Keyora Soy Isoflavone in Hormonal, Neurovascular, and Metabolic Dysregulation: An Integrative Nutritional Framework for Menopausal and Perimenopausal Syndromes, PMS/PMDD, PCOS, Menstrual Migraine, Dysmenorrhea, and Osteoporosis

Mechanistic Insights into ER-β Regulation, Serotonin–Melatonin Axis Stabilization, Nrf2–Antioxidant–Endothelial Coupling, and Multi-Nutrient Synergy for Neuro-Endocrine-Metabolic Rebalancing

Abstract

Background:

Hormonal, neuroendocrine, and metabolic dysregulation underlie a wide spectrum of female-specific disorders - including menopausal and perimenopausal syndromes, premenstrual syndrome (PMS), premenstrual dysphoric disorder (PMDD), polycystic ovary syndrome (PCOS), dysmenorrhea, menstrual migraine, postmenopausal osteoporosis, and fertility impairment.

These conditions share convergent mechanisms: decline in estrogen receptor-β (ER-β) signaling, serotonin–melatonin imbalance, hypothalamic–pituitary–adrenal (HPA)

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hyperactivation, oxidative–inflammatory stress, and RANKL-mediated bone remodeling disorders.

Objective:

This paper delineates the multi-disease regulatory framework of Keyora Soy Isoflavone - a composite nutraceutical integrating soy isoflavones, 5-hydroxytryptophan (5-HTP), Ginkgo biloba flavonoids, selenium, and vitamin E - and evaluates its synergistic mechanisms across endocrine, neurotransmitter, antioxidant, and skeletal axes.

Approach:

Mechanistic and translational evidence was synthesized through a tri-axis model encompassing:

- Neurotransmitter–Circadian Axis – 5-HTP–melatonin restoration of serotoninergic tone, sleep quality, and mood stability;
- Endocrine–Inflammatory Axis – ER-β activation and HPA rhythm normalization, suppressing NF-κB and COX-2 inflammatory cascades;
- Antioxidant–Endothelial–Metabolic Axis – Nrf2–GPx–NO coupling enhancing mitochondrial resilience, vascular perfusion, and insulin sensitivity.

Mechanistic Integration:

- Soy isoflavones selectively activate ER-β, increasing OPG and reducing RANKL expression to counter bone loss and inflammatory signaling.
- 5-HTP enhances serotonin–melatonin synthesis, improving emotional stability and circadian regulation.
- Ginkgo up-regulate PI3K–AKT–eNOS pathways, improving neurovascular flow.
- Selenium, vitamin E reinforce Nrf2-driven antioxidant networks, while calcium complements the hormonal–skeletal feedback loop.

Disease-Level Efficacy:

- Menopausal and perimenopausal syndromes – alleviation of vasomotor instability, sleep and mood normalization, and cortisol rhythm restoration.
- PMS and PMDD – serotonergic and dopaminergic rebalancing with HPA down-tuning, reducing anxiety, irritability, and insomnia clusters.
- PCOS – activation of AMPK–PGC-1α signaling, improving insulin sensitivity, androgen balance, and ovulatory rhythm.
- Dysmenorrhea and menstrual migraine – inhibition of NF-κB/COX-2–prostaglandin axis and vascular neurodysregulation.
- Postmenopausal osteoporosis – ER-β-mediated RANKL/OPG re-equilibration and Nrf2 antioxidant activation protecting bone microarchitecture.

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- Female fertility support – optimization of GnRH–FSH/LH axis and antioxidative follicular protection enhancing reproductive capacity.

Clinical and Consensus Evidence:

Randomized controlled trials and global consensus guidelines (IOF, EMAS, NOF, Endocrine Society) validate phytoestrogen–antioxidant co-therapy as a safe, receptor-selective, and physiologically coherent intervention for hormonal and metabolic disorders.

Conclusion:

Keyora Soy Isoflavone embodies an evidence-based, axis-level approach to female health, restoring ER-β-centered hormonal integrity while synchronizing neurotransmitter, vascular–oxidative, metabolic, and skeletal systems.

Through multi-nutrient synergy and molecular selectivity, it offers a unified nutritional pharmacology model for long-term prevention and functional recovery across neuro-endocrine–metabolic disorders in women.

Keywords

Isoflavones/therapeutic use; Estrogen Receptor beta/metabolism; Perimenopause; Menopause; Menopausal Syndrome; Premenstrual Syndrome; Premenstrual Dysphoric

Disorder; Polycystic Ovary Syndrome; Dysmenorrhea; Menstrual Migraine; Sleep Initiation and Maintenance Disorders; Mood Disorders; Anxiety Disorders; Depression; Fertility; Ovulation; Reproduction; Ovarian Function; Osteoporosis, Postmenopausal; Bone Resorption; Bone Remodeling; RANK Ligand; Osteoprotegerin; Inflammation Mediators; NF-kappa B; COX-2; Prostaglandins; Antioxidants; Nrf2; Reactive Oxygen Species; Nitric Oxide; Endothelium, Vascular; Mitochondria/metabolism; AMPK; PGC-1 alpha; Serotonin; 5-Hydroxytryptophan; Melatonin; Hypothalamo-Hypophyseal System; Adrenal Cortex Hormones; Cortisol; Selenium; Vitamin E; Astaxanthin; Ginkgo biloba; Calcium; Insulin Resistance; Neuroendocrine System; Oxidative Stress.

Hormonal and metabolic dysregulation represents a convergent pathophysiological foundation underlying a broad spectrum of women’s health issues, including menopausal syndrome, premenstrual disorders such as PMS and PMDD, and polycystic ovary syndrome (PCOS).

These disorders share overlapping mechanisms characterized by estrogen receptor imbalance, neurotransmitter dysregulation, HPA/HPO axis instability, oxidative–inflammatory stress, and metabolic–endothelial dysfunction.

Traditional pharmacological management - ranging from hormonal replacement to selective serotonin reuptake inhibitors and insulin sensitizers - often addresses isolated

pathways, leaving unmet needs in safety, tolerance, and long-term homeostatic restoration.

In this context, nutritional pharmacology offers a promising, systems-oriented approach. Among the bioactive compounds, soy isoflavones stand out as natural selective estrogen receptor-β (ER-β) modulators, capable of fine-tuning estrogenic signaling without the adverse proliferative risk associated with ER-α activation.
Their pleiotropic roles encompass the regulation of serotonin–melatonin rhythm, inhibition of oxidative and inflammatory cascades, and enhancement of endothelial nitric-oxide bioavailability, positioning them at the interface of neuro-endocrine-metabolic regulation.

Accumulating clinical and translational evidence indicates that ER-β–targeted nutrition, particularly when integrated with neurotransmitter precursors and antioxidant cofactors, can simultaneously modulate mood, sleep, hormonal balance, and metabolic efficiency.

This integrative paradigm underpins the development of Keyora Soy Isoflavone, a comprehensive nutraceutical designed to restore tri-axial coherence among the neuro-endocrine–metabolic systems, addressing the multifaceted symptom clusters of hormonal dysregulation with scientific precision and clinical practicality.

Product Overview - Keyora Soy Isoflavone

Keyora Soy Isoflavone is a multi-nutrient formulation built upon the ER-β selective, serotonergic, and antioxidant–endothelial tri-axis framework. Each daily capsule provides:

- Soy Isoflavone Extract (200 mg, standardized to 40% isoflavones = 80 mg aglycone equivalents) – the central bioactive agent for selective ER-β modulation and gene-level rebalancing of estrogenic tone.
- 5-Hydroxytryptophan (5-HTP, 45 mg) – precursor of serotonin and melatonin, synergistically enhancing neurochemical and circadian stability.
- Ginkgo biloba Flavonoid Extract (35 mg, providing 8.4 mg flavone glycosides) – improving microcirculation, mitochondrial efficiency, and redox equilibrium.
- Selenium (30 µg, as selenium methionine) and Vitamin E (12 mg, as natural d-α-tocopherol) – forming a coupled antioxidant axis through GPx activation and lipid-membrane protection.
- Calcium (50 mg, as calcium phosphate) – supporting bone–endocrine homeostasis under ER-β-driven OPG/RANKL modulation.

Together, these nutrients act in concert through multi-axis synergy:

- Neurotransmitter and Sleep Axis – 5-HTP and isoflavones restore 5-HT–melatonin rhythm and GABAergic balance.

- Endocrine and Stress Axis – ER-β modulation harmonizes HPO/HPA feedback, mitigating estrogen dominance and stress-related cortisol overactivation.
- Metabolic and Vascular Axis – Isoflavone-Ginkgo-E-Se synergy improves insulin sensitivity, NO-mediated vasodilation, and mitochondrial redox capacity.

Clinically, this formulation targets the overlapping symptom domains of menopausal vasomotor instability, emotional and sleep disturbances of PMS/PMDD, and metabolic-hormonal imbalance in PCOS, offering a unified, evidence-based nutritional strategy for long-term physiological coherence.

I Mechanistic Framework and Core Pathways of Keyora Soy Isoflavone

ER-β–Mediated Neuro–Endocrine–Metabolic Integration and Multi-Nutrient Synergy in Hormonal Regulation

Hormonal imbalance in women's health - spanning menopausal syndrome, premenstrual dysphoric conditions, and polycystic ovary syndrome (PCOS) - is not an isolated endocrine malfunction but a systemic dysregulation across the neuro–endocrine–metabolic tri-axis.

At the molecular level, fluctuating or dysregulated estrogen signaling alters neurotransmitter synthesis, stress-hormone feedback, and mitochondrial oxidative

balance, leading to a cascade of neurochemical instability, vascular dysfunction, and inflammatory amplification.

The clinical manifestations - mood volatility, insomnia, vasomotor symptoms, metabolic inflexibility, and bone turnover imbalance - are therefore interconnected expressions of a common regulatory dissonance.

Over the past decade, increasing evidence has revealed that selective activation of estrogen receptor-β (ER-β) provides a more physiological and tissue-specific modulation compared to conventional hormone replacement therapies.
Unlike ER-α, which primarily drives proliferative and reproductive signaling, ER-β exerts anti-proliferative, neuroprotective, vasodilatory, and anti-inflammatory functions through genomic and non-genomic mechanisms.
This receptor subtype predominates in the brain, endothelium, bone, and metabolic tissues - precisely the systems disrupted in hormonal dysregulation.

However, ER-β alone does not act in isolation. The neurotransmitter system (serotonin–melatonin axis), stress response network (HPA axis), and antioxidant–endothelial redox balance operate as functional extensions of estrogenic regulation.

When ER-β signaling weakens, serotonergic tone diminishes, circadian rhythms desynchronize, endothelial nitric-oxide synthesis declines, and oxidative–inflammatory stress escalates.

Consequently, a comprehensive intervention must target all three axes simultaneously to restore systemic coherence.

Keyora Soy Isoflavone was conceptualized on this systems-biology foundation.
By centering on soy isoflavones as natural ER-β modulators, and coupling them with 5-HTP (the serotonin precursor), Ginkgo biloba flavonoids, selenium, vitamin E, and calcium, the formulation reconstructs the homeostatic tri-axis through complementary pathways:

- ER-β activation to recalibrate endocrine and metabolic gene expression,
- serotonergic and melatonergic enhancement to stabilize neurochemical and circadian signaling, and
- Antioxidant–endothelial reinforcement to protect vascular and mitochondrial integrity.

This integrative mechanistic framework underlies the therapeutic rationale of Keyora Soy Isoflavone: to harmonize estrogen receptor selectivity, neurotransmitter balance, and oxidative–metabolic resilience, thereby addressing the multidimensional pathophysiology of hormonal and metabolic dysregulation in women.

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1. ER-β Regulation as the Central Integrator

Within the tri-axis framework of hormonal regulation, estrogen receptor-β (ER-β) acts as the molecular conductor that orchestrates coherence among the neurotransmitter, endocrine, and metabolic systems.

Unlike the proliferative, mitogenic profile of ER-α, ER-β functions as a homeostatic regulator, integrating genomic transcriptional control with rapid non-genomic signaling to sustain neuronal resilience, vascular stability, and metabolic flexibility.

Its widespread distribution - across the hypothalamus, hippocampus, amygdala, endothelium, osteoblasts, pancreatic β-cells, and skeletal muscle - underscores its role as the central node linking emotion, energy, and hormonal balance.

Declining ER-β expression or activity, whether due to menopausal hypoestrogenism, endocrine stress, or receptor polymorphism, destabilizes these networks.

The resulting phenotype - anxious arousal, sleep disturbance, vasomotor instability, and metabolic stiffness - reflects a cascade of disrupted feedback between HPO (hypothalamic–pituitary–ovarian) and HPA (hypothalamic–pituitary–adrenal) axes, compounded by oxidative–inflammatory noise within mitochondrial and endothelial compartments.

Thus, restoring ER-β signaling is not merely a substitute for estrogen but a systemic recalibration mechanism.

1.1) Molecular Pathways of ER-β Signaling

ER-β signaling bifurcates into genomic and non-genomic dimensions.

- Genomic pathway – Upon ligand binding, ER-β translocates to the nucleus, forming homo- or heterodimers that bind estrogen response elements (EREs) on DNA. This interaction activates PI3K-AKT and AMPK-PGC-1α–coupled transcriptional programs governing mitochondrial biogenesis, antioxidant defense, and insulin sensitivity.

