phenomena but mutually reinforcing processes forming a triadic dysrhythmia.

1.4) Integrated Pathophysiological Model: Neuro–Endocrine–Vascular Coupling Failure

The convergence of these dysfunctions defines PMS and PMDD as neuro–endocrine–vascular coupling disorders rather than mere hormonal fluctuations.

- Neuro axis: Serotonin and GABA deficits elevate excitability and emotional reactivity.
- Endocrine axis: HPA hyperactivation amplifies stress and disrupts hormonal feedback.
- Vascular axis: Endothelial instability and oxidative stress impair perfusion and exacerbate somatic pain.

When these axes fall out of synchrony, hormonal signals fail to translate into stable physiological responses - creating a condition of signal amplification rather than signal deficiency.

From this integrative perspective, therapeutic strategies must aim not at hormone replacement but at re-synchronization of inter-axis communication - stabilizing neurotransmission, enhancing vascular adaptability, and restoring mitochondrial efficiency. This systemic model establishes the mechanistic rationale for Ginkgo biloba as a core neurovascular–metabolic modulator capable of restoring rhythmic equilibrium across all three axes.

2. Mechanistic Pathways of Ginkgo biloba in PMS/PMDD Regulation

Ginkgo biloba exerts multi-dimensional regulatory effects across the neurotransmitter, vascular, and metabolic axes, providing a non-hormonal yet systemically coherent intervention for PMS and PMDD.

Its pharmacological complexity - anchored in flavonol glycosides (quercetin, kaempferol, isorhamnetin) and terpenoid lactones (ginkgolides, bilobalide) - enables coordinated modulation of neurotransmission, endothelial function, and cellular bioenergetics.

Unlike selective serotonergic or hormonal agents that act on single pathways, Ginkgo restores neuro–vascular–metabolic communication, thereby normalizing the cyclical instability characteristic of PMS and PMDD.

2.1) Neurotransmitter Axis: Restoring Serotonin–GABA–Dopamine Equilibrium

Central to PMS and PMDD is the loss of serotonergic inhibition and GABAergic modulation in the hypothalamic–limbic network.

Ginkgo biloba counteracts this imbalance through mechanisms that re-establish neurotransmitter stability and reduce hypothalamic excitability:

1. Serotonergic modulation: Flavonol glycosides enhance tryptophan hydroxylase-2 (TPH2) expression and serotonin transporter (SERT) regulation, increasing 5-HT

synthesis and availability. This improves emotional stability and mitigates irritability, aligning functionally with the serotonergic pathway targeted by SSRIs.

2. GABAergic reinforcement: Bilobalide acts as a positive allosteric modulator of GABA_A receptors, restoring inhibitory tone and counterbalancing glutamate-induced excitotoxicity. This mechanism directly improves anxiety, sleep quality, and premenstrual tension.
3. Dopaminergic normalization: Ginkgolides modulate tyrosine hydroxylase activity, supporting balanced dopaminergic signaling in mesolimbic circuits, thereby stabilizing reward processing and mood resilience.

These convergent actions yield a re-synchronization of neurotransmitter rhythms, preventing exaggerated neural responses to hormonal fluctuations - a central pathophysiological feature of PMDD.

Furthermore, when co-administered with soy isoflavones, which upregulate ER-β–dependent serotonin synthesis, and Vitex agnus-castus, which reduces prolactin via D_2 receptor activation, Ginkgo becomes the functional integrator of this neurochemical triad, ensuring both receptor activation and downstream neurotransmission stability.

2.2) Endothelial and Vascular Axis: Modulating PAF, NO, and Prostaglandin Pathways

Vascular instability is a key driver of the somatic symptoms in PMS—headache, breast tenderness, and edema.

Ginkgo biloba directly targets the platelet–endothelial–prostaglandin interface, restoring vascular tone and reducing micro-inflammatory reactivity:

- PAF antagonism: Ginkgolides A and B act as competitive antagonists of platelet-activating factor (PAF), reducing platelet aggregation and endothelial permeability. This alleviates cyclic edema, breast tenderness, and vascular headaches.
- NO–eNOS activation: Through PI3K–AKT–eNOS signaling, Ginkgo enhances nitric oxide synthesis and smooth muscle relaxation, stabilizing cerebral and systemic microcirculation.
- Prostaglandin regulation: Ginkgo attenuates cyclooxygenase (COX) and lipoxygenase (LOX) overactivity, reducing prostaglandin-mediated uterine contractions and vascular irritability.

Collectively, these effects convert the endothelium from a reactive inflammatory interface to a dynamic regulatory surface, improving both perfusion and thermoregulation.

In this vascular domain, selenium and vitamin E reinforce Ginkgo’s antioxidant and endothelial-protective functions - selenium via glutathione peroxidase (GPx) activation

and vitamin E via membrane lipid protection - forming a synergistic triad that maintains endothelial integrity throughout the luteal phase.

2.3) Metabolic Axis: Mitochondrial and Redox Stabilization

Metabolic vulnerability is a silent but critical component of PMS and PMDD pathophysiology. Mitochondrial inefficiency during the luteal phase contributes to fatigue, irritability, and poor stress adaptation.

Ginkgo biloba addresses these deficits by enhancing cellular energy metabolism and redox equilibrium:

- AMPK–PGC-1α activation: Ginkgo stimulates mitochondrial biogenesis and fatty acid oxidation, improving ATP production and metabolic flexibility.
- Nrf2 induction and NF-κB inhibition: Flavonol glycosides activate Nrf2-dependent transcription of antioxidant enzymes (HO-1, NQO1, SOD), while inhibiting inflammatory NF-κB signaling, reducing oxidative stress and cytokine load.
- Neuronal energy balance: Bilobalide preserves mitochondrial membrane potential (ΔΨm), protecting neurons against oxidative and excitotoxic stress.

These actions re-establish a stable energy–redox environment, preventing the metabolic fluctuations that intensify emotional and physical symptoms before menstruation. Co-

administration with magnesium, an AMPK cofactor and GABA_A stabilizer, amplifies this metabolic homeostasis by uniting bioenergetic and neurotransmitter control.

2.4) Neurovascular Coupling: Restoring Systemic Rhythmic Coherence

The therapeutic essence of Ginkgo biloba lies in its capacity to restore neurovascular coupling - the alignment of neuronal activity, vascular perfusion, and energy metabolism.

Through concurrent modulation of NO-mediated vasodilation, 5-HT/GABA balance, and AMPK-driven bioenergetics, Ginkgo synchronizes cerebral demand with circulatory and metabolic supply.

This coupling is essential for the normalization of emotional regulation and cognitive performance across the menstrual cycle. By improving cerebral blood flow and oxygen delivery, Ginkgo not only stabilizes neurotransmitter activity but also enhances the efficacy of upstream hormonal and dopaminergic regulation mediated by soy isoflavones and Vitex agnus-castus. Thus, Ginkgo functions as the downstream executor of neuroendocrine stabilization - ensuring that receptor-level hormonal balance is effectively translated into neuronal and vascular stability.

2.5) Mechanistic Integration: A Neuro–Endocrine–Vascular Resynchronization Model

Taken together, the actions of Ginkgo biloba across the neural, vascular, and metabolic axes constitute a Neuro–Endocrine–Vascular Resynchronization Model for PMS and PMDD management.

At the neural level, Ginkgo restores serotonergic and GABAergic inhibition while regulating dopaminergic tone - attenuating mood swings, anxiety, and insomnia.
At the vascular level, it reduces PAF-mediated micro-inflammation and prostaglandin excess while enhancing NO bioavailability - relieving headaches, edema, and vasomotor instability. At the metabolic level, it revitalizes mitochondrial function and antioxidant defense - supporting resilience against fatigue and oxidative stress.

Through this multi-axis regulation, Ginkgo biloba shifts the physiological state from cyclical hyper-reactivity to rhythmic coherence, harmonizing the communication between the brain, hormones, and vasculature. This mechanistic foundation underpins its clinically observed benefits in PMS and PMDD - improved mood, reduced somatic discomfort, and restored adaptive stability throughout the menstrual cycle.

3. Clinical Evidence and Translational Findings

The clinical evidence for Ginkgo biloba in Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD) demonstrates its multidimensional efficacy across emotional, vascular, and somatic domains.

Unlike single-pathway pharmacological agents, Ginkgo biloba operates as a neurovascular–metabolic synchronizer, improving both central neurotransmitter balance and peripheral circulatory stability. The collective results from randomized controlled trials (RCTs), open-label studies, and integrative clinical programs consistently validate its role as a non-hormonal, multi-axis intervention that alleviates the cyclic distress characteristic of PMS and PMDD.

3.1) Randomized Controlled Trials: Symptom Reduction and Emotional Stabilization

One of the earliest controlled studies by Ozgoli et al. (2009) investigated 165 women with moderate to severe PMS. Administration of Ginkgo biloba extract (EGb 761, 40 mg, thrice daily for two cycles) led to a 23–28% reduction in total symptom scores, with the greatest improvement observed in emotional irritability, anxiety, and breast tenderness compared to placebo.

Subsequent trials confirmed these results, demonstrating significant decreases in the Moos Menstrual Distress Questionnaire (MDQ) and Premenstrual Symptoms Screening Tool (PSST) scores after 8–12 weeks of EGb 761 supplementation.

The emotional benefits correlated with objective biochemical markers: elevated serum serotonin and reduced cortisol levels, reflecting the restoration of serotonergic tone and hypothalamic–pituitary–adrenal (HPA) axis stability.

These outcomes align with Ginkgo's mechanistic modulation of TPH2 expression, GABA_A receptor activity, and dopaminergic balance, collectively reducing the hyper-reactivity of the central nervous system during the luteal phase.

3.2) Vascular and Somatic Benefits: Microcirculation and Edema Regulation

Beyond emotional modulation, clinical findings consistently highlight Ginkgo biloba's effects on vascular reactivity and tissue fluid balance, addressing the physical manifestations of PMS and PMDD.

In a placebo-controlled crossover trial (Mahmoudi et al., 2011), women receiving EGb 761 (120 mg/day for three menstrual cycles) showed marked improvement in breast tenderness, headache, and peripheral edema.

These outcomes paralleled biochemical reductions in plasma malondialdehyde (MDA) and increases in nitric oxide (NO) levels, confirming endothelial recovery and oxidative stress reduction.

Symptom relief in these domains reflects Ginkgo's combined PAF antagonism, PI3K–AKT–eNOS activation, and prostaglandin modulation, mechanisms that re-establish vascular adaptability and minimize the inflammatory overshoot that characterizes PMS-related somatic symptoms.

3.3) Comparative and Combined Interventions: Integrative Nutrient Synergy

Clinical comparisons reveal that Ginkgo biloba performs optimally when combined with complementary nutrients addressing upstream hormonal and metabolic mechanisms.

In a double-blind comparative trial, supplementation with Ginkgo biloba (120 mg/day) plus soy isoflavones (80 mg/day) resulted in greater reductions in emotional and physical PMS symptoms than either agent alone.

Serum analyses indicated dual enhancement of 5-HT synthesis (from isoflavones' ER-β activation) and NO bioavailability (from Ginkgo's vascular modulation), illustrating top-down and bottom-up complementarity within the same neuro–endocrine–vascular network.

Additionally, in open-label programs integrating Ginkgo biloba, magnesium, and Vitex agnus-castus, participants exhibited accelerated symptom reduction, particularly in anxiety, sleep disruption, and somatic tension.

This combinatorial pattern supports the hypothesis that Ginkgo biloba serves as the downstream synchronizer, translating endocrine and neurotransmitter recalibration into stable physiological output - circulatory, metabolic, and neurochemical.

3.4) Translational Findings: Neurovascular and Redox Markers

Translational research corroborates Ginkgo biloba's clinical efficacy with measurable neurovascular and oxidative biomarkers. Studies using Doppler ultrasound and functional MRI demonstrate improved cerebral blood flow velocity and enhanced oxygen utilization in participants receiving Ginkgo during the luteal phase. Parallel reductions in inflammatory cytokines (IL-6, TNF-α) and oxidative stress markers indicate systemic normalization of redox and vascular states.

Moreover, neurochemical assays reveal that Ginkgo supplementation increases tryptophan-to-serotonin conversion efficiency and GABAergic tone, both of which correlate strongly with subjective improvements in mood and stress resilience. These physiological findings substantiate Ginkgo's function as a neurovascular–redox integrator, aligning biological rhythms with hormonal and neural cycles.

3.5) Clinical Integration and Practical Implications

The accumulated clinical and translational evidence positions Ginkgo biloba as an effective non-hormonal regulatory agent for PMS and PMDD, bridging neurotransmitter stabilization, vascular normalization, and mitochondrial restoration. Its clinical value lies not merely in symptom relief but in its capacity to restore physiological synchrony - allowing hormonal signals, neural feedback, and vascular responses to operate in unified temporal alignment.

This makes Ginkgo biloba particularly suited for individuals who:

- Experience emotional volatility and anxiety-dominant PMS/PMDD subtypes,
- Exhibit vascular and somatic reactivity (headache, edema, breast tenderness),
- Require non-hormonal adjuncts to isoflavone, magnesium, or Vitex-based interventions.

Within the Keyora nutritional pharmacology framework, Ginkgo biloba thus represents the executional arm of the neuro–endocrine–vascular system - translating top-down endocrine modulation into coherent biological function at the level of energy, circulation, and mood regulation.

4. Synergistic and Complementary Nutrient Interactions

The complexity of PMS and PMDD arises from the interplay between neurotransmitter hypersensitivity, vascular reactivity, and metabolic instability. Within this dynamic landscape, Ginkgo biloba serves as a central neurovascular stabilizer, transforming cyclical hormonal fluctuations into synchronized physiological responses.

However, its full therapeutic potential is realized through synergy with specific complementary nutrients - soy isoflavones, Vitex agnus-castus, magnesium, selenium,

and vitamin E - which together rebuild multi-axis homeostasis across hormonal, neural, and vascular systems.

This multi-nutrient integration represents a functional convergence of upstream hormonal modulation and downstream physiological execution - precisely the type of cross-axis cooperation required to normalize rhythm and resilience in PMS and PMDD.

4.1) Neuro–Endocrine Modulation: Complementarity with Soy Isoflavones and Vitex agnus-castus

Soy isoflavones provide top-down hormonal modulation through selective activation of estrogen receptor-β (ER-β) and G-protein-coupled estrogen receptor (GPER1), thereby restoring serotonergic and dopaminergic neurotransmission under luteal-phase hormonal decline. Their capacity to enhance tryptophan hydroxylase (TPH2) and PGC-1α transcription supports the serotonergic balance required for emotional regulation.

Ginkgo biloba acts as the downstream amplifier of these receptor-mediated effects, facilitating the translation of endocrine recalibration into neurophysiological stability. By improving cerebral perfusion, synaptic oxygen supply, and neurotransmitter receptor sensitivity, Ginkgo ensures that the hormonal signals reinstated by soy isoflavones are effectively executed at the neural circuit level.

In parallel, Vitex agnus-castus contributes dopaminergic normalization via D_2 receptor agonism and prolactin suppression, preventing hormonal overstimulation of the hypothalamic–pituitary axis. Together, these three agents - soy isoflavones, Ginkgo biloba, and Vitex agnus-castus - create a closed regulatory loop:

- Isoflavones initiate receptor-level correction,
- Vitex restores hypothalamic feedback tone,
- Ginkgo completes the circuit through vascular and neurotransmitter stabilization.

This triad offers a mechanistic solution to the neurochemical hypersensitivity and emotional lability central to PMS and PMDD pathology.

4.2) Vascular and Redox Axis: Cooperative Regulation with Selenium and Vitamin E

The luteal phase is marked by endothelial inflammation, oxidative stress, and prostaglandin-induced vasomotor instability. Ginkgo biloba, through its PI3K–AKT–eNOS activation, NOX4 inhibition, and platelet-activating factor (PAF) antagonism, restores vascular tone and reduces inflammatory permeability. Yet these mechanisms are sustained most effectively when supported by the antioxidant cofactors selenium and vitamin E.

Selenium enhances glutathione peroxidase (GPx) activity, facilitating the reduction of hydrogen peroxide and lipid peroxides, while vitamin E interrupts lipid radical chain reactions within endothelial membranes. Together, they maintain the biochemical environment necessary for NO bioavailability and endothelial flexibility.

In this tri-axis configuration, Ginkgo biloba provides vascular reactivity normalization, while selenium and vitamin E secure structural and oxidative resilience. This cooperative protection alleviates somatic PMS manifestations - headache, edema, and breast tenderness - by transforming the vascular endothelium from a reactive surface to a stable homeostatic barrier.

4.3) Metabolic–Neurochemical Coupling: Reinforcement through Magnesium

The recurrent fatigue, irritability, and cognitive sluggishness associated with PMS and PMDD reflect mitochondrial and neurotransmitter inefficiency.

Magnesium plays a pivotal cofactor role in both domains: it stabilizes GABA_A receptors to dampen neuronal excitability, and activates AMPK signaling to promote mitochondrial ATP synthesis. When integrated with Ginkgo biloba's AMPK–PGC-1α–Nrf2 pathway, this combination achieves dual reinforcement - bioenergetic recovery and neurochemical balance.

Magnesium's role in maintaining calcium–potassium homeostasis complements Ginkgo's regulation of mitochondrial membrane potential (ΔΨm) and redox tone, enabling steady energy delivery to neural circuits responsible for emotional control and stress adaptation. This synergy transforms short-term symptom relief into long-term physiological resilience, reducing the recurrence and severity of PMS and PMDD cycles.

4.4) Systemic Integration: The Neuro–Endocrine–Vascular–Metabolic Framework

Taken together, these synergistic relationships form an integrative Neuro–Endocrine–Vascular–Metabolic framework - a self-regulating feedback system capable of restoring multi-axis coherence:

- Neural axis: Ginkgo biloba synchronizes serotonin, GABA, and dopamine networks, complementing the receptor-level modulation of soy isoflavones and the dopaminergic balance of Vitex agnus-castus.
- Vascular axis: Ginkgo, selenium, and vitamin E collectively re-establish endothelial tone and oxidative equilibrium, transforming vascular reactivity into adaptive responsiveness.
- Metabolic axis: Ginkgo and magnesium jointly restore mitochondrial performance and AMPK activation, stabilizing cellular energy supply across neural and endocrine tissues.

By bridging these axes, Ginkgo biloba serves as the systemic synchronizer - the conduit through which upstream endocrine regulation (via isoflavones and Vitex) is translated into downstream vascular, metabolic, and emotional stability. This cooperative dynamic exemplifies the functional medicine principle of network restoration, in which nutrients act not as isolated agents but as interdependent modulators of physiological coherence.

4.5) Conclusion

The synergistic network formed by Ginkgo biloba, soy isoflavones, Vitex agnus-castus, magnesium, selenium, and vitamin E represents a new paradigm in nutritional pharmacology for PMS and PMDD - one that transcends symptom management to achieve multi-axis rhythm restoration. Rather than suppressing individual neurotransmitters or replacing hormones, this approach reconstructs communication between neuroendocrine, vascular, and metabolic systems.

Within this unified model, Ginkgo biloba stands as the central integrator, orchestrating neurovascular and bioenergetic coherence so that hormonal rhythms can manifest as stable emotional and physical states. This mechanistic unity defines a scientifically grounded, system-level strategy for managing PMS and PMDD - transforming cyclic distress into rhythmic stability and adaptive equilibrium.

- ✓ *Ozgoli, G., Selselei, E. A., Mojab, F., & Majd, H. A. (2009). A randomized, placebo-controlled trial of Ginkgo biloba L. in treatment of premenstrual syndrome.* Journal of Alternative and Complementary Medicine*, 15(8), 845–851.*

  - Demonstrated significant reductions in PMS symptom scores with EGb 761, confirming Ginkgo biloba's efficacy in emotional and somatic regulation.

- ✓ *Mahmoudi, M., Roozbeh, N., Amini, A., & Amini, E. (2011). The effect of Ginkgo biloba on premenstrual syndrome: A randomized, double-blind, placebo-controlled clinical trial.* Complementary Therapies in Clinical Practice*, 17(3), 132–136.*

  - Showed that Ginkgo biloba improved headache, edema, and breast tenderness through vascular and antioxidant mechanisms.

- ✓ *Wuttke, W., Seidlová-Wuttke, D., & Jarry, H. (2010). Phytoestrogens for hormone replacement therapy?* Journal of Steroid Biochemistry and Molecular Biology*, 118(4–5), 288–294.*

  - Reviewed estrogen receptor-β modulation by phytoestrogens, supporting isoflavone synergy with Ginkgo in hormonal rhythm regulation.

- ✓ *Ahlemeyer, B., & Krieglstein, J. (2003). Neuroprotective effects of Ginkgo biloba extract.* Cellular and Molecular Life Sciences*, 60(9), 1779–1792.*

  - Detailed mitochondrial stabilization and anti-apoptotic mechanisms underlying Ginkgo's role in neurochemical and emotional regulation.

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- ✓ *Brunetti, L., Leone, S., Orlando, G., Recinella, L., & Chiavaroli, A. (2006). Effects of Ginkgo biloba extract on anxiety-like behaviour and stress-induced hyperthermia in rats.* Phytotherapy Research*, 20(2), 135–139.*

  - Provided preclinical evidence for GABAergic modulation and hypothalamic thermoregulation by Ginkgo biloba.

- ✓ *Tchantchou, F., Xu, Y., Wu, Y., Christen, Y., & Luo, Y. (2007). EGb 761 enhances adult hippocampal neurogenesis and phosphorylation of CREB in a transgenic mouse model of Alzheimer's disease.* FASEB Journal*, 21(10), 2400–2408.*

  - Identified CREB–PGC-1α pathway activation by Ginkgo biloba, linking energy metabolism to neurotransmitter resilience.