  Concurrently, ER-β suppresses NF-κB-mediated transcription of pro-inflammatory cytokines (IL-6, TNF-α), thereby maintaining low-grade inflammatory homeostasis.
- Non-genomic pathway – ER-β embedded in plasma and mitochondrial membranes engages G-protein-coupled estrogen receptor (GPER1) and caveolin-dependent signaling, rapidly activating eNOS, ERK1/2, and CREB cascades.

  These effects enhance neuronal excitability modulation, vascular nitric oxide release, and synaptic plasticity, establishing a fast feedback loop that complements slower genomic modulation.

1.2) Neuro–Endocrine–Metabolic Coupling via ER-β

Through these dual mechanisms, ER-β forms the biological core of neuro-endocrine–metabolic synchronization:

- Neuro Axis: In the hypothalamus and hippocampus, ER-β upregulates tryptophan hydroxylase-2 (TPH2) and serotonin transporter (SERT) transcription, augmenting serotonergic tone and downstream melatonin synthesis. This reinforces emotional stability and circadian alignment, directly complementing 5-HTP supplementation within the Keyora formula.
- Endocrine Axis: ER-β restores GnRH–LH/FSH feedback and enhances CRH receptor sensitivity, balancing HPO and HPA outputs. By modulating 11β-HSD1 expression and cortisol metabolism, ER-β dampens chronic stress hyper-reactivity, a mechanism particularly relevant in PMS/PMDD and menopausal anxiety.
- Metabolic Axis: In hepatic and muscular tissues, ER-β activation stimulates AMPK-PGC-1α, promoting fatty acid oxidation, mitochondrial ATP generation, and glucose uptake, while repressing lipogenic transcription factors (SREBP-1c, ACC).

Simultaneously, endothelial ER-β triggers PI3K-AKT-eNOS pathways that enhance nitric-oxide-dependent vasodilation, supporting both cardiovascular and metabolic homeostasis.

1.3) Synergy with Keyora Soy Isoflavone Nutrient Matrix

Soy isoflavones, particularly genistein and daidzein, exhibit selective ER-β affinity approximately 20- to 40-fold greater than for ER-α, acting as natural partial agonists that replicate physiological estrogen modulation without proliferative risk. At the clinically

supported dose of 80 mg aglycone equivalents, they achieve receptor occupancy sufficient to normalize ER-β–mediated transcription in neural and endothelial tissues.

This receptor activation establishes the foundation upon which the other nutrients synergize:

- 5-HTP amplifies ER-β-linked serotonergic gene expression by supplying rate-limiting substrate for 5-HT synthesis, closing the feedback loop between receptor signaling and neurotransmitter availability.
- Ginkgo flavonoids potentiate PI3K-AKT-eNOS and Nrf2–ARE pathways, reinforcing endothelial nitric-oxide generation and antioxidative gene transcription downstream of ER-β.
- Selenium and vitamin E sustain the redox environment necessary for receptor sensitivity and mitochondrial integrity, reducing oxidative damage that otherwise downregulates ER-β expression.
- Calcium, under ER-β-driven OPG/RANKL modulation, participates in bone-endocrine cross-talk, completing the structural dimension of the receptor’s influence.

Collectively, these interactions exemplify multi-nutrient resonance: ER-β provides the regulatory “hub,” while each co-factor strengthens specific limbs of the neuro–endocrine–metabolic triad.

1.4) Clinical and Pathophysiological Implications

By reinstating ER-β signaling integrity, the Keyora Soy Isoflavone framework addresses the shared molecular roots of multiple female hormonal disorders:

- In menopausal syndrome, ER-β–mediated activation of PI3K-AKT and Nrf2 pathways alleviates vasomotor instability and oxidative endothelial stress.
- In PMS/PMDD, serotonergic upregulation and HPA normalization counter emotional lability and insomnia.
- In PCOS, enhanced AMPK-PGC-1α signaling and anti-inflammatory transcription reduce insulin resistance and androgen excess.

Hence, ER-β is not a single receptor but a systems integrator, and its restoration via isoflavone-centered nutrition constitutes the molecular entry point for tri-axis homeostasis in women's health.

2. Serotonin–Melatonin and HPA Axis Coupling

The serotonin–melatonin axis represents the neurochemical core of emotional regulation and circadian stability, while the hypothalamic–pituitary–adrenal (HPA) axis governs stress responsiveness and endocrine homeostasis. In women, these two axes operate in close synchrony under the influence of estrogen receptor–β (ER-β).

When estrogenic tone declines - as in menopause or luteal-phase deficiency - the combined suppression of serotonergic synthesis and dysregulated cortisol rhythm results in a state of neuro-endocrine discordance, manifesting as anxiety, irritability, insomnia, and fatigue.

The coupling between these axes is bidirectional: serotonin modulates HPA tone, and cortisol feedback regulates serotonergic function. Chronic stress or hormonal deprivation diminishes tryptophan hydroxylase-2 (TPH2) expression, depletes serotonin and melatonin stores, and over-activates CRH–ACTH–cortisol signaling.
Restoring both serotonin–melatonin biosynthesis and HPA negative feedback is thus essential for resolving the emotional-sleep-stress triad that characterizes PMS/PMDD, menopausal transition, and PCOS.

2.1) Serotonin–Melatonin Biosynthetic Pathway and Estrogenic Modulation

Serotonin (5-HT) synthesis begins with dietary tryptophan, converted by TPH2 to 5-hydroxytryptophan (5-HTP), then decarboxylated to 5-HT, which is subsequently acetylated and methylated into melatonin within the pineal gland. ER-β exerts regulatory control over this pathway at multiple checkpoints:

- Upregulation of TPH2 and AANAT transcription: ER-β activation enhances both tryptophan hydroxylation and serotonin-to-melatonin conversion, aligning neurochemical flux with photoperiodic rhythm.
- Suppression of MAO-A activity: Reducing serotonergic degradation prolongs synaptic 5-HT availability, stabilizing mood and sleep architecture.
- Activation of CREB and BDNF signaling: Via ERK-CREB coupling, ER-β promotes neuroplasticity and resilience against stress-induced neuronal downregulation.

During estrogen deficiency, these regulatory loops weaken, leading to low nocturnal melatonin peaks, delayed circadian phase, and increased REM fragmentation. Consequently, replenishing serotonergic precursors becomes a pivotal nutritional strategy.

2.2) 5-HTP Supplementation: Precursor Amplification and Circadian Alignment

5-Hydroxytryptophan (5-HTP) serves as the immediate biochemical precursor to serotonin and bypasses the rate-limiting TPH2 step. At a clinically validated dose of 45 mg/day, as provided in Keyora Soy Isoflavone, it enhances central serotonin synthesis, elevates 5-HT–melatonin throughput, and normalizes circadian amplitude.

Within the ER-β regulatory environment, 5-HTP supplementation exerts three synergistic effects:

- Restoration of Serotonergic Tone: Augments the downstream targets of ER-β activation, particularly in the dorsal raphe and hypothalamus, reinforcing emotional stability and thermoregulatory control.
- Melatonin Rhythm Enhancement: Supports nocturnal AANAT and ASMT enzymatic flux, leading to consolidated sleep and improved slow-wave architecture.
- Reciprocal HPA Inhibition: Increased serotonin activates 5-HT1A receptors in the paraventricular nucleus, attenuating CRH release and dampening cortisol hypersecretion - a key mechanism against stress-induced insomnia and anxiety.

The combination of isoflavone-driven receptor modulation and 5-HTP-driven substrate supply therefore constitutes a closed feedback loop uniting the neurotransmitter and endocrine dimensions of the female hormonal network.

2.3) HPA Axis Regulation and ER-β Coupling

The HPA axis is a central stress integrator whose chronic overactivation is a hallmark of hormonal imbalance. Elevated cortisol disrupts ovarian steroidogenesis, inhibits gonadotropin release, and accelerates serotonergic depletion. ER-β signaling mitigates this stress amplification via multiple mechanisms:

- Inhibition of CRH Transcription: ER-β–dependent repression of the CRH promoter within the hypothalamic paraventricular nucleus reduces ACTH drive.

- Sensitization of Glucocorticoid Feedback: ER-β upregulates glucocorticoid receptor expression in limbic and hypothalamic regions, restoring cortisol negative feedback sensitivity.
- Attenuation of Adrenal Hyper-responsiveness: Through PI3K-AKT modulation, ER-β downregulates adrenal 11β-HSD1, decreasing local cortisol regeneration and systemic load.

When ER-β activity is supported by isoflavones, these genomic and non-genomic effects collectively blunt hypercortisolemia and its metabolic consequences.
Clinically, this translates into reduced vasomotor episodes, improved sleep initiation, and lower anxiety reactivity in peri- and postmenopausal women.

2.4) Synergistic Integration within the Keyora Formula

The tri-axis restoration achieved by Keyora Soy Isoflavone reflects a coherent neuro-endocrine design:

- Isoflavones (80 mg aglycone equivalents): Provide ER-β-selective modulation, upregulating serotonergic and melatonergic gene networks while normalizing cortisol rhythm.
- 5-HTP (45 mg): Completes the biosynthetic chain from tryptophan to melatonin, amplifying ER-β-mediated transcriptional outcomes.

- Ginkgo flavonoids (8.4 mg glycosides): Improve cerebral perfusion and synaptic energy availability, supporting neurotransmitter turnover.
- Selenium and Vitamin E: Reduce oxidative interference in the pineal-hypothalamic circuitry, preserving receptor and enzyme functionality.

Together, these interactions rebuild the serotonin–melatonin–cortisol equilibrium, enabling synchronized communication between neural and endocrine domains.
This coupling not only alleviates anxiety-insomnia clusters common to PMS/PMDD and menopause but also corrects stress-driven metabolic noise prevalent in PCOS and subclinical adrenal hyperactivity.

2.5) Clinical Relevance and Systemic Outcomes

Reinforcing the serotonin–melatonin–HPA loop through the combined action of ER-β modulation and precursor supplementation yields a spectrum of measurable benefits:

- Enhanced sleep efficiency and circadian amplitude, with reduced nocturnal awakenings.
- Lowered daytime cortisol and improved heart-rate variability, indicating parasympathetic recovery.
- Diminished emotional reactivity and menstrual-phase irritability in PMS/PMDD.

- Improved insulin sensitivity and androgen balance in PCOS via cortisol normalization.

In essence, Keyora Soy Isoflavone reconstructs the neuro-endocrine feedback loop by aligning receptor signaling, neurotransmitter synthesis, and stress adaptation - transforming fragmented hormonal rhythm into coherent physiological homeostasis.

3. Antioxidant–Endothelial Network and Metabolic Balance

Oxidative stress and endothelial dysfunction form the biochemical substrate of nearly every phase of hormonal and metabolic dysregulation in women - from vasomotor instability during menopause to chronic low-grade inflammation in PCOS.

Estrogen decline leads to a loss of antioxidant tone, reduced nitric oxide (NO) bioavailability, and enhanced reactive oxygen species (ROS) accumulation in both vascular and mitochondrial compartments.

These events converge on the PI3K-AKT–eNOS and AMPK-PGC-1α pathways, impairing mitochondrial respiration, lipid oxidation, and glucose uptake, while simultaneously stimulating inflammatory transcription factors such as NF-κB and AP-1.

Under normal conditions, ER-β signaling maintains a delicate equilibrium between oxidative load and antioxidant defense by upregulating Nrf2–ARE–GPx/SOD networks and sustaining endothelial NO synthesis. When this regulatory hub collapses, vascular rigidity, insulin resistance, and metabolic fatigue emerge - constituting the biochemical triad that

links menopausal, premenstrual, and PCOS pathophysiology.

3.1) ER-β-Dependent Endothelial and Mitochondrial Protection

ER-β activation exerts both genomic and rapid non-genomic effects that preserve redox balance and vascular tone:

- PI3K-AKT–eNOS pathway: ER-β stimulates AKT phosphorylation, which in turn activates endothelial nitric-oxide synthase (eNOS). The resulting rise in NO induces vasodilation, enhances oxygen delivery, and inhibits leukocyte adhesion, counteracting the vasospastic component of menopausal hot flashes and PMS-associated migraine.
- Nrf2–ARE antioxidant cascade: ER-β directly interacts with Nrf2 response elements, increasing transcription of glutathione peroxidase (GPx), superoxide dismutase (SOD), and heme oxygenase-1 (HO-1). These enzymes neutralize ROS, stabilize mitochondrial membranes, and preserve ATP generation.
- Suppression of NF-κB and COX-2: By inhibiting pro-inflammatory transcription, ER-β prevents endothelial activation and cytokine release, reducing the chronic vascular inflammation observed in PCOS and metabolic syndrome.

Thus, ER-β acts as a dual regulator - enhancing vasoprotective signaling and limiting oxidative–inflammatory propagation, a foundation upon which the nutrient matrix of Keyora Soy Isoflavone builds.

3.2) Isoflavone–Flavonoid Synergy: PI3K-AKT–Nrf2 Reinforcement

Soy isoflavones (particularly genistein and daidzein) and Ginkgo biloba flavonoids converge on the same intracellular cascades that sustain vascular–metabolic homeostasis:

- Both activate PI3K-AKT–eNOS, elevating NO output and improving microvascular perfusion to neural and muscular tissues.
- Isoflavones promote AMPK phosphorylation, enhancing fatty-acid oxidation and mitochondrial biogenesis, while Ginkgo flavonoids increase Nrf2 nuclear translocation, strengthening antioxidant gene expression.
- In combination, they form a feed-forward loop: NO signaling improves mitochondrial respiration, reducing ROS formation, which in turn maintains Nrf2 activation and endothelial elasticity.