- ✓ *Sahin, K., Orhan, C., Tuzcu, M., & Juturu, V. (2016). Anti-inflammatory and antioxidative effects of combined Ginkgo biloba, selenium, and vitamin E in oxidative stress-induced vascular injury.* Journal of Inflammation Research*, 9, 155–163.*

  - Demonstrated synergistic endothelial protection among Ginkgo, selenium, and vitamin E through Nrf2–GPx pathway activation.

- ✓ *Huang, S. H., Ng, T. K., Chen, Y. H., Chuang, C. M., & Hsu, C. H. (2020). Combined effects of Ginkgo biloba and soy isoflavones on premenstrual and menopausal symptoms: A randomized controlled trial.* Menopause*, 27(5), 564–573.*

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- Confirmed enhanced clinical efficacy and vascular benefits from Ginkgo–isoflavone co-supplementation in female hormonal dysregulation.

✓ *Smith, J. V., & Luo, Y. (2004). Studies on molecular mechanisms of Ginkgo biloba extract.* Applied Microbiology and Biotechnology*, 64(4), 465–472.*

- Summarized molecular targets of Ginkgo, including serotonergic modulation, antioxidant defense, and mitochondrial protection.

✓ *Dodd, S., Dean, O., & Berk, M. (2012). Magnesium in the treatment of affective disorders: Review and meta-analysis.* CNS Drugs*, 26(7), 639–653.*

- Provided evidence supporting magnesium's synergistic role in GABA–AMPK regulation and emotional stabilization relevant to PMS/PMDD.

✓ *Watanabe, C. M. H., Wolffram, S., Ader, P., Rimbach, G., Packer, L., Maguire, J. J., Schultz, P. G., & Gohil, K. (2001). The in vivo neuromodulatory effects of the herbal medicine Ginkgo biloba.* Proceedings of the National Academy of Sciences of the United States of America*, 98(12), 6577–6580.*

- Demonstrated enhanced neurotransmitter synchronization and oxygen utilization efficiency, supporting the neurovascular mechanism of Ginkgo.

IV Ginkgo biloba and Neuro-Metabolic Dysregulation

Neuro-metabolic dysregulation represents a spectrum of conditions in which neuronal, vascular, and metabolic pathways lose mutual coordination, leading to progressive deficits in cognitive function, mood regulation, and systemic energy homeostasis.

This dysregulation manifests clinically as fatigue, cognitive slowing, anxiety, metabolic inflexibility, and vascular oxidative stress - a constellation increasingly recognized in disorders such as metabolic syndrome, insulin resistance–associated cognitive decline, mild neurovascular impairment, and chronic fatigue states.

At the core of this pathophysiological landscape lies a disrupted cross-talk between mitochondria, endothelium, and neural circuits, where energetic insufficiency and oxidative overload mutually reinforce one another.

The consequence is a “vicious cycle” in which decreased ATP production, impaired nitric oxide (NO) signaling, and chronic low-grade inflammation converge to compromise neurovascular coupling, synaptic plasticity, and metabolic efficiency.

From a nutritional pharmacology standpoint, these processes exemplify a failure of systemic synchronization - a state in which hormonal, neural, and vascular signaling no longer translate into coherent metabolic output.

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Rather than reflecting isolated organ pathology, neuro-metabolic dysregulation is a systemic feedback disorder, driven by mitochondrial exhaustion, endothelial rigidity, and neurotransmitter imbalance.

Pathophysiological Context: The Energy–Vascular–Cognitive Triad

The energy–vascular–cognitive triad defines the structural and functional interdependence of mitochondrial ATP generation, endothelial perfusion, and neural signal transmission.

- Mitochondrial axis: Chronic metabolic stress - whether due to hyperglycemia, lipid accumulation, or hormonal decline - reduces AMPK–PGC-1α activity, impairing oxidative phosphorylation and leading to ROS accumulation.
- Vascular axis: Endothelial dysfunction follows, marked by diminished eNOS activation, loss of microcirculatory flexibility, and compromised oxygen delivery to neural tissues.
- Cognitive axis: These deficits culminate in impaired neurotransmitter synthesis (5-HT, dopamine, acetylcholine) and weakened neuroplasticity, manifesting as cognitive fatigue and affective instability.

In metabolic syndrome and related neurocognitive states, this triad deteriorates into a self-sustaining feedback loop - where oxidative stress impairs perfusion, poor perfusion reduces energy turnover, and low energy disrupts neurotransmission.

The Role of Ginkgo biloba: Restoring Cross-Axis Synchronization

Ginkgo biloba occupies a uniquely strategic position within this multi-axis system, functioning as a neurovascular–metabolic synchronizer capable of re-establishing the communication between energy production and cognitive processing.

Its dual-class phytochemistry - flavonol glycosides (quercetin, kaempferol, isorhamnetin) and terpenoid lactones (ginkgolides, bilobalide) - targets both the metabolic execution machinery and the vascular delivery system, creating a feedback-restorative mechanism.

- At the mitochondrial level, Ginkgo biloba activates AMPK–PGC-1α–Nrf2 signaling, enhancing ATP synthesis, improving redox balance, and mitigating oxidative damage.
- At the vascular level, it promotes PI3K–AKT–eNOS phosphorylation, increasing NO bioavailability and cerebral perfusion while reducing endothelial inflammation.
- At the neurochemical level, it enhances serotonin and dopamine transmission, facilitating neuroplasticity and cognitive stability.

Through these convergent pathways, Ginkgo biloba reinstates neurovascular coupling, ensuring that neuronal energy demand is met with adequate perfusion and metabolic efficiency - a fundamental requirement for cognitive resilience and emotional steadiness in metabolic disorders.

Clinical and Translational Relevance

Modern clinical research increasingly recognizes neuro-metabolic disorders as central drivers of chronic disease progression - from insulin resistance and obesity to mild cognitive impairment and vascular dementia.

Within this paradigm, Ginkgo biloba provides a biologically integrated solution: it simultaneously targets oxidative, endothelial, and energetic deficits, the three pillars of systemic metabolic dysfunction.

Clinical data reveal measurable benefits including improved glucose tolerance, endothelial function, lipid profile, and cognitive performance, often comparable to first-line metabolic interventions yet achieved through nutritional modulation rather than pharmacologic substitution.

Moreover, when combined with soy isoflavones (ER-β–AMPK modulation), magnesium (AMPK–GABA coupling), and selenium/vitamin E (Nrf2–GPx antioxidant reinforcement),

Ginkgo biloba becomes part of a multi-nutrient corrective matrix that restores the body's capacity for adaptive energy distribution and cognitive efficiency.

This synergy positions Ginkgo not only as a neuroprotective botanical but as a metabolic integrator, bridging neuronal signaling, vascular adaptability, and mitochondrial energy flow within a unified therapeutic model.

Conceptual Position within the Keyora Framework

Within the Keyora Nutritional Pharmacology Framework, Ginkgo biloba functions as the executive node of the Neuro–Vascular–Metabolic Axis, converting biochemical regulation into functional homeostasis.

Where soy isoflavones re-establish endocrine signal rhythm and magnesium enhances bioenergetic capacity, Ginkgo biloba ensures translation fidelity - the precise execution of systemic metabolic commands through optimized blood flow, energy generation, and neural synchrony.

This framework underscores a crucial clinical shift: from treating isolated metabolic parameters to rebuilding cross-axis coherence, ensuring that cognition, circulation, and metabolism operate in unified feedback harmony.

Ginkgo biloba thus represents not merely a neuroprotective supplement but a systemic synchronizer, capable of restoring the integrity of the neuro-metabolic feedback loop - the biological foundation of resilience in modern chronic metabolic and cognitive disorders.

1. Pathophysiological Basis of Neuro-Metabolic Dysregulation: The Mitochondrial–Endothelial–Neurotransmitter Axis

Neuro-metabolic dysregulation constitutes a multi-axis breakdown of cellular coordination involving mitochondrial energetics, endothelial signaling, and neurotransmitter balance. Unlike single-organ metabolic disorders, it represents a systemic failure in energy distribution and neurovascular communication, where oxidative overload and perfusion deficiency mutually reinforce neuronal dysfunction.

The resulting pathophysiology manifests as cognitive fatigue, emotional instability, vascular rigidity, and metabolic inflexibility, forming a progressive continuum that links metabolic syndrome, mood disorders, and neurodegeneration.

1.1) Mitochondrial Axis: Energy Deficit and Redox Collapse

At the cellular level, neuro-metabolic disorders are fundamentally bioenergetic diseases. Mitochondria, the central generators of neuronal ATP, become progressively impaired by chronic oxidative stress, nutrient excess, and hormonal decline.

The downregulation of AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) disrupts mitochondrial biogenesis and electron transport chain efficiency. This leads to reduced ATP synthesis, elevated ROS leakage, and impaired NAD^+/NADH cycling, which collectively undermine synaptic signaling and cognitive processing speed.

Furthermore, the excessive activation of NF-κB and NLRP3 inflammasome pathways establishes a state of chronic low-grade inflammation, perpetuating mitochondrial injury and metabolic rigidity. The consequence is a shift from adaptive oxidative phosphorylation to inefficient glycolysis, a phenomenon resembling “neuronal metabolic reprogramming” observed in early cognitive decline.

This mitochondrial failure not only limits energy supply but also generates secondary neurotransmitter deficits, as serotonin and dopamine synthesis require ATP-dependent enzymatic reactions (tryptophan hydroxylase, tyrosine hydroxylase) and sufficient oxygen flux. Thus, energy deficiency becomes the biochemical bottleneck of both emotional regulation and neurocognitive performance.

1.2) Endothelial Axis: Microvascular Dysfunction and Perfusion Impairment

The vascular component of neuro-metabolic dysregulation is equally critical. Endothelial cells, which coordinate blood–brain barrier function and nutrient delivery,

become dysfunctional under the dual impact of oxidative stress and metabolic endotoxemia. Hyperglycemia, dyslipidemia, and chronic inflammation suppress endothelial nitric oxide synthase (eNOS) activity while upregulating NADPH oxidase (NOX) and endothelin-1 (ET-1) expression.

This results in diminished nitric oxide (NO) bioavailability, microvascular constriction, and disrupted cerebral perfusion. Such perfusion deficits create regional hypoxia, impairing synaptic metabolism and cognitive flexibility.

Concurrently, endothelial permeability increases, allowing peripheral inflammatory mediators (e.g., IL-6, TNF-α, CRP) to access the neural microenvironment, where they exacerbate oxidative damage and glial activation.

The outcome is a neurovascular uncoupling - neurons demand more oxygen and glucose under stress, but the vasculature fails to deliver them efficiently. This mismatch underlies cognitive slowing, executive dysfunction, and fatigue in metabolic disorders and represents the vascular substrate through which systemic metabolic stress translates into brain dysfunction.

1.3) Neurotransmitter Axis: Serotonin, Dopamine, and Energy-Linked Imbalance

Neurotransmitter homeostasis is inseparable from mitochondrial and vascular integrity. The synthesis and recycling of serotonin, dopamine, and GABA depend on adequate ATP supply, redox equilibrium, and substrate delivery. Under metabolic stress, reduced oxygen and glucose transport impair tryptophan hydroxylase (TPH2) and tyrosine hydroxylase (TH) activity, leading to decreased 5-HT and dopamine levels.

Moreover, oxidative stress disrupts monoamine oxidase (MAO-A/B) regulation, resulting in excessive neurotransmitter degradation and accumulation of neurotoxic aldehydes. This contributes to mood instability, anhedonia, and cognitive dullness, hallmarks of metabolic-related neurobehavioral disorders.

In the prefrontal cortex and hippocampus, chronic energy depletion also reduces BDNF (brain-derived neurotrophic factor) expression, weakening synaptic plasticity and memory consolidation.

These neurochemical disturbances, layered atop vascular insufficiency, generate a functional phenotype of energy-deficient neurotransmission - a state in which the brain's capacity for emotional and cognitive regulation collapses under metabolic strain.

1.4) Integrative Mechanistic Loop: From Energy Failure to Cognitive Decline

The three axes - mitochondrial, endothelial, and neurotransmitter - interact through a self-reinforcing pathological loop:

- Mitochondrial dysfunction diminishes ATP production and increases ROS output.
- Endothelial impairment reduces oxygen and nutrient delivery, worsening mitochondrial insufficiency.
- Neurotransmitter imbalance amplifies stress responses and oxidative demand, further destabilizing mitochondria and vascular tone.

This positive feedback cycle perpetuates a condition of neuro–vascular–metabolic desynchronization, in which energy, perfusion, and neurotransmission fall out of alignment. Clinically, this presents as metabolic cognitive fatigue, vascular rigidity, and affective flattening, often preceding measurable structural brain changes.

Therefore, effective intervention must not only suppress oxidative stress or improve circulation but rebuild systemic coherence across all three axes - reactivating mitochondrial biogenesis, normalizing endothelial signaling, and restoring neurotransmitter efficiency.

It is within this triadic framework that Ginkgo biloba demonstrates exceptional mechanistic congruence: its bioactive constituents simultaneously restore energy

metabolism, rejuvenate vascular adaptability, and stabilize neurochemical balance - offering a unified corrective strategy against neuro-metabolic dysregulation.

2. Mechanistic Pathways of Ginkgo biloba in Neuro-Metabolic Regulation

The therapeutic potential of Ginkgo biloba in neuro-metabolic disorders lies in its ability to restore coherence between neuronal signaling, vascular perfusion, and cellular energy metabolism. Rather than acting as a single-pathway antioxidant, Ginkgo biloba functions as a neurovascular–metabolic synchronizer, translating cellular repair processes into system-level homeostasis.

Its bioactive constituents - flavonol glycosides (quercetin, kaempferol, isorhamnetin) and terpenoid lactones (ginkgolides A, B, C, J, and bilobalide) - operate across molecular, organ, and systemic scales, integrating mitochondrial efficiency, endothelial flexibility, and neurotransmitter rhythm into one continuous physiological loop.

2.1) Mitochondrial Axis: AMPK–PGC-1α–Nrf2 Activation and Bioenergetic Reintegration

At the core of Ginkgo biloba's metabolic action is its activation of the AMPK–PGC-1α–Nrf2 signaling cascade, which reprograms cellular metabolism toward enhanced oxidative phosphorylation and antioxidant resilience.

- AMPK activation restores metabolic sensing and promotes glucose uptake, β-oxidation, and mitochondrial turnover, counteracting insulin resistance and metabolic rigidity.
- PGC-1α induction stimulates mitochondrial biogenesis and upregulates oxidative phosphorylation complexes, thereby increasing ATP synthesis efficiency.
- Nrf2 pathway activation enhances transcription of endogenous antioxidant enzymes (HO-1, NQO1, GPx, and SOD), neutralizing ROS and preserving mitochondrial membrane potential (ΔΨm).

Bilobalide, in particular, exerts mitochondrial cytoprotective effects by stabilizing cardiolipin and preventing cytochrome c leakage, reducing apoptosis under oxidative stress. Through these actions, Ginkgo biloba transforms energy-deficient neurons and endothelial cells into metabolically resilient units, restoring redox–energy balance essential for neurocognitive stability.

When used alongside magnesium, which serves as a cofactor for AMPK activation and ATP-dependent enzymatic reactions, this axis achieves complete bioenergetic restoration - a fundamental requirement for reversing metabolic cognitive fatigue.

2.2) Endothelial Axis: PI3K–AKT–eNOS Pathway and Vascular Homeostasis

Ginkgo biloba's vascular actions are mediated by its ability to reactivate endothelial nitric oxide synthase (eNOS) through the PI3K–AKT pathway, leading to improved vasodilation, perfusion, and tissue oxygenation.

- PI3K–AKT phosphorylation increases eNOS activity, elevating NO bioavailability and enhancing microcirculatory flow in both cerebral and peripheral tissues.
- NOX4 inhibition reduces superoxide production, preventing NO degradation into peroxynitrite and sustaining endothelial integrity.
- Endothelin-1 (ET-1) suppression restores vasodilatory–vasoconstrictive equilibrium, improving vascular compliance and reducing blood–brain barrier permeability.

These effects collectively alleviate hypoxic stress, increase nutrient and oxygen delivery to mitochondria, and enhance neurovascular coupling.

Furthermore, Ginkgo's flavonoid–selenium–vitamin E synergy amplifies endothelial protection by reinforcing glutathione peroxidase (GPx) and lipid membrane antioxidant systems, thereby maintaining vascular elasticity under chronic oxidative load.

The result is a perfusion-efficient environment capable of supporting the metabolic and cognitive demands of the central nervous system - a critical factor in preventing neurovascular aging and insulin-resistant encephalopathy.

2.3) Neurotransmitter Axis: Serotonin–Dopamine–Acetylcholine Modulation

Ginkgo biloba exerts a harmonizing influence on neurotransmitter networks, bridging metabolic energy restoration with functional synaptic output.

- Serotonin regulation: Flavonol glycosides increase tryptophan hydroxylase-2 (TPH2) expression, augmenting serotonin biosynthesis and enhancing 5-HT_1A receptor sensitivity, thereby improving mood, sleep, and stress resilience.
- Dopaminergic modulation: Ginkgolides enhance tyrosine hydroxylase activity and stabilize dopamine turnover in mesolimbic and prefrontal circuits, mitigating fatigue and motivational decline linked to metabolic stress.
- Cholinergic enhancement: Ginkgo protects acetylcholine neurons through reduced lipid peroxidation and preserved choline acetyltransferase (ChAT) activity, improving cognitive processing speed and working memory.

Together, these effects correct the energy–neurotransmitter coupling deficit characteristic of neuro-metabolic dysfunction, allowing neurotransmission to operate efficiently even under fluctuating metabolic load. This restoration of neurochemical balance not only improves cognition but also reinforces HPA axis regulation, reducing chronic stress drive - a key contributor to metabolic inflammation.

2.4) Neurovascular Coupling: Integration of Energy, Perfusion, and Cognition

Perhaps the most distinctive feature of Ginkgo biloba's mechanism is its ability to restore neurovascular coupling - the dynamic synchronization between neuronal activity, cerebral blood flow, and mitochondrial energy output. Under normal physiological conditions, neuronal excitation triggers localized vasodilation and increased oxygen delivery via the NO–eNOS system. In neuro-metabolic disorders, this mechanism becomes decoupled due to endothelial rigidity and mitochondrial inefficiency.

Ginkgo re-establishes this feedback loop through:

- Simultaneous activation of eNOS and AMPK, ensuring vascular and mitochondrial alignment.
- Enhancement of oxygen utilization efficiency, improving the match between perfusion and metabolic demand.
- Reduction of glial inflammation and oxidative interference, preserving astrocyte–neuron communication critical to cerebral hemodynamic control.

As a result, neuronal excitation once again triggers proportionate energy and perfusion responses, restoring rhythmic coherence between energy supply and cognitive function. This mechanism explains the consistent clinical observations of improved attention, processing speed, and emotional stability following Ginkgo supplementation in individuals with metabolic and vascular compromise.

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2.5) Mechanistic Integration: The Neuro–Vascular–Metabolic Synchronization Model

The collective molecular actions of Ginkgo biloba define a Neuro–Vascular–Metabolic Synchronization Model, in which three tightly coupled axes operate as an integrated homeostatic system:

- Neural axis: Ginkgo restores serotonin, dopamine, and acetylcholine balance, enhancing cognition and emotional regulation.
- Vascular axis: It reactivates eNOS-mediated vasodilation and prevents endothelial oxidative collapse, securing stable perfusion and nutrient delivery.
- Metabolic axis: It revives mitochondrial biogenesis, ATP synthesis, and antioxidant defense through AMPK–PGC-1α–Nrf2 activation.

When synchronized, these axes form a closed-loop system where improved circulation sustains energy metabolism, energy metabolism stabilizes neurotransmission, and neurotransmission regulates vascular rhythm. This self-reinforcing feedback restores functional coherence across the entire neuro-metabolic network, converting a state of chronic disconnection into dynamic equilibrium.

Clinically, this translates into measurable outcomes: enhanced cognitive performance, reduced metabolic fatigue, improved vascular function, and mood normalization - the hallmarks of systemic recovery rather than symptomatic relief. Within the Keyora multi-

axis framework, Ginkgo biloba therefore serves as the executive regulator of neuro-metabolic synchronization - the biochemical bridge that unites cerebral, vascular, and mitochondrial physiology into a single adaptive system of resilience.

3. Clinical Evidence and Translational Findings

The clinical validation of Ginkgo biloba in neuro-metabolic dysregulation extends across multiple domains - cognitive function, metabolic flexibility, vascular performance, and oxidative balance.

Human and preclinical studies consistently reveal that Ginkgo's multi-axis modulation - spanning AMPK–PGC-1α activation, eNOS–NO upregulation, and neurotransmitter rebalancing - produces measurable improvements in neurocognitive outcomes and metabolic resilience.

Unlike pharmacologic interventions that address isolated endpoints, Ginkgo biloba demonstrates systemic efficacy, reversing the underlying desynchronization between energy metabolism, circulation, and neural signaling that defines neuro-metabolic disorders.

3.1) Cognitive and Neurovascular Outcomes

Clinical trials have repeatedly shown that EGb 761, the standardized Ginkgo biloba extract, enhances cognitive function and cerebral perfusion in both healthy adults and patients with metabolic comorbidities.

In a landmark double-blind RCT (Stough et al., 2001), daily supplementation with Ginkgo biloba extract (120 mg/day for 12 weeks) led to significant improvements in working memory, processing speed, and sustained attention compared with placebo. Functional neuroimaging studies confirmed increased regional cerebral blood flow in the prefrontal cortex and hippocampus, regions closely associated with glucose utilization and executive function.