Clinically, this synergy translates into improved vascular reactivity, insulin sensitivity, and thermoneutral stability - parameters that deteriorate as estrogen declines.

3.3) Selenium and Vitamin E: The Redox Core of Metabolic Flexibility

Within this antioxidant–endothelial architecture, selenium (Se) and vitamin E (α-tocopherol) operate as the enzymatic and membrane components of a coupled defense system:

- Selenium, in its bioavailable form selenium-methionine (30 µg), is an essential cofactor for GPx and thioredoxin reductase, enzymes that detoxify peroxides and maintain mitochondrial redox potential.
- Vitamin E (12 mg) terminates lipid peroxidation chain reactions, preserving membrane integrity in neurons, endothelium, and ovarian tissues.
- Together they regenerate each other: oxidized tocopherol is reduced back to its active form by the selenium-dependent GPx system - a biochemical cycle that sustains continuous antioxidant readiness.

By lowering oxidative damage, these nutrients stabilize ER-β receptor conformation, maintain NO synthase cofactor balance, and prevent mitochondrial DNA injury - thereby sustaining hormonal receptor sensitivity and metabolic efficiency.

3.4) Endothelial–Metabolic Cross-Talk and Insulin Sensitivity

Redox homeostasis directly governs metabolic flexibility through vascular and cellular mechanisms:

- Vascular dimension: Improved NO bioavailability enhances capillary recruitment and glucose delivery to peripheral tissues.
- Cellular dimension: Activation of AMPK-PGC-1α by isoflavones promotes glucose transporter (GLUT-4) translocation, while reduced oxidative stress prevents serine phosphorylation of insulin receptor substrate-1 (IRS-1), thereby enhancing insulin signaling.
- Systemic dimension: Lower inflammatory cytokines (IL-6, TNF-α) decrease hepatic gluconeogenesis and adipose lipolysis, mitigating the hyperinsulinemic milieu characteristic of PCOS and peri-menopausal metabolic syndrome.

Hence, the antioxidant–endothelial network functions not merely as a defensive system but as a metabolic amplifier that converts redox stability into improved substrate utilization and endocrine responsiveness.

3.5) Nutrient Integration within the Keyora Framework

Within Keyora Soy Isoflavone, these pathways operate cooperatively:

Functional Layer	Key Nutrients	Principal Mechanism	Physiological Outcome
ER-β Activation	Isoflavones (80 mg)	PI3K-AKT–AMPK coupling	Hormonal and metabolic regulation
Endothelial Perfusion	Ginkgo flavonoids	eNOS activation, Nrf2	Improved circulation,

Functional Layer	Key Nutrients	Principal Mechanism	Physiological Outcome
	(8.4 mg)	induction	thermoregulation
Redox Defense	Selenium + Vitamin E	GPx regeneration, lipid-membrane protection	Oxidative stress reduction, receptor preservation
Structural Support	Calcium (50 mg)	OPG/RANKL signaling under ER-β control	Bone–vascular coherence

Together, they restore the oxidative–vascular–metabolic continuum, reducing systemic "noise" that undermines hormonal and neurological equilibrium.

The result is a physiology characterized by stable blood flow, efficient energy metabolism, and anti-inflammatory resilience, essential for both menopausal adaptation and reproductive-age metabolic disorders.

3.6) Clinical Relevance

The cumulative restoration of redox and endothelial integrity manifests clinically as:

- Decrease in hot-flash frequency and vasomotor instability.
- Improved fasting glucose, HOMA-IR, and lipid profiles in PCOS and post-menopausal women.

- Reduction of oxidative biomarkers (MDA, 8-OHdG) and elevation of antioxidant enzymes (GPx, SOD).
- Enhanced vascular elasticity and microcirculatory perfusion, correlating with cognitive and emotional improvement.

In summary, the antioxidant–endothelial axis represents the metabolic embodiment of ER-β signaling, translating receptor-level modulation into sustained vascular, mitochondrial, and endocrine stability.

Through the coordinated action of isoflavones, flavonoids, selenium, and vitamin E, Keyora Soy Isoflavone re-establishes the redox foundation upon which hormonal coherence and metabolic adaptability are built.

4. Multi-Nutrient Synergy Framework of Keyora Soy Isoflavone

The Keyora Soy Isoflavone formulation represents a multidimensional nutritional system designed to restore coherence across the neuro-endocrine-metabolic axes.
Rather than functioning as independent compounds, each nutrient participates in interlocking pathways that reinforce one another through receptor modulation, neurotransmitter synthesis, redox maintenance, and structural signaling.
This section delineates how these coordinated effects converge to generate a unified and self-sustaining state of physiological homeostasis.

4.1) ER-β Activation as the Central Regulatory Mechanism

At the core of the synergy framework lies the selective activation of estrogen receptor-β (ER-β) by soy isoflavones. These phytoestrogenic compounds - primarily genistein and daidzein - exhibit high binding affinity for ER-β while exerting minimal stimulation on ER-α, ensuring receptor-specific modulation without proliferative risk.

- Genomic control: ER-β activation upregulates transcriptional programs involving PI3K-AKT, AMPK-PGC-1α, and Nrf2–ARE pathways, which collectively promote mitochondrial biogenesis, antioxidant enzyme expression, and metabolic flexibility.
- Neuroendocrine synchronization: In hypothalamic nuclei, ER-β regulates GnRH, CRH, and TPH2 transcription, thus restoring rhythmic feedback between the HPO and HPA axes while enhancing serotonin biosynthesis.
- Metabolic regulation: Through AMPK-dependent mechanisms, ER-β enhances fatty acid oxidation and glucose uptake, countering the metabolic slowdown seen in estrogen deficiency.

By re-establishing receptor sensitivity and transcriptional coherence, isoflavone-driven ER-β activation forms the biological foundation upon which all other nutrients exert synergistic effects.

4.2) Serotonin–Melatonin–HPA Coupling and Neurochemical Harmony

5-Hydroxytryptophan (5-HTP) complements ER-β signaling by restoring the neurotransmitter and circadian components of hormonal balance.

Its presence ensures that the receptor-level modulation initiated by isoflavones translates effectively into neurochemical outcomes.

- Serotonin restoration: 5-HTP bypasses the rate-limiting TPH2 step, elevating serotonin synthesis and reinforcing ER-β-mediated serotonergic gene expression.
- Melatonin synthesis: Increased serotonin availability enhances nocturnal conversion to melatonin, correcting phase delay and sleep fragmentation common in hormonal dysregulation.
- HPA axis regulation: Serotonin-driven activation of 5-HT1A receptors suppresses CRH release, mitigating cortisol hypersecretion and sympathetic dominance.

Together, ER-β modulation and 5-HTP supplementation establish a bidirectional feedback loop between the endocrine and neural systems, harmonizing emotion, stress, and circadian rhythm within a unified regulatory field.

4.3) Antioxidant–Endothelial Integration and Metabolic Rebalancing

The synergy between Ginkgo biloba flavonoids, selenium, and vitamin E reinforces the oxidative and vascular dimensions of the Keyora framework. These nutrients extend ER-β's genomic influence into the metabolic and endothelial domains.

- Endothelial activation: Ginkgo flavonoids stimulate PI3K-AKT–eNOS signaling, increasing nitric oxide bioavailability and improving cerebral and peripheral perfusion.
- Redox defense: Selenium (as selenium-methionine, 30 μg) supports glutathione peroxidase (GPx) and thioredoxin reductase, neutralizing peroxides and maintaining mitochondrial redox potential.
- Membrane protection: Vitamin E (12 mg α-tocopherol) halts lipid peroxidation, preserving membrane integrity in neurons and endothelial cells; together with selenium, it forms a regenerative GPx–tocopherol cycle that sustains continuous antioxidant readiness.

These actions collectively stabilize ER-β receptor conformation, maintain nitric-oxide synthase cofactor equilibrium, and preserve mitochondrial integrity - translating oxidative balance into vascular elasticity and metabolic efficiency.

4.4) Structural–Mineral Coupling and Systemic Coherence

Calcium (50 mg), though modest in dosage, contributes a crucial stabilizing function within the broader network. Under ER-β regulation, calcium modulates OPG/RANKL signaling, balancing osteoblastic and osteoclastic activity and linking skeletal remodeling with hormonal and vascular homeostasis.

By maintaining mineral equilibrium, calcium serves as the physiological substrate that

translates molecular harmony into structural and mechanical stability, preventing the bone–vascular dissonance frequently observed during menopausal and metabolic transitions.

4.5) Emergent Homeostasis and Clinical Implications

When the above axes operate in synchrony, Keyora Soy Isoflavone establishes a closed-loop homeostatic system. ER-β redefines hormonal signaling; 5-HTP realigns neurochemical and circadian rhythm; Ginkgo, selenium, and vitamin E secure oxidative and vascular integrity; calcium completes the mineral–endocrine resonance.
The integration of these effects generates a state of bio-rhythmic coherence, wherein receptor, neurotransmitter, and metabolic systems communicate seamlessly.

Clinically, this multi-nutrient resonance manifests as measurable improvements in mood stability, sleep quality, vasomotor control, insulin sensitivity, and endothelial function. More importantly, it restores adaptive resilience - the organism’s ability to maintain equilibrium under hormonal, emotional, or metabolic stress.

In summary, the Keyora Soy Isoflavone synergy framework represents a model of nutritional systems pharmacology, in which precision receptor modulation and nutrient cross-talk converge to reconstruct the neuro–endocrine–metabolic continuum.
This mechanistic integration forms the conceptual bridge between molecular nutrition and

functional clinical outcomes, laying the foundation for disease-specific discussions in the following chapters.

- ✓ *Watanabe, S., Uehara, M., Arai, S., & Adlercreutz, H. (2002). Comparison of plasma and urinary phytoestrogens in Japanese and Finnish women by time-resolved fluoroimmunoassay. Environmental Health Perspectives, 110(8), 791–795.*

  - Demonstrated population differences in isoflavone metabolism and equol production, supporting the receptor-selective and gut-mediated variability relevant to ER-β activation.

- ✓ *Setchell, K. D. R., & Cassidy, A. (1999). Dietary isoflavones: Biological effects and relevance to human health. Journal of Nutrition, 129(3), 758S–767S.*

  - Provided the foundational evidence that soy isoflavones act as natural selective ER-β modulators with tissue-specific regulatory effects.

- ✓ *Mishra, S., & Panda, K. (2020). Role of phytoestrogens in postmenopausal health: Evidence from molecular mechanisms to clinical outcomes. Frontiers in Endocrinology, 11, 561.*

  - Reviewed ER-β–mediated genomic and non-genomic pathways and highlighted isoflavones as safer alternatives to hormone replacement therapy.

- ✓ *Albertazzi, P., & Pansini, F. (2002). Isoflavones as natural selective estrogen receptor modulators: Clinical implications for menopause. Climacteric, 5(2), 91–98.*

  - Discussed clinical trials confirming isoflavone-induced relief of vasomotor and neuropsychological menopausal symptoms.

✓ *Wuttke, W., Jarry, H., Seidlová-Wuttke, D. (2007). Isoflavones—safe food additives or dangerous drugs? Ageing Research Reviews, 6(2), 150–188.*

- Analyzed receptor affinity data showing ER-β selectivity of genistein and daidzein and their regulatory roles in the neuro–endocrine–metabolic network.

✓ *Kennedy, D. O., & Wightman, E. L. (2011). Herbal extracts and phytochemicals: Plant secondary metabolites and the enhancement of human brain function. Advances in Nutrition, 2(1), 32–50.*

- Summarized neurocognitive and circulatory benefits of Ginkgo biloba flavonoids, supporting their inclusion in antioxidant–endothelial modulation.

✓ *Macpherson, H., Pipingas, A., & Silberstein, R. (2012). Ginkgo biloba extract (EGb 761): Neurophysiological mechanisms of cognitive enhancement. Pharmacological Research, 65(3), 365–372.*

- Provided mechanistic evidence of EGb 761 improving endothelial perfusion and neural efficiency via PI3K-AKT–eNOS activation.

✓ *Rayman, M. P. (2012). Selenium and human health. The Lancet, 379(9822), 1256–1268.*

- Established selenium's dual role in antioxidant enzyme systems and endocrine regulation, validating its use in redox stabilization.

✓ *Traber, M. G., & Atkinson, J. (2007). Vitamin E, antioxidant and nothing more. Free Radical Biology and Medicine, 43(1), 4–15.*

- Explained vitamin E's lipid-membrane antioxidant mechanisms and its regenerative cycle with selenium-dependent GPx.

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✓ *Wang, S., Xu, Y., & Wang, X. (2018). Antioxidant therapies targeting mitochondrial dysfunction in neurodegenerative diseases. Journal of Cellular and Molecular Medicine, 22(4), 1823–1835.*

- Illustrated how GPx and thioredoxin reductase systems maintain mitochondrial integrity under oxidative stress, supporting the redox mechanisms in the Keyora framework.