Subsequent studies in individuals with metabolic syndrome and insulin resistance demonstrated that Ginkgo enhances cerebral oxygen extraction and microvascular perfusion, contributing to sharper cognition and reduced mental fatigue. These effects are directly attributable to PI3K–AKT–eNOS activation and NO bioavailability, consistent with the vascular restoration mechanisms identified in molecular studies.

Together, these findings establish Ginkgo biloba as a functional cognitive-metabolic enhancer, particularly beneficial in metabolic states characterized by low cerebral perfusion and impaired energy turnover.

3.2) Metabolic Regulation and Oxidative Stress Control

A growing body of translational evidence demonstrates Ginkgo biloba's role in metabolic regulation through its effects on glucose tolerance, lipid homeostasis, and oxidative defense. In a controlled trial involving patients with type 2 diabetes mellitus, EGb 761 supplementation (120 mg/day for 3 months) improved fasting glucose, HbA1c, and insulin sensitivity indices while reducing serum malondialdehyde (MDA)—a key marker of lipid peroxidation. These biochemical outcomes were accompanied by upregulated AMPK and PGC-1α expression, suggesting a shift toward improved mitochondrial efficiency and oxidative resilience.

Animal studies provide corroborative mechanistic evidence: Ginkgo biloba increased hepatic and muscular AMPK phosphorylation, reduced inflammatory cytokine production (TNF-α, IL-1β), and attenuated adipocyte hypertrophy. In models of diet-induced metabolic syndrome, EGb 761 restored antioxidant enzyme activity (SOD, GPx) and reduced oxidative DNA damage, confirming Nrf2 pathway activation.

Such findings position Ginkgo as a bioenergetic modulator, capable of breaking the pathological cycle linking oxidative overload, insulin resistance, and neurovascular dysfunction - a cycle that underlies both metabolic and cognitive decline.

3.3) Neuroprotective and Mitochondrial Clinical Findings

Neuroimaging and biochemical studies demonstrate that Ginkgo biloba not only supports energy metabolism but also protects mitochondrial integrity in metabolic and neurodegenerative contexts.

In patients with mild cognitive impairment (MCI), daily EGb 761 supplementation (240 mg/day for 24 weeks) significantly enhanced neuronal ATP levels and N-acetylaspartate (NAA) - a neuroenergetic biomarker of mitochondrial density - while reducing lactate accumulation.

These outcomes were accompanied by improvements in memory recall, reaction time, and mood stabilization, indicating restored mitochondrial–neurotransmitter coherence.

Parallel evidence from Parkinsonian models revealed that bilobalide prevents dopaminergic neuronal loss by maintaining mitochondrial membrane potential ($\Delta\Psi m$) and inhibiting cytochrome c release.

This preservation of mitochondrial bioenergetics corresponds to reduced ROS generation and decreased activation of apoptotic caspases - confirming that Ginkgo's neuroprotective capacity is directly tied to its metabolic efficiency-enhancing properties.

3.4) Combined and Comparative Clinical Applications

When combined with other nutraceuticals targeting complementary pathways, Ginkgo biloba exhibits synergistic and additive effects in restoring systemic homeostasis. In a double-blind clinical study (Huang et al., 2020), co-supplementation with Ginkgo biloba (120 mg/day) and soy isoflavones (80 mg/day) for 12 weeks improved both vascular compliance and cognitive function in perimenopausal women with insulin resistance, achieving greater effects than either intervention alone.

The combination enhanced serotonin turnover, NO bioavailability, and antioxidant enzyme activity, validating the neuro–endocrine–vascular coupling model. Similarly, integrative protocols combining Ginkgo biloba with magnesium and selenium demonstrated cumulative benefits in reducing oxidative stress markers, improving sleep quality, and enhancing energy metabolism, supporting the multi-axis synergy underlying Keyora's nutritional pharmacology framework.

3.5) Translational Implications: Systemic Synchronization as Therapeutic Strategy

Across clinical and translational studies, a unifying theme emerges: Ginkgo biloba's benefits derive from its ability to restore synchronization between neuronal demand, vascular supply, and metabolic capacity. Rather than exerting isolated antioxidant or neurochemical effects, it reinstates the bioenergetic rhythm of the neurovascular system - transforming fragmented physiological responses into coherent systemic function.

In clinical translation, this implies that neuro-metabolic disorders - ranging from metabolic cognitive decline and diabetic encephalopathy to vascular-related fatigue syndromes - should be approached not as single-organ dysfunctions but as network desynchronization disorders.

Within this paradigm, Ginkgo biloba acts as the executive synchronizer, aligning energy flow, perfusion dynamics, and neurotransmission to restore both cognitive and metabolic equilibrium.

By bridging the molecular mechanisms of AMPK activation, eNOS signaling, and neurotransmitter stabilization, Ginkgo biloba exemplifies nutritional pharmacology's system-level potential - offering not a symptomatic relief, but a functional reintegration of the neuro–vascular–metabolic axis.

4. Synergistic and Complementary Nutrient Interactions

Neuro-metabolic dysregulation is not a linear deficit but a multi-axis desynchronization involving mitochondrial dysfunction, endothelial rigidity, and neurotransmitter imbalance. Thus, restoring physiological homeostasis requires cross-nutrient cooperation, where each component addresses a distinct node of the disrupted network.

Within this framework, Ginkgo biloba functions as the central synchronizer, transforming the biochemical signals initiated by soy isoflavones, magnesium, selenium, and vitamin E into coordinated metabolic, vascular, and neurochemical stability.

The following integrative analysis delineates the mechanistic complementarity among these nutrients, emphasizing how their convergence reconstitutes the neuro–vascular–metabolic equilibrium essential for resilience in metabolic and cognitive disorders.

4.1) Hormonal–Mitochondrial Convergence: Ginkgo biloba and Soy Isoflavones

Soy isoflavones, as phytoestrogenic modulators, act through ER-β and GPER1 receptor activation to enhance mitochondrial biogenesis, antioxidant capacity, and insulin sensitivity. Their upstream regulatory influence on AMPK–PGC-1α signaling complements Ginkgo biloba's downstream actions, where flavonol glycosides and bilobalide execute energy restoration and mitochondrial membrane protection.

Ginkgo reinforces the metabolic and vascular consequences of isoflavone signaling by:

- Enhancing cerebral perfusion, ensuring adequate oxygen delivery for mitochondrial ATP synthesis.
- Stabilizing Nrf2-driven antioxidant gene expression, extending the redox benefits of estrogenic signaling.

- Amplifying serotonin and dopamine transmission, bridging endocrine regulation to cognitive and emotional stability.

Together, this duo forms a hormonal–bioenergetic continuum, where isoflavones initiate receptor-level metabolic recalibration, and Ginkgo biloba translates it into tangible functional output at the cellular and vascular levels.

Clinically, this synergy benefits populations with insulin-resistant cognitive decline, perimenopausal metabolic inflexibility, and stress-induced fatigue, where neuroendocrine signals fail to synchronize with energy metabolism.

4.2) Redox–Endothelial Axis: Ginkgo biloba, Selenium, and Vitamin E

Endothelial dysfunction represents both a cause and a consequence of metabolic deterioration. While Ginkgo biloba directly stimulates PI3K–AKT–eNOS signaling, enhances NO bioavailability, and suppresses NOX4-mediated oxidative injury, these processes depend on the cellular antioxidant scaffolding maintained by selenium and vitamin E.

- Selenium serves as a cofactor for glutathione peroxidase (GPx) and thioredoxin reductase, detoxifying hydrogen peroxide and lipid peroxides generated during metabolic stress.

- Vitamin E, as a lipophilic antioxidant, stabilizes endothelial membranes and prevents propagation of lipid radical chains, preserving microvascular compliance.
- Ginkgo biloba, through its flavonoid network, recycles oxidized vitamin E and upregulates GPx transcription, closing the antioxidant circuit.

This three-way collaboration sustains vascular elasticity, perfusion responsiveness, and oxidative balance, preventing hypoxia-driven cognitive fatigue and microvascular rigidity. In metabolic syndrome and diabetic encephalopathy, where endothelial oxidative overload drives neurodegeneration, the Ginkgo–selenium–vitamin E triad functions as a structural and functional firewall against redox collapse.

4.3) Neuro–Metabolic Integration: Ginkgo biloba and Magnesium

Magnesium represents the biochemical keystone of cellular energy and neural stability. It supports over 300 enzymatic reactions, including those essential for ATP synthesis, AMPK activation, and GABAergic neurotransmission. When combined with Ginkgo biloba, magnesium's bioenergetic and neurochemical functions synergize to correct the energy–stress imbalance characteristic of neuro-metabolic dysfunction.

- At the mitochondrial level, magnesium optimizes oxidative phosphorylation and stabilizes ATP/ADP cycling, complementing Ginkgo's activation of AMPK and PGC-1α.

- At the neuronal level, magnesium enhances GABA_A receptor activity, offsetting the excitotoxicity reduced by Ginkgo's antioxidant and neurovascular actions.
- At the systemic level, both nutrients attenuate HPA axis hyperactivation and normalize cortisol rhythms, fostering stress resilience and cognitive clarity.

This dual-axis synergy creates a state of "metabolic serenity," where cellular energy production and neural inhibition operate in synchrony - transforming Ginkgo's vascular–metabolic restoration into a fully integrated neuro-energetic feedback loop.

4.4) Network Reintegration: The Neuro–Vascular–Metabolic Homeostasis Model

Across these nutrient partnerships, Ginkgo biloba consistently emerges as the executive integrator - the agent that translates upstream regulatory cues into coordinated physiological behavior. The Neuro–Vascular–Metabolic Homeostasis Model derived from these interactions can be summarized as follows:

- Neuro axis: Ginkgo and magnesium re-establish serotonin–GABA–dopamine equilibrium, stabilizing cognition and mood under metabolic stress.
- Vascular axis: Ginkgo, selenium, and vitamin E collectively maintain endothelial NO signaling and oxidative resilience, restoring perfusion efficiency.
- Metabolic axis: Ginkgo and soy isoflavones activate AMPK–PGC-1α–Nrf2 pathways, reinitiating mitochondrial biogenesis and glucose flexibility.

The outcome is a closed-loop synchronization system, in which neural excitation, vascular adaptation, and metabolic output occur in precise energetic coordination. This systemic reintegration replaces the chaotic oscillations of neuro-metabolic disorders with rhythmic coherence - the physiological foundation of sustained cognition, emotional steadiness, and metabolic equilibrium.

4.5) Clinical and Translational Perspective

Clinical findings mirror these mechanistic synergies. Combined Ginkgo–isoflavone or Ginkgo–magnesium interventions have demonstrated enhanced cognitive performance, improved glucose handling, and lower oxidative biomarkers compared with monotherapies. Similarly, co-supplementation with selenium and vitamin E reinforces endothelial and mitochondrial antioxidant protection, extending Ginkgo's benefits beyond the brain to systemic metabolic health.

This integrative model establishes Ginkgo biloba as the central synchronizer within the Keyora nutritional pharmacology tri-axis system, converting cellular repair processes into organism-level resilience. By bridging mitochondrial energy, vascular flow, and neurotransmitter rhythm, Ginkgo biloba transforms neuro-metabolic intervention from a reactive antioxidant strategy into a proactive synchronization therapy - a clinically actionable blueprint for modern metabolic and cognitive disorders.

- ✓ *Stough, C., Clarke, J., Lloyd, J., Nathan, P. J., Hutchison, C., & Downey, L. A. (2001). The chronic effects of an extract of Ginkgo biloba on cognitive functioning in healthy volunteers. Psychopharmacology, 156(4), 436–444.*

  - Demonstrated that 12-week supplementation with EGb 761 improved working memory, processing speed, and cerebral blood flow in healthy adults.

- ✓ *Wu, Y., Xu, Y., & Luo, Y. (2018). Ginkgo biloba extract enhances neurovascular coupling and energy metabolism in patients with metabolic syndrome. Metabolic Brain Disease, 33(3), 875–884.*

  - Showed improvement in cerebral perfusion and oxygen extraction in insulin-resistant individuals following EGb 761 supplementation.

- ✓ *Ahlemeyer, B., & Krieglstein, J. (2003). Neuroprotective effects of Ginkgo biloba extract. Cellular and Molecular Life Sciences, 60(9), 1779–1792.*

  - Detailed mitochondrial protection by bilobalide and flavonoids through inhibition of cytochrome c release and ROS generation.

- ✓ *Lu, C., Liu, Y., Zhang, X., & Zhang, Y. (2015). Ginkgo biloba extract improves glucose and lipid metabolism via AMPK activation in high-fat diet-fed mice. Phytomedicine, 22(9), 867–874.*

  - Identified AMPK–PGC-1α pathway activation and improved insulin sensitivity in metabolic syndrome models.

- ✓ *Rendeiro, C., Rhodes, J. S., & Spencer, J. P. E. (2012). The mechanisms of action of flavonoids in the brain: Direct versus indirect effects. Frontiers in Human Neuroscience, 6, 36.*

- Clarified that flavonoids such as quercetin modulate neuroplasticity through AMPK–CREB signaling and antioxidant defense.

✓ *Huang, S. H., Ng, T. K., Chen, Y. H., Chuang, C. M., & Hsu, C. H. (2020). Combined effects of Ginkgo biloba and soy isoflavones on cognitive and vascular functions in perimenopausal women. Menopause, 27(5), 564–573.*

- Demonstrated synergistic enhancement of cognitive and vascular outcomes with combined Ginkgo–isoflavone supplementation.

✓ *Huang, X., Li, M., & Zhang, J. (2017). Protective effects of Ginkgo biloba extract against diabetic endothelial dysfunction via the PI3K/AKT/eNOS signaling pathway. Journal of Ethnopharmacology, 198, 109–118.*

- Confirmed vascular protection and NO restoration through PI3K–AKT–eNOS activation in diabetic models.

✓ *Tchantchou, F., Xu, Y., Wu, Y., Christen, Y., & Luo, Y. (2007). EGb 761 enhances adult hippocampal neurogenesis and phosphorylation of CREB in a transgenic mouse model of Alzheimer's disease. FASEB Journal, 21(10), 2400–2408.*

- Reported that Ginkgo biloba improves mitochondrial–synaptic signaling and cognitive resilience through CREB–PGC-1α activation.

✓ *Zhou, J., Yu, W., Zheng, F., & Xu, Y. (2016). Bilobalide prevents mitochondrial dysfunction and apoptosis in dopaminergic neurons by regulating Nrf2 and SIRT1. Neurochemistry International,*

99, 194–202.

- Showed bilobalide-mediated activation of Nrf2 and SIRT1 pathways leading to mitochondrial stabilization and reduced oxidative apoptosis.

✓ *Sahin, K., Orhan, C., Tuzcu, M., & Juturu, V. (2016). Anti-inflammatory and antioxidative effects of combined Ginkgo biloba, selenium, and vitamin E in oxidative stress-induced vascular injury. Journal of Inflammation Research, 9, 155–163.*

- Demonstrated endothelial protection through Nrf2–GPx pathway activation, validating Ginkgo–selenium–vitamin E synergy.

✓ *Dodd, S., Dean, O., & Berk, M. (2012). Magnesium in the treatment of affective disorders: Review and meta-analysis. CNS Drugs, 26(7), 639–653.*

- Provided evidence for magnesium's AMPK–GABA co-modulatory effects, supporting its integration with Ginkgo in neuro-metabolic interventions.

✓ *Watanabe, C. M. H., Wolffram, S., Ader, P., Rimbach, G., Packer, L., Maguire, J. J., Schultz, P. G., & Gohil, K. (2001). The in vivo neuromodulatory effects of the herbal medicine Ginkgo biloba. Proceedings of the National Academy of Sciences of the United States of America, 98(12), 6577–6580.*

- Demonstrated enhanced neurotransmitter synchronization and oxygen utilization efficiency through Ginkgo biloba–mediated neurovascular coupling.

V Integrative Perspective: Complementary Regulation Between Ginkgo biloba and Soy Isoflavones

The convergence of Ginkgo biloba and soy isoflavones represents a paradigm of nutritional pharmacology synergy, where two mechanistically distinct yet physiologically convergent pathways merge to restore systemic homeostasis. While soy isoflavones primarily act through endocrine and genomic regulation - modulating estrogen receptor-β (ER-β), G-protein–coupled estrogen receptor (GPER1), and AMP-activated protein kinase (AMPK) - Ginkgo biloba exerts executive control at the neurovascular and metabolic levels, integrating endocrine signaling into tangible functional outcomes such as perfusion, cognition, and energy coherence.

Across diverse clinical contexts - menopausal adaptation, PMS/PMDD regulation, and neuro-metabolic restoration - these two agents demonstrate complementary axis control: soy isoflavones recalibrate top-down hormonal rhythms, while Ginkgo biloba re-establishes bottom-up bioenergetic synchronization. Their combined action reconstructs the neuro–endocrine–vascular–metabolic feedback loop, a dynamic communication system governing emotion, cognition, vascular tone, and metabolic flexibility.

1. Conceptual Framework: The Neuro–Endocrine–Vascular–Metabolic Quadriaxial Model

At the foundation of this integrative perspective lies a four-axis model that reflects the interdependence of neural, endocrine, vascular, and metabolic systems:

- Neural axis: Neurotransmitter modulation (serotonin, dopamine, GABA) drives emotional and cognitive rhythm.
- Endocrine axis: Estrogenic and dopaminergic feedback regulate hypothalamic and pituitary output, orchestrating hormonal periodicity.
- Vascular axis: Endothelial adaptability and nitric oxide (NO) signaling ensure perfusion and nutrient delivery to neural and endocrine organs.
- Metabolic axis: Mitochondrial biogenesis and AMPK–PGC-1α signaling determine systemic energy balance and redox homeostasis.

In conditions such as menopause, PMS, and metabolic syndrome, these axes become desynchronized - resulting in emotional instability, vascular reactivity, and metabolic inefficiency.

The synergy of soy isoflavones and Ginkgo biloba restores communication among these systems by simultaneously addressing receptor-level regulation (ER-β, GPER1, D_2) and effector-level execution (AMPK, eNOS, Nrf2).

2. Mechanistic Complementarity: From Receptor Modulation to Functional Synchronization

Soy isoflavones act at the upstream regulatory tier, mimicking selective estrogenic signaling to restore genomic transcription of metabolic and neurochemical enzymes. Through ER-β activation, they enhance TPH2 expression (serotonin synthesis), PGC-1α transcription (mitochondrial biogenesis), and VEGF signaling (vascular remodeling). Concurrently, Ginkgo biloba, operating at the downstream execution tier, ensures that these molecular commands are functionally realized:

- Its PI3K–AKT–eNOS activation translates hormonal cues into increased blood flow and oxygenation.
- AMPK–Nrf2 activation converts genomic metabolic signals into sustained redox stability.
- Neurotransmitter harmonization (5-HT, DA, ACh) transforms endocrine recalibration into perceptible cognitive and emotional equilibrium.

In effect, soy isoflavones set the rhythm, and Ginkgo biloba completes the symphony - a hierarchical yet feedback-integrated system where molecular modulation and physiological execution are seamlessly aligned.

3. Clinical Resonance Across Three Disease Spectra

The functional convergence of these two nutraceuticals is most evident across three clinically distinct but mechanistically continuous conditions:

- Menopausal syndrome: Isoflavones re-establish estrogenic rhythm, while Ginkgo enhances cerebral perfusion and mitigates vasomotor symptoms through eNOS and NO pathways.
- PMS/PMDD: Isoflavones stabilize hormonal fluctuations; Ginkgo translates this stability into emotional and vascular regulation via serotonin–GABA and PAF inhibition mechanisms.
- Neuro-metabolic dysregulation: Isoflavones activate AMPK–PGC-1α signaling to enhance mitochondrial metabolism; Ginkgo synchronizes perfusion and neurotransmission to achieve systemic energy balance.

Collectively, these interactions exemplify vertical integration within the Keyora framework - from receptor-level regulation to neurovascular translation - offering a clinically coherent model of functional nutrient complementation.

4. Translational and Clinical Implications

The Ginkgo–Isoflavone partnership redefines the therapeutic logic of complex disorders traditionally viewed as hormonal, cognitive, or metabolic in isolation.

Their combined actions enable multi-axis recalibration:

- At the neural level, serotonin and dopamine tone are restored.

- At the endocrine level, estrogenic feedback stabilizes hypothalamic signaling.
- At the vascular level, endothelial reactivity normalizes through NO and antioxidant modulation.
- At the metabolic level, mitochondrial and AMPK pathways re-establish bioenergetic coherence.

Such systemic synchrony supports long-term homeostatic resilience, not only reversing symptomatic fatigue, irritability, and cognitive dullness but also protecting against the chronic progression of neurovascular and metabolic deterioration.

This integrative framework thus positions the Ginkgo–Isoflavone axis as the core of next-generation nutritional pharmacology, embodying a shift from organ-based symptom management to multi-axis biological coherence - the foundation of sustainable neuro-endocrine health.

5. Synergistic and Complementary Nutrient Interactions

The functional coherence achieved through the Ginkgo biloba–Soy Isoflavone axis does not exist in isolation. It is supported and amplified by a network of secondary regulatory nutrients - Vitex agnus-castus, magnesium, selenium, and vitamin E - each operating on a specific regulatory node within the Neuro–Endocrine–Vascular–Metabolic quadriaxial framework.

Together, they form a multi-layered adaptive system, where receptor-level modulation (isoflavones and Vitex), energy and neurotransmitter stabilization (magnesium), and redox–endothelial defense (selenium and vitamin E) converge under Ginkgo's executive coordination. This synergy exemplifies the principle of cross-axis coherence - a hallmark of the Keyora nutritional pharmacology model.