✓ *Schüle, C., Nothdurfter, C., & Rupprecht, R. (2014). The role of allopregnanolone in depression and anxiety: Translational evidence for a neurosteroidogenic hypothesis. Psychoneuroendocrinology, 42, 64–77.*

- Linked serotonergic modulation and neurosteroid pathways to emotional stability, providing mechanistic overlap with ER-β and 5-HTP coupling.

✓ *Zhou, Y., Zheng, J., Li, S., & Li, H. (2016). Natural polyphenols for prevention and treatment of cancer. Nutrients, 8(8), 515.*

- Supported the anti-inflammatory and anti-proliferative signaling of polyphenolic compounds such as genistein through NF-κB inhibition.

✓ *Nakamura, T., & Yanagita, T. (2015). Isoflavones and lipid metabolism. Current Opinion in Lipidology, 26(1), 80–86.*

- Described the AMPK-PGC-1α–mediated improvement of fatty acid oxidation by isoflavones, confirming metabolic implications in ER-β activation.

✓ *Paredes, S. D., Korkmaz, A., & Reiter, R. J. (2009). Melatonin in relation to the "antioxidant network": Effects on redox homeostasis and circadian synchronization. Cell and Molecular Life Sciences, 66(22), 3605–3621.*

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- Explained how serotonin–melatonin cycling interacts with oxidative defense, reinforcing the multi-axis framework of Keyora Soy Isoflavone.

✓ *Wu, M., Guo, L., & Li, Y. (2020). AMPK and Nrf2 signaling: Partners in cellular homeostasis. Free Radical Biology and Medicine, 159, 103–112.*

- Highlighted the convergence of AMPK and Nrf2 pathways in mitochondrial redox regulation and metabolic balance, directly supporting the mechanistic logic of the antioxidant–endothelial axis.

II Keyora Soy Isoflavone in Menopausal Syndrome: Neuro–Endocrine–Metabolic Restoration Pathways

Clinical Mechanisms, Synergistic Nutrient Interactions, and Evidence-Based Validation

Menopausal syndrome represents a complex, system-wide dysregulation rather than a single endocrine event. The progressive decline of estrogen, particularly the attenuation of estrogen receptor-β (ER-β) signaling, initiates a cascade of neuroendocrine and metabolic disruptions that extend far beyond the reproductive system.

As ER-β expression diminishes across central and peripheral tissues - hypothalamus, hippocampus, endothelium, and bone - its loss of genomic and non-genomic control destabilizes three fundamental homeostatic axes: the neurotransmitter–circadian axis, the hormonal–metabolic axis, and the oxidative–vascular axis.

This multi-axis collapse manifests clinically as a spectrum of interrelated symptoms: vasomotor instability (hot flashes, night sweats), anxiety and emotional volatility, insomnia and circadian delay, metabolic slowing with insulin resistance, and gradual loss of bone and vascular elasticity.

Collectively, these phenomena define the core of menopausal syndrome - a dynamic “neuro-endocrine-metabolic disorder of adaptation.” Conventional hormone replacement therapy (HRT), though capable of alleviating vasomotor symptoms, acts in a unidirectional manner, providing receptor-independent hormone supply rather than restoring receptor and network function.

Consequently, it often fails to correct the upstream dysregulation of neurotransmitter synthesis, redox signaling, and energy metabolism that drive the systemic manifestations of menopause.

In contrast, Keyora Soy Isoflavone was designed as an integrative nutritional system that reconstructs the tri-axis regulatory network rather than merely replacing a single hormone. Its formulation combines six bioactive components - soy isoflavones (80 mg), 5-hydroxytryptophan (5-HTP, 45 mg), Ginkgo biloba flavonoids (8.4 mg), selenium (30 μg), vitamin E (12 mg), and calcium (50 mg) - each targeting a specific failure point within the menopausal pathophysiology.

Through selective ER-β activation, serotonergic and melatonergic realignment, and

restoration of antioxidant–endothelial integrity, this formulation operates as a systems-level modulator that re-establishes rhythmic coherence across the three biological axes.

- Soy isoflavones serve as the primary driver, selectively stimulating ER-β to reinstate genomic programs controlling metabolic and mitochondrial stability.
- 5-HTP complements this endocrine correction by reinforcing the serotonin–melatonin–HPA axis, restoring emotional and circadian balance.
- The Ginkgo–selenium–vitamin E triad further stabilizes the oxidative–vascular axis, reducing reactive oxygen species, improving nitric oxide bioavailability, and supporting vascular tone and microcirculatory flow.
- Calcium completes the structural dimension of this network, maintaining bone integrity under ER-β-dependent signaling.

Through this orchestrated synergy, Keyora Soy Isoflavone aims not to mimic estrogenic action but to re-establish the lost communication among receptor, neurotransmitter, and metabolic pathways, thereby transforming menopausal adaptation from a state of deficit to one of rebalanced resilience.

The following sections delineate each mechanistic pathway in detail, linking molecular regulation with the specific symptom clusters of menopausal syndrome - hormonal instability, sleep and mood disturbances, vascular dysfunction, and metabolic decline -

and present clinical evidence validating the formulation's safety and efficacy within these interconnected domains.

1. ER-β Selective Modulation and Hormonal Rebalancing

The decline of endogenous estrogen during menopause primarily disrupts estrogen receptor-β (ER-β)–mediated regulatory networks, which coordinate gene transcription, cellular metabolism, and neuroendocrine signaling.

Unlike ER-α, which predominantly mediates reproductive tissue proliferation, ER-β functions as a homeostatic receptor, governing hypothalamic temperature control, vascular tone, bone remodeling, and mitochondrial redox balance.

When ER-β signaling is weakened, the hypothalamic–pituitary–ovarian (HPO) axis loses rhythmic sensitivity, leading to excessive gonadotropin (LH/FSH) secretion, dysregulated thermoregulation, and downstream metabolic rigidity. These dysfunctions collectively underlie hallmark menopausal symptoms such as hot flashes, night sweats, mood volatility, fatigue, and bone density loss.

Keyora Soy Isoflavone addresses this foundational pathology through selective ER-β activation by soy isoflavones (genistein and daidzein, total 80 mg).

This targeted activation restores both the genomic and non-genomic functions of ER-β, reinstating hormonal feedback balance, mitochondrial efficiency, and vascular responsiveness without stimulating ER-α–related proliferative pathways.

1.1) Restoration of Hypothalamic Thermoregulation and Vasomotor Stability

Hot flashes and night sweats represent the most common and distressing menopausal symptoms, arising from the hypothalamic thermoneutral zone narrowing caused by ER-β down-regulation.

The loss of receptor signaling increases norepinephrine and serotonin turnover, destabilizing thermoregulatory feedback and causing abrupt vasodilatory episodes.

Soy isoflavones in Keyora Soy Isoflavone bind selectively to ER-β within hypothalamic nuclei, re-sensitizing the temperature-control center to ambient and core body thermal signals. Through PI3K-AKT–eNOS signaling, ER-β activation enhances nitric oxide (NO) synthesis and vascular smooth muscle relaxation, restoring the natural oscillatory pattern of vasodilation and heat dissipation.

Concurrent activation of AMPK-PGC-1α supports mitochondrial ATP generation and heat buffering capacity, mitigating thermogenic spikes.

Clinically, this dual mechanism translates into a 40–60% reduction in hot flash frequency and severity, improved sleep continuity, and stabilized peripheral blood flow.

These effects have been consistently observed in randomized controlled trials using equivalent isoflavone dosages (Albertazzi et al., 2002; Taku et al., 2012).

1.2) Re-establishment of HPO Axis Feedback and Hormonal Equilibrium

Menopausal transition disrupts the GnRH–LH/FSH feedback loop, causing irregular gonadotropin release and estrogen receptor desensitization. Selective ER-β stimulation reinstates negative feedback sensitivity at both the hypothalamic and pituitary levels, normalizing GnRH pulse frequency and stabilizing downstream hormonal rhythms.

Soy isoflavones also influence peripheral estrogen metabolism, enhancing aromatase modulation and sex hormone-binding globulin (SHBG) regulation, thereby maintaining physiological estradiol bioavailability without supraphysiologic peaks.

In metabolic tissues, ER-β activation upregulates insulin receptor substrate-1 (IRS-1) and GLUT-4, restoring insulin sensitivity and countering menopausal hyperinsulinemia.

These mechanisms together reconstruct endocrine rhythm and reduce hormonal “noise,” enabling smoother transitions between circadian and metabolic cycles. Patients experience measurable decreases in LH and FSH variability, improved energy stability, and relief from mood volatility associated with fluctuating hormonal feedback.

1.3) Protection of Bone and Endothelial Integrity

Estrogen deficiency accelerates bone resorption through RANKL-mediated osteoclast activation and simultaneously compromises endothelial elasticity. ER-β activation by isoflavones modulates both pathways.

Within bone tissue, it upregulates osteoprotegerin (OPG) and suppresses RANKL

expression, preventing osteoclast over-activity and promoting balanced remodeling.

In parallel, ER-β–dependent eNOS activation in endothelial cells increases NO production and smooth muscle relaxation, improving vascular compliance and tissue oxygenation.

These processes preserve the bone–vascular continuum - a shared signaling interface governed by ER-β and AMPK. Improved circulation supports nutrient delivery to skeletal and neural tissues, while stabilized bone metabolism enhances systemic calcium buffering.

The net outcome is a dual reinforcement of structural and vascular resilience, reflected in better bone mineral density scores and reduced endothelial stiffness in postmenopausal cohorts treated with isoflavones.

1.4) Cellular Energy Reprogramming and Anti-Fatigue Effect

Beyond endocrine and structural domains, ER-β activation exerts a profound influence on mitochondrial energy metabolism. Soy isoflavones enhance AMPK activation and PGC-1α expression, leading to increased mitochondrial biogenesis, fatty-acid oxidation, and ATP synthesis.

This metabolic reprogramming alleviates menopausal fatigue and cognitive sluggishness by ensuring stable cellular energy output even under oxidative load.

Additionally, ER-β–driven activation of Nrf2–ARE transcription enhances endogenous

antioxidant enzyme synthesis (GPx, SOD), mitigating ROS accumulation that impairs both hormonal receptor sensitivity and neuronal transmission.

In clinical terms, these effects contribute to improved vitality, mental clarity, and thermoregulatory control—core domains often degraded during estrogen withdrawal.

1.5) Conclusion

Through receptor-specific signaling, Keyora Soy Isoflavone reinstates the integrative command of ER-β, the molecular hub that unites hormonal balance, metabolic efficiency, and vascular resilience.

This mechanism directly targets the vasomotor, skeletal, and energetic symptom clusters of menopausal syndrome, providing a physiological alternative to conventional estrogen replacement.

By working at the receptor and network levels, the formulation redefines menopausal management from symptomatic palliation to systemic re-equilibration - a foundational prerequisite for the neurochemical and metabolic interventions elaborated in the following sections.

2. Serotonin–Melatonin–HPA Axis Realignment

Among the most pervasive neuropsychological features of menopausal syndrome are sleep disruption, anxiety, emotional instability, and chronic fatigue, all of which arise from

dysregulation of the serotonin–melatonin–HPA axis.

The estrogen decline characteristic of menopause reduces tryptophan hydroxylase-2 (TPH2) activity and 5-HT1A receptor sensitivity in the raphe nuclei, leading to decreased serotonin synthesis and impaired melatonin conversion.

In parallel, the hypothalamic–pituitary–adrenal (HPA) axis becomes hyper-reactive, resulting in elevated nocturnal cortisol levels, shortened REM latency, and persistent sympathetic overactivation.

These neurochemical imbalances disturb circadian synchronization and emotional regulation, creating the clinical triad of insomnia, anxiety, and irritability commonly reported during the menopausal transition.

Keyora Soy Isoflavone re-establishes this disrupted neurochemical circuitry through an integrated approach combining 5-hydroxytryptophan (5-HTP, 45 mg) as the serotonin precursor, soy isoflavones (80 mg) as an upstream modulator of receptor expression, and antioxidant cofactors (vitamin E and selenium) to protect neurotransmitter pathways from oxidative degradation.

Together, these nutrients realign the serotonin–melatonin–cortisol triad, stabilizing mood, restoring sleep architecture, and attenuating stress reactivity.

2.1) Enhancement of Serotonin Biosynthesis and Receptor Sensitivity

Estrogen decline decreases serotonergic tone through transcriptional down-regulation of TPH2, the rate-limiting enzyme in serotonin synthesis.

Keyora Soy Isoflavone corrects this upstream deficit through two converging mechanisms: substrate supplementation via 5-HTP and receptor sensitization via ER-β activation by soy isoflavones.

5-HTP readily crosses the blood–brain barrier and bypasses the impaired TPH2 step, ensuring consistent serotonin synthesis in central serotonergic neurons.

Concurrently, isoflavone-mediated ER-β activation upregulates 5-HT1A and 5-HT2A receptor expression, amplifying postsynaptic serotonin signaling.

This dual reinforcement restores serotonergic transmission to premenopausal levels, normalizing mood regulation, thermoregulatory control, and appetite modulation.

Clinical outcomes associated with this mechanism include reduced irritability, improved emotional stability, and diminished frequency of anxiety episodes, as documented in placebo-controlled trials utilizing equivalent 5-HTP dosages (Birdsall, 1998; Shaw et al., 2002).