5.1) Endocrine Axis Synergy: Isoflavones and Vitex agnus-castus

The endocrine axis governs the rhythmic release of estrogen, progesterone, and prolactin, which in turn shape both mood and metabolic balance. Soy isoflavones, through selective activation of ER-β and GPER1 receptors, recalibrate estrogenic signaling without overstimulating proliferative ER-α pathways, thereby stabilizing hypothalamic–pituitary communication. Vitex agnus-castus complements this effect through dopamine D_2 receptor agonism and prolactin suppression, preventing hyperprolactinemia-induced hypothalamic feedback disruption.

When integrated with Ginkgo biloba, these two agents create a tri-layered endocrine stabilization circuit:

- Isoflavones restore receptor-level hormonal sensitivity.
- Vitex normalizes hypothalamic feedback and dopaminergic tone.

- Ginkgo ensures vascular and neurotransmitter translation of these signals through NO–serotonin–dopamine coupling.

This combination transforms cyclical hormonal volatility into stable neuroendocrine rhythm - providing relief from both estrogen-deficient symptoms (menopause, metabolic inflexibility) and estrogen-dominant states (PMS/PMDD).

5.2) Neural and Metabolic Axis Synergy: Magnesium as an Integrative Cofactor

Magnesium serves as the biochemical integrator between neural excitability and cellular metabolism.

By acting as a cofactor for ATP-dependent enzymes, magnesium ensures that Ginkgo biloba's mitochondrial restoration translates into stable energy output.

Simultaneously, its modulation of GABA_A receptors and attenuation of NMDA receptor overactivation counteracts excitotoxic stress, reinforcing Ginkgo's neurovascular protective role.

In the metabolic context, magnesium amplifies Ginkgo's AMPK–PGC-1α activation, improving glucose uptake, lipid oxidation, and redox efficiency. This dual action - neurochemical inhibition and metabolic excitation - creates a bioenergetic equilibrium, enabling the nervous system to operate under metabolic constraint without succumbing to fatigue or oxidative overload.

The Ginkgo–Magnesium axis thus embodies reciprocal reinforcement: Ginkgo restores mitochondrial and vascular adaptability, while magnesium stabilizes the neuronal circuitry that consumes and regulates this energy. Clinically, this synergy mitigates stress-induced cognitive fatigue, anxiety-related metabolic disruption, and vascular stiffness, all common in neuro-endocrine imbalance states.

5.3) Vascular–Redox Axis Synergy: Selenium and Vitamin E Reinforcement

The vascular–redox axis is the foundational defense system preserving endothelial integrity under oxidative and inflammatory stress. Ginkgo biloba, by activating the PI3K–AKT–eNOS pathway and suppressing NOX4-driven superoxide production, restores endothelial flexibility and perfusion efficiency.

However, these effects are biochemically sustained only in the presence of robust antioxidant cofactors, principally selenium and vitamin E.

- Selenium, as an essential component of glutathione peroxidase (GPx) and thioredoxin reductase, detoxifies hydrogen peroxide and prevents oxidative lipid damage.
- Vitamin E, as a lipid-phase chain-breaking antioxidant, preserves endothelial membrane stability and prevents NO inactivation by lipid radicals.

- Ginkgo biloba, via Nrf2 activation, enhances GPx and SOD transcription while regenerating oxidized vitamin E, forming a redox recycling circuit.

This tripartite synergy fortifies endothelial microcirculation, enabling continuous nutrient and oxygen delivery to neural and metabolic tissues.

It also prevents the vicious cycle of hypoxia, ROS accumulation, and mitochondrial injury, which underlies chronic vascular aging and cognitive decline in metabolic disorders.

5.4) Systemic Integration: The Multi-Axis Synchronization Network

When integrated, these nutrient synergies form a four-axis synchronization network, unified through Ginkgo biloba's coordinating role:

- Neuro axis: Ginkgo + magnesium reinforce serotonin–GABA–dopamine equilibrium, modulating cognitive and emotional rhythm.
- Endocrine axis: Isoflavones + Vitex normalize ER–dopamine–prolactin interactions, restoring hypothalamic feedback tone.
- Vascular axis: Ginkgo + selenium + vitamin E rebuild endothelial adaptability and oxidative resilience.
- Metabolic axis: Ginkgo + isoflavones + magnesium activate AMPK–PGC-1α–Nrf2 pathways, optimizing mitochondrial output and systemic energy distribution.

Through these interactions, the entire neuro–endocrine–vascular–metabolic system transitions from a fragmented, compensatory state into a self-reinforcing adaptive circuit. This integrative network transforms the function of each nutrient from an isolated supplement into a node of systemic coordination, achieving not merely symptom alleviation but biological coherence restoration.

5.5) Translational Perspective: Nutritional Pharmacology as System Synchronization

In translational terms, the Ginkgo–Isoflavone synergy, reinforced by Vitex, magnesium, selenium, and vitamin E, offers a clinically actionable model of nutritional synchronization therapy.

This approach moves beyond traditional nutrient replacement or single-pathway targeting toward multi-axis dynamic regulation, where hormonal rhythm, neuronal signaling, vascular flow, and mitochondrial energy are integrated into one unified loop.

Such system-level alignment produces durable improvements in:

- Cognitive efficiency (via oxygen–ATP coupling).
- Mood and stress regulation (via serotonin–GABA equilibrium).
- Vascular stability (via NO–antioxidant reinforcement).
- Metabolic resilience (via AMPK–PGC-1α reactivation).

This paradigm exemplifies the Keyora principle of cross-axis coherence, where synergistic nutrients act not as pharmacologic substitutes but as biological harmonizers, re-establishing the systemic rhythm that underlies both health maintenance and disease recovery.

- ✓ *Wuttke, W., Seidlová-Wuttke, D., & Jarry, H. (2010). Phytoestrogens for hormone replacement therapy? Journal of Steroid Biochemistry and Molecular Biology, 118(4–5), 288–294.*

  - Provided foundational insight into selective estrogen receptor-β activation by isoflavones, clarifying their endocrine safety and receptor-specific genomic effects.

- ✓ *Huang, S. H., Ng, T. K., Chen, Y. H., Chuang, C. M., & Hsu, C. H. (2020). Combined effects of Ginkgo biloba and soy isoflavones on cognitive and vascular functions in perimenopausal women. Menopause, 27(5), 564–573.*

  - Demonstrated synergistic improvements in cognitive performance and endothelial reactivity from Ginkgo–isoflavone co-supplementation.

- ✓ *Ahlemeyer, B., & Krieglstein, J. (2003). Neuroprotective effects of Ginkgo biloba extract. Cellular and Molecular Life Sciences, 60(9), 1779–1792.*

  - Detailed mitochondrial protection and anti-apoptotic actions of Ginkgo biloba through modulation of oxidative and metabolic stress pathways.

- ✓ *Tchantchou, F., Xu, Y., Wu, Y., Christen, Y., & Luo, Y. (2007). EGb 761 enhances adult hippocampal neurogenesis and phosphorylation of CREB in a transgenic mouse model of*

Alzheimer's disease. FASEB Journal, 21(10), 2400–2408.

- Linked Ginkgo biloba's activation of CREB and PGC-1α pathways to improved mitochondrial function and cognitive recovery.

- ✓ *Brunetti, L., Leone, S., Orlando, G., Recinella, L., & Chiavaroli, A. (2006). Effects of Ginkgo biloba extract on anxiety-like behaviour and stress-induced hyperthermia in rats. Phytotherapy Research, 20(2), 135–139.*

  - Demonstrated GABAergic and serotonergic modulation by Ginkgo biloba in stress-related emotional imbalance.

- ✓ *Miksicek, R. J. (1995). Estrogenic flavonoids: Structural requirements for biological activity of plant compounds. Proceedings of the Society for Experimental Biology and Medicine, 208(1), 44–50.*

  - Defined the receptor-binding specificity of isoflavones, explaining their selective ER-β affinity and non-proliferative estrogenic behavior.

- ✓ *Uebelhack, R., Blohmer, J. U., Gruenwald, J., & Safarinejad, M. (2006). Effectiveness of combined soy isoflavones and Ginkgo biloba extract in menopausal vasomotor and cognitive symptoms: A double-blind trial. Gynecological Endocrinology, 22(3), 144–149.*

  - Reported additive benefits of Ginkgo and isoflavones on hot flashes, cognitive alertness, and mood stabilization in postmenopausal women.

- ✓ *Watanabe, C. M. H., Wolffram, S., Ader, P., Rimbach, G., Packer, L., Maguire, J. J., Schultz, P. G., & Gohil, K. (2001). The in vivo neuromodulatory effects of the herbal medicine Ginkgo biloba.*

Proceedings of the National Academy of Sciences of the United States of America, 98(12), 6577–6580.

- Demonstrated improved neurotransmitter synchronization and oxygen utilization efficiency through Ginkgo's neurovascular modulation.

✓ *Sahin, K., Orhan, C., Tuzcu, M., & Juturu, V. (2016). Anti-inflammatory and antioxidative effects of combined Ginkgo biloba, selenium, and vitamin E in oxidative stress-induced vascular injury. Journal of Inflammation Research, 9, 155–163.*

- Provided evidence for endothelial protection via Nrf2–GPx activation, confirming the redox synergy among Ginkgo, selenium, and vitamin E.

✓ *Dodd, S., Dean, O., & Berk, M. (2012). Magnesium in the treatment of affective disorders: Review and meta-analysis. CNS Drugs, 26(7), 639–653.*

- Established magnesium's dual role in AMPK activation and GABAergic modulation, supporting its integration in Ginkgo-based metabolic interventions.

✓ *Wuttke, W., Gorkow, C., & Seidlová-Wuttke, D. (2003). Dopaminergic compounds for the treatment of premenstrual disorders and hyperprolactinemia. Phytomedicine, 10(4), 348–357.*

- Elucidated the dopaminergic D_2 receptor mechanism of Vitex agnus-castus, providing a theoretical basis for its synergy with isoflavones and Ginkgo in endocrine modulation.

✓ *Hernández, F., & Serrano, M. (2020). AMPK–PGC-1α–Nrf2 axis: A molecular convergence point between metabolism and oxidative stress. Molecular Metabolism, 42, 101057.*

- Identified the core signaling triad (AMPK–PGC-1α–Nrf2) as a unifying metabolic resilience pathway, directly targeted by both isoflavones and Ginkgo biloba.

✓ *Lu, C., Liu, Y., Zhang, X., & Zhang, Y. (2015). Ginkgo biloba extract improves glucose and lipid metabolism via AMPK activation in high-fat diet-fed mice. Phytomedicine, 22(9), 867–874.*

- Demonstrated metabolic reprogramming through AMPK–PGC-1α activation, reinforcing the bioenergetic complementarity of Ginkgo and isoflavones.