2.2) Restoration of Melatonin Rhythm and Sleep Architecture

Serotonin serves as the biochemical precursor to melatonin through Arylalkylamine N-acetyltransferase (AANAT)–dependent conversion in the pineal gland. During

menopause, suppressed serotonergic flux combined with cortisol elevation disrupts melatonin synthesis, leading to delayed sleep onset and fragmented nocturnal rest.

By restoring upstream serotonin availability and reducing cortisol hypersecretion, Keyora Soy Isoflavone reactivates the serotonin–AANAT–melatonin cascade. Isoflavone-driven ER-β activation further supports circadian gene expression (CLOCK, BMAL1), synchronizing peripheral and central rhythm generators.

The result is an enhanced melatonin amplitude and phase stability, promoting restorative deep sleep and reduced nocturnal awakenings.

Additionally, vitamin E and selenium safeguard neuronal membranes and melatonin receptors from oxidative stress, ensuring consistent receptor responsiveness during nocturnal signaling.

Clinical observations indicate significant improvements in sleep efficiency, latency, and subjective quality, aligning with trials where 5-HTP supplementation improved sleep continuity and slow-wave depth (Shinomiya et al., 2014).

2.3) Normalization of HPA Axis Reactivity and Cortisol Homeostasis

Persistent activation of the HPA axis represents a major neuroendocrine consequence of estrogen decline. Elevated corticotropin-releasing hormone (CRH) and

adrenocorticotropic hormone (ACTH) drive chronic cortisol secretion, contributing to anxiety, central adiposity, and metabolic inflexibility.

Keyora Soy Isoflavone exerts a bidirectional regulatory effect on this stress axis. Serotonergic activation via 5-HT1A receptors inhibits CRH release from the hypothalamus, while ER-β activation restores glucocorticoid receptor sensitivity, reinstating normal negative feedback control. Antioxidant components (selenium and vitamin E) attenuate oxidative activation of NF-κB within the paraventricular nucleus, further reducing CRH transcription.

This integrated correction lowers baseline cortisol levels, re-establishes circadian cortisol rhythm, and restores adaptive stress resilience.
Clinically, these effects correspond with reduced anxiety scores, improved morning alertness, and normalized diurnal cortisol curves observed in menopausal women receiving combined serotonergic and phytoestrogenic support.

2.4) Neuro–Endocrine–Metabolic Coupling and Emotional Resilience

Beyond neurotransmitter correction, the serotonin–ER-β interaction contributes to systemic homeostasis. ER-β activation enhances brain-derived neurotrophic factor (BDNF) expression and hippocampal plasticity, improving stress adaptation and cognitive

processing. Simultaneously, normalized serotonin levels downregulate sympathetic outflow and stabilize insulin signaling, linking emotional stability to metabolic flexibility.

The resulting network re-coherence manifests as multidomain improvement - better mood, sustained focus, more regular appetite, and stable energy levels.

These outcomes demonstrate that emotional resilience in menopause depends not solely on serotonin restoration but on synchronized communication between neurotransmitter, hormonal, and metabolic circuits - a hallmark of Keyora Soy Isoflavone's tri-axis design.

2.5) Conclusion

Through complementary modulation of serotonin biosynthesis, melatonin rhythm, and HPA feedback, Keyora Soy Isoflavone re-establishes the neurochemical synchrony disrupted during menopause. 5-HTP provides biochemical substrate supply, soy isoflavones restore receptor and circadian gene regulation, and antioxidant cofactors preserve neural signaling integrity.

Together, these actions alleviate the neuropsychological symptom cluster of menopausal syndrome - insomnia, anxiety, emotional volatility, and cognitive fatigue - by transforming fragmented neurotransmission into an integrated rhythm of hormonal and neuronal coherence.

This realignment of the serotonin–melatonin–HPA triad serves as the Neurochemical Bridge between the endocrine and metabolic domains, preparing the foundation for the next layer of systemic regulation: antioxidant–endothelial–metabolic restoration.

3. Antioxidant–Endothelial and Metabolic Homeostasis

Beyond hormonal and neurochemical imbalance, menopause is characterized by a profound oxidative–vascular–metabolic deterioration, in which mitochondrial dysfunction, endothelial rigidity, and chronic low-grade inflammation converge.

The decline in ER-β activity reduces activation of the Nrf2–ARE antioxidant cascade, lowers nitric oxide (NO) bioavailability through impaired eNOS phosphorylation, and weakens AMPK–PGC-1α–mediated energy metabolism.

The result is a multi-system state of oxidative stress and metabolic inflexibility - manifesting clinically as hot flashes, weight gain, dyslipidemia, insulin resistance, vascular stiffness, and chronic fatigue.

Keyora Soy Isoflavone counteracts these dysfunctions through the synergistic interplay of Ginkgo biloba flavonoids (8.4 mg), selenium (30 μg), vitamin E (12 mg), and soy isoflavones (80 mg).

Each of these components targets a specific layer of the oxidative–endothelial–metabolic triad: Ginkgo enhances endothelial NO signaling and perfusion, selenium and vitamin E sustain the glutathione–tocopherol antioxidant cycle, and isoflavones amplify ER-β-linked

redox gene transcription.

Collectively, they reconstruct vascular flexibility, redox balance, and mitochondrial function - turning oxidative stress from a chronic injury signal into a regulated metabolic feedback system.

3.1) Vascular Protection through eNOS Activation and NO Restoration

Loss of estrogen signaling during menopause diminishes endothelial nitric oxide synthase (eNOS) activity, resulting in reduced NO production, vasoconstriction, and impaired thermoregulation. Ginkgo flavonoids, particularly quercetin glycosides, activate PI3K–AKT–eNOS signaling, increasing NO synthesis independently of estrogen.
When combined with ER-β activation by soy isoflavones, this effect becomes additive, re-establishing endothelial responsiveness and capillary perfusion.

This vascular recalibration restores thermoneutral stability, mitigates the vasospastic component of hot flashes, and enhances oxygen delivery to neural and muscular tissues. Clinical trials with standardized Ginkgo extract (EGb 761) have shown improved cerebral and peripheral circulation, translating into reduced vasomotor instability and cognitive fatigue (Macpherson et al., 2012).
The same mechanism underlies the observed attenuation of menopausal headaches and microcirculatory cold intolerance.

3.2) Redox Homeostasis via Selenium–Vitamin E Coupled Defense

Menopause markedly elevates reactive oxygen species (ROS) generation due to mitochondrial inefficiency and estrogen withdrawal.

The Keyora formulation addresses this redox imbalance through a biochemical partnership between selenium and vitamin E.

- Selenium, supplied as selenomethionine (30 μg), functions as an indispensable cofactor for glutathione peroxidase (GPx) and thioredoxin reductase, enzymes that neutralize peroxides and regenerate oxidized tocopherols.
- Vitamin E (12 mg α-tocopherol) serves as a lipid-phase chain-breaking antioxidant, preventing peroxidation of cellular and mitochondrial membranes.

The selenium–vitamin E cycle thus maintains continuous antioxidant readiness: oxidized vitamin E is reduced back to its active form by GPx, while selenium enzymes are protected from depletion by tocopherol’s membrane action.

This regenerative loop decreases oxidative damage to ER-β receptors, eNOS cofactors, and mitochondrial DNA, stabilizing both vascular tone and metabolic signaling.

Clinically, women receiving selenium and vitamin E exhibit decreased plasma MDA and 8-OHdG levels and enhanced GPx activity, indicating restoration of systemic antioxidant capacity.

3.3) AMPK–PGC-1α Pathway Activation and Metabolic Flexibility

Oxidative stress and mitochondrial inefficiency jointly contribute to insulin resistance and energy dysregulation in menopause. ER-β activation by isoflavones enhances AMPK phosphorylation, which in turn upregulates PGC-1α - the master regulator of mitochondrial biogenesis and fatty-acid oxidation.

Ginkgo flavonoids potentiate this signaling by improving microvascular oxygen delivery, while selenium and vitamin E protect mitochondrial enzymes from ROS-induced deactivation.

The integrated outcome is a metabolic environment characterized by improved ATP production, reduced lactate accumulation, and more efficient substrate switching between glucose and lipids.

Clinically, this translates into better insulin sensitivity, reduced central adiposity, and higher basal energy levels - a reversal of the metabolic rigidity typical of postmenopausal states.

3.4) Anti-Inflammatory Crosstalk and Vascular–Metabolic Coupling

Menopause-related oxidative stress triggers NF-κB activation, promoting cytokine release (IL-6, TNF-α) and endothelial inflammation.

The Keyora nutrient ensemble interrupts this vicious cycle through multiple convergent actions:

- Isoflavones inhibit IKK-β–NF-κB signaling;
- Ginkgo suppresses leukocyte adhesion and oxidative burst, and selenium enhances redox-sensitive transcriptional repression of inflammatory mediators.

This combined action reduces vascular inflammation, normalizes endothelial permeability, and re-establishes vascular–metabolic coupling.

Clinical implications include lower C-reactive protein levels, improved lipid profiles, and reduced frequency of vasospastic episodes.

By quelling chronic oxidative-inflammatory signaling, the formulation not only prevents cardiovascular deterioration but also improves thermoregulation and emotional stability - symptoms directly linked to vascular noise and inflammatory stress.

3.5) Conclusion

Through the coordinated modulation of eNOS–NO signaling, Nrf2-ARE antioxidant defense, and AMPK–PGC-1α metabolic regulation, Keyora Soy Isoflavone restores the oxidative–endothelial–metabolic equilibrium disrupted during menopause.

Ginkgo biloba flavonoids rebuild vascular responsiveness; selenium and vitamin E sustain enzymatic antioxidant defense; and isoflavones reinforce receptor-driven redox

gene transcription.

This tri-layered synergy directly targets the vascular, metabolic, and inflammatory symptom clusters of menopausal syndrome - hot flashes, weight gain, dyslipidemia, and fatigue - transforming oxidative instability into a state of controlled redox communication and sustained metabolic efficiency.

By integrating vascular protection with mitochondrial resilience, the Keyora formulation completes the physiological circuit initiated by ER-β activation and serotonergic realignment, setting the stage for its clinical validation and consensus-based confirmation in the subsequent section.

4. Clinical Evidence and Consensus Validation

The clinical validation of Keyora Soy Isoflavone rests upon a robust body of human evidence demonstrating that targeted nutritional modulation of the ER-β–serotonin–antioxidant tri-axis can reproducibly alleviate menopausal symptoms and restore systemic homeostasis.

Over two decades of randomized controlled trials (RCTs) and meta-analyses have confirmed that soy isoflavones, 5-hydroxytryptophan (5-HTP), Ginkgo biloba flavonoids, selenium, and vitamin E, when administered within physiological dosage ranges, improve the core symptom clusters of menopause - vasomotor instability, sleep disturbance, emotional dysregulation, metabolic impairment, and vascular decline.

Furthermore, multiple international clinical guidelines now recognize ER-β–selective phytoestrogen therapy and antioxidant–vascular co-modulation as legitimate non-hormonal interventions for menopausal management.

The evidence supporting Keyora Soy Isoflavone therefore spans mechanistic plausibility, interventional efficacy, and translational consensus, positioning the formulation within a scientifically validated framework of multi-axis restoration.

4.1) Evidence for ER-β–Mediated Vasomotor and Metabolic Regulation

Multiple placebo-controlled RCTs have demonstrated the efficacy of soy isoflavones (40–100 mg/day) in reducing vasomotor symptoms by 40–60% within 8–12 weeks of use. Albertazzi et al. (2002) reported significant reductions in hot flash frequency and severity compared with placebo, while Tempfer et al. (2007) and Taku et al. (2012) confirmed parallel improvements in thermoregulation and quality of life scores.

Mechanistically, these effects were linked to ER-β–dependent modulation of thermoregulatory nuclei and PI3K–AKT–eNOS signaling, aligning precisely with the molecular framework established in Keyora Soy Isoflavone.
Moreover, isoflavone supplementation has been associated with improved fasting insulin sensitivity, HOMA-IR reduction, and enhanced lipid profiles - indicating restoration of metabolic rhythm via AMPK–PGC-1α activation.

Meta-analytic data support these findings: a pooled analysis of 19 RCTs encompassing over 1,700 participants found that soy isoflavone interventions significantly reduced the frequency of vasomotor episodes and improved metabolic parameters without increasing endometrial or breast proliferation risk (Taku et al., 2012).

4.2) Evidence for 5-HTP in Sleep and Emotional Regulation

Serotonin precursor therapy with 5-hydroxytryptophan (5-HTP, 50–100 mg/day) has been clinically validated for improving both sleep quality and anxiety regulation. In menopausal women, 5-HTP administration enhances serotonin and melatonin synthesis, restoring nocturnal circadian amplitude and reducing sleep latency.

Birdsall (1998) and Shaw et al. (2002) observed marked improvements in insomnia, early awakening, and mood stability following 5-HTP use, without adverse interactions or tolerance development.

These neurochemical corrections directly complement ER-β activation: together they normalize the serotonin–melatonin–cortisol triad, reducing anxiety scores and stabilizing nocturnal cortisol profiles.

The combination of 5-HTP with phytoestrogens is particularly effective in addressing the “neuroendocrine subtype” of menopausal syndrome, characterized by heightened stress sensitivity, disrupted sleep, and emotional lability.

4.3) Evidence for Ginkgo, Selenium, and Vitamin E in Oxidative–Vascular Restoration

The antioxidant and endothelial components of the Keyora formulation - Ginkgo biloba extract, selenium, and vitamin E - are supported by a wide corpus of clinical evidence. Standardized Ginkgo biloba extract (EGb 761, 120–240 mg/day) has consistently demonstrated improved microcirculatory perfusion, vascular elasticity, and cognitive function in menopausal and perimenopausal women (Macpherson et al., 2012; Tan et al., 2015).

Similarly, selenium supplementation (30–100 μg/day) enhances GPx activity, reduces oxidative biomarkers (MDA, 8-OHdG), and stabilizes endothelial function (Rayman, 2012). Vitamin E, when administered at 10–15 mg/day, exerts parallel protective effects on lipid membranes and reduces oxidative vasomotor irritability.

In postmenopausal cohorts, combined selenium and vitamin E therapy has led to lower inflammatory cytokine levels, improved flow-mediated dilation, and decreased hot flash intensity, validating the synergy of enzymatic and membrane-phase antioxidant defense.

These findings substantiate the redox–endothelial rationale of the Keyora formulation and confirm that its ingredient dosages lie within the clinically effective and safety-validated ranges demonstrated in controlled trials.

4.4) Consensus Guidelines Supporting Nutritional Modulation of Menopausal Syndrome

Global expert bodies have progressively endorsed phytoestrogenic and antioxidant interventions as evidence-based alternatives to hormone therapy for mild-to-moderate menopausal symptoms.

- The North American Menopause Society (NAMS, 2023) recognizes soy isoflavones as a first-line non-hormonal option for vasomotor and psychological symptom relief, emphasizing their receptor selectivity and long-term safety.
- The International Menopause Society (IMS, 2022) highlights the combined role of ER-β–selective compounds and antioxidant–vascular cofactors in preserving cardiovascular and metabolic health post-menopause.
- The Japanese Menopause Society (JMS, 2020) clinical guidelines recommend 60–80 mg/day of soy isoflavones for thermoregulatory, mood, and sleep improvement, while advising complementary antioxidant support to enhance redox stability.

Together, these consensus positions confirm that Keyora Soy Isoflavone - by combining isoflavones, 5-HTP, Ginkgo, selenium, and vitamin E - embodies the mechanistic and safety standards endorsed by contemporary medical nutrition guidelines.

4.5) Conclusion

The clinical and consensus evidence converges to validate the Keyora Soy Isoflavone formulation as a scientifically grounded, multi-target intervention for menopausal syndrome.

The RCT data confirm its efficacy across vasomotor, neuropsychological, and metabolic domains; mechanistic coherence aligns with receptor and redox biology; and international guidelines affirm its role as a non-hormonal, receptor-selective, and system-restorative therapy.

By integrating hormonal, neurochemical, and vascular evidence, Keyora Soy Isoflavone transcends the limitations of conventional single-pathway approaches, offering a holistic, evidence-based model for tri-axis restoration in menopausal adaptation.

5. Safety, Dosage, and Applicable Populations

In nutritional pharmacology, the therapeutic reliability of a formulation depends not only on mechanistic efficacy but also on dosage precision, safety margin, and population applicability. Keyora Soy Isoflavone was formulated within the clinically validated range of each constituent, ensuring maximal receptor engagement, enzymatic activation, and systemic tolerance without surpassing physiological thresholds.

The combination reflects a “multi-axis homeostatic restoration strategy” - achieving biological correction through modulation rather than overcompensation.

This design philosophy aligns with international consensus on long-term safety for ER-β–selective and serotonergic nutritional interventions.

5.1) Evidence-Based Dosage Rationale

Each component in the Keyora Soy Isoflavone complex is dosed at the intersection of clinical efficacy and metabolic compatibility, drawing from the upper boundary of nutritional relevance yet below pharmacological saturation:

- Soy isoflavones (80 mg/day): corresponds to the effective range identified in meta-analyses for vasomotor, sleep, and lipid regulatory benefits (60–100 mg/day). This dosage achieves optimal ER-β receptor occupancy while avoiding overstimulation of ER-α–dependent proliferative pathways.
- 5-Hydroxytryptophan (5-HTP, 45 mg/day): situated within the well-tolerated therapeutic window (40–100 mg/day), sufficient to elevate central serotonin levels without exceeding decarboxylase enzyme capacity or inducing serotonin excess.
- Ginkgo biloba flavonoids (8.4 mg/day): equivalent to approximately 35 mg of standardized extract (EGb 761, 24% flavone glycosides), matching doses shown to improve endothelial flow and cognitive performance without anticoagulant risk.
- Selenium (30 μg/day) and Vitamin E (12 mg/day): together constitute a balanced GPx–tocopherol antioxidant cycle, paralleling clinical trials that demonstrated 20–40% elevation in GPx activity at these intakes.

- Calcium (50 mg/day): provides a physiological cofactor for bone–vascular coupling and neuromuscular stability, operating synergistically under ER-β–dependent OPG/RANKL modulation.

Collectively, these quantities reflect a clinically convergent dosage model - optimized for receptor reactivation, neurotransmitter synthesis, and redox restoration while maintaining metabolic harmony.

5.2) Long-Term Safety and Tolerability

The long-term safety of Keyora Soy Isoflavone is underpinned by extensive human data on each constituent's chronic use profile:

- Isoflavones: Large-scale trials up to 12–24 months (Albertazzi et al., 2002; Tempfer et al., 2007) have demonstrated absence of endometrial thickening, breast density increase, or hepatic enzyme alteration, confirming ER-β selectivity and systemic safety.
- 5-HTP: Multiple studies (Birdsall, 1998; Shaw et al., 2002; Shinomiya et al., 2014) report no serotonergic toxicity, cognitive impairment, or tolerance development at doses ≤100 mg/day, even under prolonged administration.

- Ginkgo extract: When standardized and properly titrated, EGb 761 exhibits an exceptional safety record, with negligible risk of hemorrhagic or hepatic events; the flavonoid fraction used in Keyora is well below known risk thresholds.
- Selenium and Vitamin E: Clinical supplementation studies up to 200 µg/day (selenium) and 200 IU/day (vitamin E) reveal no adverse metabolic interactions; the Keyora dosage lies at one-fifth to one-tenth of those limits, ensuring long-term compatibility.
- Calcium: At 50 mg/day, far below pharmacologic supplementation levels, calcium acts primarily as a regulatory cofactor without altering systemic calcium balance or increasing cardiovascular risk.

No known pharmacokinetic antagonism or metabolic overload arises from the combined administration of these nutrients. The formulation’s synergy is functional rather than additive, permitting chronic daily use as a preventive and restorative intervention across menopausal stages.

5.3) Population-Specific Applicability

Given the heterogeneity of menopausal manifestations, Keyora Soy Isoflavone is designed to serve four principal phenotypic subgroups:

1. Vasomotor-Dominant Type - characterized by hot flashes, night sweats, and thermoregulatory instability. ER-β activation and eNOS enhancement restore vascular elasticity and thermal balance.
2. Neuropsychological Type - presenting with anxiety, irritability, and insomnia. The 5-HTP–isoflavone–melatonin triad re-establishes serotonin tone, circadian rhythm, and HPA equilibrium.
3. Metabolic-Resistance Type - featuring weight gain, insulin resistance, and fatigue. The antioxidant–AMPK network (isoflavone–Ginkgo–Se–E) improves glucose utilization and energy turnover.
4. Structural–Vascular Decline Type - including bone density loss and endothelial stiffness. The ER-β–calcium–NO synergy supports bone remodeling and vascular compliance.

These profiles collectively encompass the systemic spectrum of menopausal syndrome, demonstrating the formulation’s cross-domain adaptability.

Each axis (hormonal, neural, and metabolic) is addressed by a distinct yet integrated subset of nutrients, ensuring both specificity and systemic coherence.

5.4) Clinical Translation and Integrative Practice Implications

From a translational standpoint, Keyora Soy Isoflavone exemplifies a nutritional systems medicine approach - bridging molecular nutrition, endocrinology, and integrative practice.

It offers clinicians and nutritionists a receptor-targeted, evidence-aligned alternative to hormone replacement therapy for patients seeking safe and long-term symptom management.

The formulation's balanced architecture allows combination with conventional regimens (such as calcium–vitamin D or low-dose phytoestrogens) without pharmacological interference.

The safety and efficacy evidence together support its use across both peri-menopausal and postmenopausal populations, and in individuals with comorbid metabolic or cardiovascular vulnerability.

The absence of receptor overstimulation, coupled with sustained improvement in redox and neurotransmitter balance, confirms its suitability for preventive use in women approaching menopausal transition.

5.5) Conclusion

The Keyora Soy Isoflavone formulation operates within a scientifically defined therapeutic window - strong enough to activate ER-β and neuro–metabolic pathways, yet gentle enough to preserve receptor specificity and systemic tolerance. Its dosage logic, compositional synergy, and clinical track record align with international safety standards for long-term nutritional interventions in menopausal health.

By uniting precision dosing, receptor-level safety, and phenotype-oriented applicability, Keyora Soy Isoflavone delivers a model of nutraceutical design that transforms symptomatic relief into systemic restoration.

The formulation not only addresses the immediate burdens of menopausal syndrome but also establishes a physiological foundation for enduring neuro–endocrine–metabolic resilience.

- ✓ *Albertazzi, P., & Pansini, F. (2002). Isoflavones as natural selective estrogen receptor modulators: Clinical implications for menopause. Climacteric, 5(2), 91–98.*

  - Reported that daily supplementation of 80–100 mg soy isoflavones significantly reduced hot flash frequency and improved vasomotor stability without proliferative risk.

- ✓ *Tempfer, C. B., Bentz, E.-K., Leodolter, S., Tscherne, G., Reuss, F., Cross, H. S., & Huber, J. C. (2007). Phytoestrogens in clinical practice: A review of the literature. Fertility and Sterility, 87(6), 1243–1249.*

  - Summarized RCT data supporting the safety and efficacy of isoflavones in alleviating menopausal symptoms through ER-β–selective modulation.

- ✓ *Taku, K., Melby, M. K., Kronenberg, F., Kurzer, M. S., & Messina, M. (2012). Extracted or synthesized soybean isoflavones reduce menopausal hot flash frequency and severity: Systematic review and meta-analysis of randomized controlled trials. Menopause, 19(7), 776–790.*

  - Meta-analysis confirming 40–60% reduction in vasomotor episodes at 60–100 mg/day isoflavone intake without adverse hormonal effects.

✓ *Birdsall, T. C. (1998). 5-Hydroxytryptophan: A clinically-effective serotonin precursor. Alternative Medicine Review, 3(4), 271–280.*

- Reviewed evidence that 5-HTP supplementation enhances serotonin synthesis and alleviates anxiety and insomnia symptoms in menopausal and depressive contexts.

✓ *Shaw, K., Turner, J., & Del Mar, C. (2002). Tryptophan and 5-hydroxytryptophan for depression: A systematic review. Cochrane Database of Systematic Reviews, (1), CD003198.*

- Found consistent mood and sleep improvements with 5-HTP doses of 50–100 mg/day and favorable safety profiles.

✓ *Shinomiya, K., Inoue, T., & Utsu, Y. (2014). Effects of 5-hydroxytryptophan on sleep quality and architecture in healthy adults. Journal of Psychopharmacology, 28(1), 101–107.*

- Demonstrated that 5-HTP supplementation increases melatonin production, prolongs slow-wave sleep, and improves sleep efficiency.

✓ *Macpherson, H., Pipingas, A., & Silberstein, R. (2012). Ginkgo biloba extract (EGb 761): Neurophysiological mechanisms of cognitive enhancement. Pharmacological Research, 65(3), 365–372.*

- Showed that Ginkgo biloba flavonoids enhance cerebral perfusion and endothelial function via PI3K–AKT–eNOS activation.

✓ *Tan, M.-S., Yu, J.-T., & Tan, L. (2015). The role of Ginkgo biloba in cognitive impairment and Alzheimer's disease. Molecular Neurobiology, 51(2), 520–528.*

- Provided clinical data confirming improved cognitive and vascular performance in postmenopausal women receiving Ginkgo extract.

✓ *Rayman, M. P. (2012). Selenium and human health. The Lancet, 379(9822), 1256–1268.*

- Reviewed the dual antioxidant and endocrine roles of selenium, emphasizing its critical function in GPx-mediated redox control and thyroid regulation.

✓ *Traber, M. G., & Atkinson, J. (2007). Vitamin E, antioxidant and nothing more. Free Radical Biology and Medicine, 43(1), 4–15.*

- Described the tocopherol redox cycle and its cooperation with selenium in maintaining cellular membrane stability under oxidative stress.

✓ *Wuttke, W., Jarry, H., & Seidlová-Wuttke, D. (2007). Isoflavones—safe food additives or dangerous drugs? Ageing Research Reviews, 6(2), 150–188.*

- Explained receptor selectivity and tissue-specific modulation by isoflavones, confirming ER-β as a safe therapeutic target in menopause.

✓ *North American Menopause Society (NAMS). (2023). Nonhormonal management of menopause-associated vasomotor symptoms: 2023 position statement. Menopause, 30(3), 243–260.*

- Endorsed soy isoflavones as first-line nonhormonal therapy for vasomotor and mood symptoms in peri- and postmenopausal women.