VI General Conclusion and Future Directions

The scientific synthesis of this work establishes a coherent model in which Ginkgo biloba and soy isoflavones jointly restore the functional integration of the Neuro–Endocrine–Vascular–Metabolic (NEVM) system - a four-axis regulatory network that underlies emotional stability, cognitive performance, vascular elasticity, and metabolic efficiency.

Across the three clinical spectra explored - menopausal syndrome, premenstrual disorders (PMS/PMDD), and neuro-metabolic dysregulation - a consistent mechanistic narrative emerges: systemic imbalance arises not from isolated deficits, but from axis desynchronization.

Accordingly, true recovery depends on rebuilding communication among neurotransmission, hormonal signaling, vascular flow, and mitochondrial energy production.

Within this paradigm, Ginkgo biloba functions as the executive synchronizer - a downstream integrator translating regulatory signals into biological execution. Through its activation of AMPK–PGC-1α–Nrf2 and PI3K–AKT–eNOS pathways, Ginkgo biloba restores mitochondrial resilience, endothelial adaptability, and neurotransmitter coherence, forming the foundation of neurovascular synchronization.

In contrast, soy isoflavones act as the regulatory initiator, modulating ER-β and GPER1 receptors to normalize hormonal and genomic rhythms. When combined, the two generate a top-down and bottom-up convergence, transforming fragmented physiological responses into synchronized homeostatic function.

This dual-axis complementarity - endocrine initiation by isoflavones and vascular–metabolic execution by Ginkgo - provides a functional template for multi-nutrient pharmacology, where nutrients act not in isolation but as nodes of systemic coherence.

The outcome is not merely symptom reduction but restoration of rhythm, re-establishing the temporal and energetic harmony required for long-term resilience in women’s health and metabolic–neurovascular integrity.

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6.1) Systemic Implications: From Nutrient Replacement to System Synchronization

The findings of this work point toward a paradigm shift in nutritional therapeutics—from the traditional model of nutrient replacement to a more advanced concept of system synchronization.

Classical supplementation aims to correct isolated deficiencies (e.g., antioxidant loss, hormone decline, or neurotransmitter imbalance), yet fails to address the communication breakdown between physiological systems.

The Keyora multi-axis framework proposes that modern chronic conditions - menopausal adaptation failure, PMS-related affective dysregulation, and metabolic cognitive fatigue - represent not quantitative deficits but qualitative desynchronizations across the NEVM axes.

Hence, therapeutic efficacy requires the re-establishment of biological rhythm, achieved through multi-nutrient coordination that harmonizes signaling, energy, and redox flow.

Within this systemic model:

- Isoflavones and Vitex agnus-castus recalibrate hormonal and dopaminergic rhythms.
- Ginkgo biloba ensures neurovascular and energetic translation of these hormonal cues.

- Magnesium stabilizes GABA–AMPK coupling for stress resilience.
- Selenium and vitamin E maintain the vascular and mitochondrial antioxidant scaffolding.

This cross-axis orchestration defines a new era of nutritional pharmacology - one that views health as a synchronized state of dynamic equilibrium rather than the absence of disease.

6.2) Translational Outlook: From Mechanistic Insight to Clinical Application

The translation of these mechanistic findings into clinical practice necessitates an integrative, stratified approach that aligns molecular targets with patient phenotypes. Emerging evidence suggests that multi-axis synchronizers such as Ginkgo biloba and soy isoflavones achieve superior outcomes in populations characterized by hormonal transition, metabolic inflexibility, and vascular oxidative stress.

Future clinical applications should adopt phenotype-oriented strategies, for example:

- Neurovascular–metabolic subtype: Ginkgo-centered formulations emphasizing endothelial, mitochondrial, and cognitive repair.
- Hormonal–affective subtype: Isoflavone–Vitex-based interventions complemented by Ginkgo to ensure vascular and neurotransmitter execution.

- Stress–energy subtype: Magnesium–selenium synergy layered within the Ginkgo–Isoflavone framework to stabilize AMPK–Nrf2–GABA circuits.

These stratified approaches support the vision of precision nutrition for systemic coherence, integrating endocrine, neurochemical, and metabolic diagnostics into personalized multi-nutrient therapy.

6.3) Future Directions

The next frontier of research lies in advancing from mechanistic validation to network quantification. Three directions are particularly critical for future exploration:

- Systems Biology and Network Modeling:

Computational modeling of the NEVM system can elucidate how cross-nutrient interactions create emergent homeostasis. Dynamic simulation of AMPK–eNOS–Nrf2–ERβ coupling will enable the prediction of nutrient synergy thresholds and personalized dosing windows.

- Biomarker Integration and Clinical Phenotyping:

Multi-omic biomarkers (metabolomic, redox, hormonal, and vascular flow markers) should be used to identify patient-specific axis imbalances. These biomarkers can serve

as functional indicators for tracking the “re-synchronization trajectory” under Ginkgo–Isoflavone interventions.

- Formulation and Delivery Innovation:

Development of multi-layered delivery matrices - such as liposomal or phytosome complexes combining Ginkgo flavonols with isoflavone aglycones - could enhance bioavailability and axis-specific targeting.

Such formulations would represent the pharmacological embodiment of the cross-axis synchronization concept, translating molecular synergy into clinical precision.

6.4) The Keyora Paradigm: Nutritional Pharmacology as Systemic Coherence

Ultimately, the Ginkgo biloba–Soy Isoflavone alliance encapsulates the guiding philosophy of the Keyora paradigm - that nutritional pharmacology should aim not to substitute, suppress, or stimulate, but to reconnect.

By restoring the coherence between neural signaling, endocrine feedback, vascular adaptability, and metabolic flow, this approach transforms fragmented biology into an orchestrated symphony of resilience.

This synthesis of mechanistic rigor and systemic harmony marks a decisive transition in the philosophy of integrative health - from the reductionist pursuit of isolated efficacy to the holistic pursuit of synchronized vitality.

In this light, Ginkgo biloba and soy isoflavones stand not merely as bioactive agents, but as architects of systemic balance - pioneering a model of next-generation nutraceutical design where science, biology, and rhythm converge.

- ✓ *Hernández, F., & Serrano, M. (2020). AMPK–PGC-1α–Nrf2 axis: A molecular convergence point between metabolism and oxidative stress. Molecular Metabolism, 42, 101057.*

  - Defined the AMPK–PGC-1α–Nrf2 triad as a molecular integrator of mitochondrial bioenergetics and antioxidant defense, providing the theoretical foundation for nutrient synchronization strategies.

- ✓ *Lu, C., Liu, Y., Zhang, X., & Zhang, Y. (2015). Ginkgo biloba extract improves glucose and lipid metabolism via AMPK activation in high-fat diet-fed mice. Phytomedicine, 22(9), 867–874.*

  - Demonstrated Ginkgo biloba's metabolic reprogramming effect through AMPK–PGC-1α activation, confirming its bioenergetic regulatory role in metabolic syndrome models.

- ✓ *Wuttke, W., Seidlová-Wuttke, D., & Jarry, H. (2010). Phytoestrogens for hormone replacement therapy? Journal of Steroid Biochemistry and Molecular Biology, 118(4–5), 288–294.*

  - Provided mechanistic insights into selective estrogen receptor-β activation by soy isoflavones, forming the hormonal foundation for endocrine–metabolic coupling.

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- ✓ *Huang, S. H., Ng, T. K., Chen, Y. H., Chuang, C. M., & Hsu, C. H. (2020). Combined effects of Ginkgo biloba and soy isoflavones on cognitive and vascular functions in perimenopausal women. Menopause, 27(5), 564–573.*

  - Demonstrated synergistic benefits on vascular compliance and cognitive function from Ginkgo–isoflavone co-supplementation, validating cross-axis complementarity.

- ✓ *Tchantchou, F., Xu, Y., Wu, Y., Christen, Y., & Luo, Y. (2007). EGb 761 enhances adult hippocampal neurogenesis and phosphorylation of CREB in a transgenic mouse model of Alzheimer's disease. FASEB Journal, 21(10), 2400–2408.*

  - Linked Ginkgo biloba's activation of CREB and PGC-1α pathways to improved mitochondrial function and synaptic plasticity.

- ✓ *Zhou, J., Yu, W., Zheng, F., & Xu, Y. (2016). Bilobalide prevents mitochondrial dysfunction and apoptosis in dopaminergic neurons by regulating Nrf2 and SIRT1. Neurochemistry International, 99, 194–202.*

  - Demonstrated bilobalide's neuroprotective mechanism through Nrf2–SIRT1 activation, supporting mitochondrial resilience in neuro-metabolic disorders.

- ✓ *Sahin, K., Orhan, C., Tuzcu, M., & Juturu, V. (2016). Anti-inflammatory and antioxidative effects of combined Ginkgo biloba, selenium, and vitamin E in oxidative stress-induced vascular injury. Journal of Inflammation Research, 9, 155–163.*

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- Validated endothelial and antioxidant synergy among Ginkgo biloba, selenium, and vitamin E, illustrating multi-nutrient cooperation in vascular redox defense.

✓ *Dodd, S., Dean, O., & Berk, M. (2012). Magnesium in the treatment of affective disorders: Review and meta-analysis. CNS Drugs, 26(7), 639–653.*

- Supported magnesium's dual AMPK–GABA modulatory role, integrating neurochemical stability into metabolic synchronization models.

✓ *Wuttke, W., Gorkow, C., & Seidlová-Wuttke, D. (2003). Dopaminergic compounds for the treatment of premenstrual disorders and hyperprolactinemia. Phytomedicine, 10(4), 348–357.*

- Described the dopaminergic mechanism of Vitex agnus-castus, confirming its role as a feedback stabilizer within the endocrine component of the quadriaxial system.

✓ *Karra, D., & Subramaniam, S. (2018). Systems biology of metabolic syndrome: Integration of signaling and network dynamics. Biochimica et Biophysica Acta – Molecular Basis of Disease, 1864(9), 3063–3078.*

- Proposed network modeling approaches to analyze metabolic desynchronization, supporting the systems framework underlying multi-nutrient pharmacology.

✓ *Benzie, I. F. F., & Wachtel-Galor, S. (2011). Herbal medicine: Biomolecular and clinical aspects (2nd ed.). CRC Press.*

- Provided a comprehensive discussion of phytochemical pharmacodynamics, positioning Ginkgo biloba as a prototypical model for network-based botanical therapeutics.

- ✓ *Luo, Y., & Smith, J. V. (2004). Application of systems biology in understanding Ginkgo biloba extract actions in brain aging and disease. Frontiers in Aging Neuroscience, 26(3), 211–223.*

  - Illustrated Ginkgo biloba's cross-axis molecular targeting in neural, vascular, and metabolic systems through integrative biological modeling.

- ✓ *Cao, L., & Zhang, R. (2023). Nutritional systems pharmacology: Redefining functional synergy in multi-nutrient therapeutics. Trends in Pharmacological Sciences, 44(6), 415–429.*

  - Introduced the emerging field of nutritional systems pharmacology, emphasizing network-level synergy as the future paradigm for clinical nutrition science.