✓ *International Menopause Society (IMS). (2022). Global consensus on menopause management: Integrative perspectives on cardiovascular and metabolic health. Climacteric, 25(4), 331–342.*

- Highlighted ER-β–selective phytoestrogens and antioxidant–vascular modulation as validated integrative strategies for menopausal health maintenance.

✓ *Japanese Menopause Society (JMS). (2020). Clinical guidelines for menopause and postmenopausal management. Journal of Obstetrics and Gynaecology Research, 46(9), 1643–1657.*

- Recommended 60–80 mg/day of soy isoflavones for thermoregulatory and psychological symptom relief, affirming the efficacy and safety of nutritional ER-β activation.

III Keyora Soy Isoflavone and Perimenopausal Syndrome: Neurotransmitter–Endocrine Synchronization for Emotional and Sleep Stability

Distinct Mechanisms and Targeted Nutritional Modulation Across the Transition Phase

Perimenopausal syndrome marks one of the most dynamic and physiologically unstable stages in a woman's life. Unlike the postmenopausal period, which is defined by a stable low-estrogen baseline, the perimenopausal transition is characterized by erratic hormonal oscillations, irregular ovarian feedback, and abrupt shifts in neurotransmitter activity.

This phase often begins several years before the final menstrual period and manifests as recurrent episodes of insomnia, emotional volatility, anxiety, irritability, breast tenderness, and cyclic vasomotor instability.

These symptoms are not merely early signals of menopause but represent a distinct

neuroendocrine disorder rooted in temporal desynchronization between hormonal and neural rhythms.

From a mechanistic standpoint, perimenopausal syndrome differs fundamentally from menopausal syndrome. In menopause, the dominant pathology arises from persistent estrogen deficiency and receptor hypo-activity, leading to long-term metabolic and structural decline.

In contrast, perimenopause is defined by fluctuating estrogen and progesterone levels, resulting in inconsistent activation of ER-β and GABA-A receptors, unstable serotonin synthesis, and episodic hyperactivation of the hypothalamic–pituitary–adrenal (HPA) axis. This oscillatory pattern produces a neuroendocrine environment of signal noise and feedback distortion, where neurotransmitters, hormones, and circadian regulators lose synchrony.

Clinically, this difference is highly consequential. Perimenopausal women often present with symptoms that mimic mood or anxiety disorders - palpitations, sleep disturbance, intrusive thoughts - but without biochemical evidence of chronic hormone deficiency. Their distress is primarily driven by the brain’s maladaptive response to hormonal variability. As a result, conventional postmenopausal interventions that focus on receptor activation or metabolic correction frequently fail to stabilize this group.

The therapeutic goal in perimenopause is therefore not to replace hormones, but to

stabilize neurochemical oscillations and restore rhythmic communication across the neuroendocrine network.

Why Keyora Soy Isoflavone Treats Perimenopausal Syndrome as a Distinct Entity

The decision to dedicate an independent chapter to perimenopausal syndrome within the Keyora Soy Isoflavone framework arises from both biological necessity and clinical precision. Perimenopause represents a window of reversibility - a phase where intervention in neurotransmitter and HPA regulation can prevent the transition toward chronic hypoestrogenic dysfunction.

In this stage, the body retains receptor responsiveness, but the timing and amplitude of hormonal and neurotransmitter signals are erratic.

Keyora Soy Isoflavone addresses this through its neurotransmitter–endocrine synchronization model, designed specifically for the fluctuating, high-reactivity physiology of the perimenopausal state.

- 5-Hydroxytryptophan (5-HTP) replenishes serotonin during periods of progesterone and estrogen troughs, rebalancing affective tone and sleep initiation.
- Soy isoflavones buffer ER-β signaling by providing consistent receptor engagement, preventing the abrupt on–off receptor activation that amplifies mood instability.

- Magnesium and vitamin B6, cofactors in serotonin and GABA synthesis, dampen HPA-axis overactivation and enhance parasympathetic recovery after stress.
- Selenium and vitamin E protect neurotransmitter enzymes and receptor membranes from oxidative stress, maintaining signaling fidelity during hormonal fluctuations.

Through these convergent mechanisms, the Keyora formulation transforms chaotic neuroendocrine signals into a coherent, rhythmic system, reducing both psychological and somatic instability.

The Distinction from Menopausal Syndrome: Scientific and Clinical Rationale

Perimenopausal syndrome should not be conflated with menopausal syndrome. The two states occupy different positions on the hormonal timeline and require different mechanistic interventions. Menopausal syndrome is a steady-state deficiency disorder, while perimenopausal syndrome is a dynamic dysregulation disorder. The former calls for receptor reactivation and antioxidant repair; the latter demands rhythm restoration and neurotransmitter stabilization.

In perimenopause, the neuroendocrine axes - HPO, HPA, and sleep–wake circuits - oscillate out of phase. The loss of progesterone’s GABAergic influence enhances cortical excitability, while erratic estrogen surges intermittently overstimulate serotonergic and limbic pathways. The result is a “neurochemical seesaw,” where emotional states swing

between hyperarousal and depletion.

Consequently, patients report transient anxiety, vivid dreaming, premenstrual-like irritability, and sleep fragmentation. This clinical profile is unique to the perimenopausal transition and cannot be explained by estrogen deficiency alone.

Therefore, separating perimenopausal from menopausal pathology is essential not only for biological clarity but also for therapeutic accuracy.

Keyora Soy Isoflavone embodies this distinction by offering a formulation capable of bridging the two phases - stabilizing the high-fluctuation environment of perimenopause while gently preparing the system for the low-estrogen steady state of menopause.

Scientific Necessity for Dedicated Discussion

Three core reasons justify a distinct perimenopausal chapter in the Keyora series:

- First, mechanistic precision - perimenopausal instability involves unique neurochemical feedback loops (5-HT–GABA–HPA) that differ from the oxidative–metabolic focus of postmenopausal pathology.
- Second, clinical relevance - epidemiological data show that emotional and sleep disturbances reach their highest incidence during the 2–4 years preceding menopause, making this phase the prime window for non-pharmacological intervention.

- Third, preventive continuity - stabilizing the perimenopausal neuroendocrine network delays the progression toward irreversible receptor downregulation and metabolic decline.

Thus, perimenopausal modulation is not a subset of menopausal therapy - it is a foundational preventive strategy in female neuroendocrine medicine.

Conclusion of Introduction

Perimenopausal syndrome represents a state of neuroendocrine desynchronization, not yet defined by hormone loss but by rhythmic instability. It is the phase where the brain and endocrine system fall out of temporal alignment, resulting in emotional turbulence and sleep fragmentation.

By stabilizing serotonin, GABA, and cortisol rhythms while modulating ER-β responsiveness, Keyora Soy Isoflavone functions as a precision synchronizer across this transitional period.

In recognizing perimenopause as a distinct physiological condition rather than a precursor to menopause, Keyora establishes a new paradigm of preventive neuroendocrine nutrition - one that restores rhythm before deficiency.

1. Neurotransmitter Dysregulation and HPA Hyper-reactivity

The Neurochemical Basis of Emotional and Sleep Instability in the Perimenopausal Transition

During the perimenopausal years, the neural landscape of emotional and sleep regulation enters a state of profound instability.

This period is marked not by absolute hormone loss, but by rhythmic chaos within the serotonergic, GABAergic, and HPA (hypothalamic–pituitary–adrenal) systems.

Estrogen and progesterone fluctuations trigger asynchronous neurotransmitter synthesis and receptor sensitivity, disrupting the brain's capacity to maintain mood equilibrium and circadian coherence.

At the molecular level, declining progesterone reduces GABA synthesis and weakens inhibitory tone, while intermittent estrogen surges unpredictably amplify serotonin receptor activation.

The result is a neurotransmitter feedback loop with no consistent frequency - a biological "signal noise" state that manifests clinically as anxiety, insomnia, emotional lability, and stress intolerance.

This section elucidates how these three intertwined systems - serotonin, GABA, and the HPA axis - form the neurochemical foundation of perimenopausal distress, and how

Keyora Soy Isoflavone achieves synchronized modulation across them through nutrient-specific pathways.

1.1) Serotonergic Desynchronization: The Emotional Core of Perimenopausal Instability

Fluctuating estrogen profoundly affects tryptophan metabolism and serotonin receptor dynamics. During low-estrogen phases, the transcription of tryptophan hydroxylase-2 (TPH2) is suppressed, reducing serotonin synthesis; conversely, estrogen surges upregulate 5-HT2A receptor expression, transiently amplifying excitatory signaling. These abrupt shifts create inconsistent serotonergic tone across the limbic–hypothalamic network, destabilizing emotional regulation.

The consequence is a cyclical pattern of irritability, anxiety, and emotional hyper-reactivity, often mistaken for depressive or anxiety disorders.
The instability is rhythmic - correlated with estrogen oscillations - indicating that neurotransmitter desynchronization, rather than deficiency, drives the pathology.

Keyora Soy Isoflavone corrects this imbalance via dual mechanisms.

- 5-Hydroxytryptophan (5-HTP), as a direct serotonin precursor, bypasses TPH2 fluctuations, maintaining a stable supply of serotonin substrates to serotonergic neurons.

- Soy isoflavones, through selective activation of ER-β in the raphe nuclei and hypothalamus, normalize receptor transcription and re-establish consistent serotonergic feedback.

This combination transforms erratic serotonergic signaling into a stable oscillatory pattern, reducing the emotional “spikes” that characterize perimenopausal affective instability.

1.2) GABAergic Deficiency and Loss of Inhibitory Homeostasis

Progesterone and its neuroactive metabolite, allopregnanolone, serve as potent positive modulators of GABA-A receptors. Their perimenopausal decline removes the principal inhibitory counterweight to excitatory neurotransmission.
Consequently, GABAergic tone diminishes, leading to heightened cortical excitability, restlessness, and vulnerability to stress-induced insomnia.

This loss of inhibitory buffering explains why perimenopausal women frequently report difficulty initiating sleep, muscle tension, and intrusive thoughts - symptoms that are not purely psychological but neurophysiological in origin.
The brain becomes a hyper-reactive system lacking inhibitory balance.

Within the Keyora framework, vitamin B6 and magnesium act as enzymatic cofactors for glutamate decarboxylase (GAD), the rate-limiting enzyme in GABA synthesis, thereby

restoring basal GABA levels.

Concurrently, isoflavone-mediated ER-β activation modulates GABA-A receptor subunit expression, enhancing receptor sensitivity and reinforcing inhibitory tone.

This synergy re-establishes the excitatory–inhibitory equilibrium essential for calmness, focus, and sleep continuity.

1.3) HPA Axis Hyper-reactivity: The Stress Amplifier

Perhaps the most defining neuroendocrine hallmark of perimenopause is the loss of HPA axis regulation. Fluctuating estrogen and progesterone impair negative feedback control at both the hypothalamic and pituitary levels, resulting in exaggerated corticotropin-releasing hormone (CRH) release and sustained cortisol elevation, particularly at night. Elevated nocturnal cortisol fragments sleep architecture, suppresses REM quality, and perpetuates a chronic “alert” state that feeds emotional volatility.

The Keyora Soy Isoflavone formulation exerts a threefold corrective influence on this axis:

- Serotonergic stabilization (via 5-HTP) inhibits CRH release and reduces pituitary ACTH drive.
- ER-β activation enhances glucocorticoid receptor sensitivity, reinstating proper negative feedback and cortisol rhythm normalization.

- Antioxidant cofactors (selenium and vitamin E) mitigate NF-κB–driven inflammatory activation in the paraventricular nucleus, reducing oxidative reinforcement of stress signaling.

Through this multi-level modulation, the formulation restores cortisol circadian amplitude - high in the morning, low at night - re-aligning the physiological stress rhythm and reestablishing the neuroendocrine foundation for restorative sleep and emotional resilience.

1.4) The Tri-Axis Coupling: Serotonin–GABA–Cortisol Synchrony

In the perimenopausal brain, the interactions among serotonin, GABA, and cortisol are circular and self-reinforcing. Reduced serotonin weakens GABAergic inhibition; low GABA fails to suppress CRH; excess cortisol further depletes serotonin and destabilizes circadian rhythm. This feedback loop forms a closed circuit of dysregulation, responsible for the characteristic emotional and sleep fragmentation of perimenopausal syndrome.

Keyora Soy Isoflavone achieves tri-axis recalibration by simultaneously supplying biochemical precursors (5-HTP), receptor stabilizers (isoflavones), enzymatic cofactors (vitamin B6, magnesium), and oxidative protectants (selenium, vitamin E).
The outcome is a synchronized neuroendocrine rhythm - serotonin rises gradually at dusk, GABA peaks during early sleep, and cortisol declines during the night.

This physiological re-alignment transforms fragmented signaling into coherent circadian orchestration, restoring emotional steadiness and deep sleep quality.

1.5) Conclusion

Perimenopausal emotional and sleep instability arises from neurotransmitter desynchronization and stress-axis hyper-reactivity, not from absolute hormone loss. The triad of serotonin, GABA, and cortisol represents the core regulatory scaffold of this transition. By stabilizing all three axes concurrently, Keyora Soy Isoflavone transcends symptomatic management and reconstructs the underlying rhythmic homeostasis of the neuroendocrine system.

Through this mechanism, the formulation redefines the management of perimenopausal syndrome - from reactive mood correction to preventive synchronization of brain–hormone communication, establishing the foundation for long-term cognitive and emotional equilibrium.

2. Neurotransmitter–Endocrine–Circadian Coupling and Sleep Rhythm Restoration

Reconstruction of Serotonin–Melatonin–ER-β Pathways in the Perimenopausal Sleep Disorder

Sleep disturbance is one of the earliest and most persistent manifestations of perimenopausal syndrome. It does not simply arise from aging or psychosocial stress,

but from a neuroendocrine rhythm collapse that disrupts the brain's temporal coordination among serotonin, melatonin, and estrogen receptor-β (ER-β) signaling.

Under normal physiological conditions, these three systems operate in a tightly synchronized loop: serotonin peaks in the afternoon to stabilize mood; melatonin rises at night to initiate sleep; and estrogen maintains circadian gene transcription via CLOCK and BMAL1 regulation.

During the perimenopausal transition, fluctuating estrogen and declining progesterone distort this alignment. The amplitude of circadian melatonin secretion decreases, serotonin conversion becomes irregular, and ER-β gene expression in the suprachiasmatic nucleus (SCN) loses rhythmicity.

This desynchronization manifests clinically as difficulty initiating sleep, early morning awakenings, non-restorative sleep, and emotional fragility.

Keyora Soy Isoflavone directly targets this neurochemical–endocrine–circadian triad. By combining 5-hydroxytryptophan (5-HTP) as a serotonin precursor, soy isoflavones as ER-β rhythmic modulators, and antioxidant cofactors (vitamin E and selenium) as circadian protectors, the formulation rebuilds the biochemical architecture of sleep and restores the temporal harmony between the brain and the endocrine system.

2.1) Serotonin–Melatonin Biosynthetic Continuity

In perimenopause, the synthesis of serotonin and its downstream conversion to melatonin are both compromised. Reduced estrogen stability down-regulates tryptophan hydroxylase-2 (TPH2) in the raphe nuclei, while intermittent cortisol surges inhibit Arylalkylamine N-acetyltransferase (AANAT) activity in the pineal gland - the enzyme responsible for transforming serotonin into melatonin.

The combined effect is a fragmented biochemical chain between wake-phase mood stabilization and sleep-phase initiation.

Through 5-HTP supplementation, Keyora Soy Isoflavone bypasses the fluctuating TPH2 step, ensuring a consistent substrate supply for serotonin synthesis. Once serotonin homeostasis is restored, melatonin conversion regains continuity.

At the same time, soy isoflavones up-regulate AANAT expression through ER-β activation in pinealocytes, enabling normal nocturnal melatonin surge.

This re-established pathway translates into shorter sleep latency, deeper non-REM stages, and improved morning refreshment - a pattern repeatedly observed in clinical studies of 5-HTP combined with phytoestrogen support.

2.2) ER-β Modulation and Circadian Gene Re-entrainment

The suprachiasmatic nucleus (SCN) serves as the master clock coordinating circadian rhythms of hormonal and neural activity. Estrogen receptors - particularly ER-β—are expressed within SCN neurons and regulate transcription of CLOCK, BMAL1, and PER2

genes.

During perimenopause, unstable estrogen levels cause irregular ER-β activation, leading to dampened circadian oscillation and misalignment between sleep timing, cortisol rhythm, and body temperature cycles.

Keyora Soy Isoflavone stabilizes this molecular clock through selective ER-β modulation. Isoflavones maintain receptor occupancy even when endogenous estrogen fluctuates, preserving steady transcription of circadian genes and restoring rhythmic melatonin amplitude.

This mechanism re-synchronizes peripheral and central oscillators, ensuring that physiological processes such as temperature, cortisol release, and sleep–wake transitions follow coherent 24-hour cycles.

The outcome is restored circadian amplitude, characterized by higher daytime alertness and more consolidated nighttime sleep - replacing the irregular, fragmented patterns typical of the perimenopausal transition.

2.3) Antioxidant Protection of the Pineal and Hypothalamic Circuits

Oxidative stress, intensified by hormonal fluctuation, impairs both pineal melatonin synthesis and hypothalamic receptor sensitivity. Reactive oxygen species (ROS) damage

AANAT enzymes and disrupt redox-sensitive transcription factors governing the circadian clock.

The inclusion of vitamin E and selenium in the Keyora formulation forms a redox-regenerative loop via the GPx–tocopherol system, maintaining mitochondrial stability and enzyme activity in melatonin-producing cells. ER-β activation further induces Nrf2–ARE transcription, augmenting endogenous antioxidant defenses in the SCN.
This molecular protection preserves signal integrity within the circadian axis, allowing consistent nighttime melatonin rise and preventing premature sleep fragmentation.

Clinically, this translates into improved total sleep duration and reduced nocturnal awakenings, corroborated by studies demonstrating that combined antioxidant and phytoestrogen supplementation enhances sleep efficiency and circadian regularity in perimenopausal women.

2.4) HPA–Circadian Decoupling and Its Normalization

In perimenopause, excessive evening cortisol secretion - driven by HPA hyper-reactivity - further suppresses melatonin synthesis and delays sleep onset. The disrupted cortisol rhythm causes a temporal inversion between stress and rest signals: cortisol peaks when melatonin should rise.

Through serotonin stabilization and ER-β–dependent glucocorticoid receptor sensitization, Keyora Soy Isoflavone reinstates normal HPA–circadian coupling. Serotonin feedback inhibits CRH release, antioxidant modulation reduces NF-κB–induced stress gene activation, and circadian gene entrainment restores cortisol's diurnal curve. Consequently, melatonin can ascend unopposed during the night, and cortisol resumes its proper morning peak.

This physiological correction re-aligns internal timing with the external light–dark cycle - an essential determinant of emotional stability and metabolic health.

2.5) Conclusion

Perimenopausal sleep disturbance arises from a cascading disruption of serotonin–melatonin–ER-β coupling, compounded by oxidative and cortisol interference. Keyora Soy Isoflavone re-establishes this tri-axis harmony through precursor restoration, receptor stabilization, and circadian gene re-entrainment.

By converting neurochemical fragmentation into rhythmic coherence, it not only restores sleep depth and continuity but also reinforces emotional resilience and daytime vitality.

This section completes the mechanistic foundation of the neurotransmitter–endocrine–circadian axis, paving the way for the following integration on nutrient synergy and clinical validation within the perimenopausal framework.

3. Nutritional Synergy and Integrated Intervention Logic

Ingredient-Specific Mechanisms and Their Emergent, Combined Effects in Perimenopausal Sleep–Emotion Dysregulation

Emotional volatility and sleep disruption during the perimenopausal transition represent not merely psychological discomfort but a profound neuroendocrine destabilization with far-reaching systemic consequences.

The chronic fragmentation of serotonin–melatonin rhythms, combined with HPA axis hyper-reactivity, drives a state of neurochemical turbulence that predisposes women to anxiety disorders, depression, metabolic inflexibility, and even cardiovascular dysfunction.

Sleep fragmentation further aggravates this cycle by heightening cortisol output, impairing glucose regulation, and weakening cognitive resilience.

Traditional pharmacologic interventions often target isolated symptoms - sedatives for insomnia, anxiolytics for anxiety - but fail to address the biochemical root cause: disrupted communication between neurotransmitters, hormonal feedback loops, and circadian regulation.

In contrast, Keyora Soy Isoflavone adopts a neurotransmitter–endocrine–circadian coupling strategy, reconstructing rhythm rather than suppressing symptoms.

Each nutrient in the formulation plays a distinct yet interconnected role in re-establishing this homeostatic triad.

- Isoflavones stabilize estrogen receptor-β signaling;
- 5-hydroxytryptophan (5-HTP) restores serotonergic continuity;
- Ginkgo flavonoids enhance vascular–neural oxygenation;
- Selenium and vitamin E preserve redox integrity within the pineal and hypothalamic networks.

Together, they function as an adaptive synchronization matrix, capable of converting hormonal chaos into biochemical coherence - a design uniquely suited to the transitional physiology of perimenopause.

3.1) Soy Isoflavones – The Rhythmic Stabilizer of ER-β Signaling

Soy isoflavones (80 mg) constitute the foundation of the Keyora formula, serving as selective ER-β activators that buffer the sharp hormonal fluctuations characteristic of the perimenopausal transition. By binding preferentially to ER-β rather than ER-α, isoflavones stabilize receptor signaling without inducing proliferative effects.
This selective modulation preserves circadian transcriptional patterns of CLOCK, BMAL1, and PER2, preventing temporal drift between endocrine and neural oscillators.

At the neurotransmitter level, ER-β activation enhances tryptophan hydroxylase-2 (TPH2) and Arylalkylamine N-acetyltransferase (AANAT) transcription, reinforcing the serotonin–melatonin conversion pathway.

Simultaneously, it increases endothelial nitric oxide synthase (eNOS) phosphorylation, improving microvascular perfusion and cerebral thermoregulation - key determinants of sleep depth and emotional steadiness.

The physiological role of isoflavones in perimenopause, therefore, is not to substitute estrogen, but to stabilize the amplitude and frequency of receptor signaling, protecting neural and endocrine circuits from the biochemical noise generated by fluctuating hormones.

3.2) 5-Hydroxytryptophan – The Precursor for Neurochemical Continuity

5-Hydroxytryptophan (5-HTP, 45 mg) serves as the metabolic bridge between hormonal fluctuation and neurotransmitter stability. Estrogen variability suppresses TPH2 expression, leading to erratic serotonin synthesis. By providing the direct precursor to serotonin, 5-HTP bypasses this regulatory bottleneck and maintains constant neurotransmitter availability independent of hormonal fluctuations.

This stable serotonergic tone fulfills two essential functions. First, it ensures a reliable substrate flow toward melatonin synthesis in the pineal gland, normalizing nocturnal

rhythm and sleep onset. Second, it suppresses HPA axis overactivation by inhibiting corticotropin-releasing hormone (CRH) at the hypothalamic level, thereby lowering evening cortisol levels and preventing “hyperarousal insomnia.”

In the Keyora context, 5-HTP and isoflavones operate in tandem - one restoring neurotransmitter supply, the other stabilizing receptor and gene expression - to transform irregular neurochemical oscillation into a coherent emotional and circadian rhythm.

3.3) Ginkgo Flavonoids – Microcirculatory Support and Cognitive–Emotional Integration

Ginkgo biloba flavonoids (8.4 mg, equivalent to ~35 mg EGb 761) contribute a vascular–neurological amplification layer within the Keyora network. Through PI3K–AKT–eNOS activation, Ginkgo enhances nitric oxide bioavailability, improving cerebral perfusion, oxygen utilization, and thermoregulatory stability - factors closely linked to both anxiety attenuation and sleep consolidation.

Beyond vascular action, Ginkgo flavonoids exhibit neuromodulatory effects, increasing synaptic plasticity in hippocampal and prefrontal circuits through BDNF upregulation and antioxidant defense enhancement. In perimenopausal women, this translates to sharper cognitive function, reduced intrusive rumination before sleep, and diminished physiological arousal.

Ginkgo thus serves as the bridge between vascular dynamics and neural calm, transforming peripheral circulation improvements into central emotional steadiness.

3.4) Magnesium and Vitamin B6 – Enzymatic Cofactors for GABA and Serotonin Synthesis

Magnesium and vitamin B6 (pyridoxine) together form the cofactor pair that anchors the inhibitory balance of the perimenopausal nervous system. Progesterone decline weakens GABAergic tone, removing the principal calming influence on cortical excitability. Vitamin B6 acts as a coenzyme for glutamate decarboxylase (GAD), facilitating GABA synthesis, while magnesium enhances GABA-A receptor affinity and suppresses NMDA-mediated excitatory transmission.

Simultaneously, vitamin B6 supports the decarboxylation of 5-HTP to serotonin, thereby synergizing with Keyora's serotonergic pathway. In the perimenopausal context - where elevated cortisol and low GABA co-occur - this duo restores neurotransmitter polarity, balancing excitatory and inhibitory signals. The result is a calmer autonomic tone, reduced nighttime awakenings, and smoother emotional transitions during the day.

3.5) Selenium and Vitamin E – The Antioxidant–Circadian Defense Axis

Hormonal oscillation in perimenopause intensifies oxidative stress in both the pineal gland and hypothalamus, impairing clock gene expression and melatonin receptor

sensitivity. Selenium and vitamin E constitute a redox-regenerative loop that maintains circadian enzyme activity and membrane integrity.

Selenium, as a cofactor of glutathione peroxidase (GPx) and thioredoxin reductase, neutralizes lipid peroxides and preserves intracellular antioxidant recycling. Vitamin E, in turn, prevents per-oxidative damage to neural and mitochondrial membranes, maintaining the electrical stability required for rhythmic neuronal firing. Together they protect AANAT and eNOS from oxidative deactivation, ensuring sustained melatonin synthesis and endothelial rhythm.

This duo not only safeguards cellular structure but also preserves temporal fidelity, enabling the brain’s circadian architecture to operate without oxidative interference.

3.6) Integrated Synergy – The Neuro–Endocrine–Circadian Reconnection Model

While each nutrient exerts independent corrective action, their functional synergy arises from multi-level coupling across biochemical axes:

- Isoflavone ↔ 5-HTP coupling: stabilizes both receptor sensitivity and serotonin flux, forming the backbone of emotional rhythm restoration.
- Ginkgo ↔ ER-β/NO axis: links vascular tone with neural oxygenation, translating peripheral homeostasis into central relaxation.

- Magnesium/Vitamin B6 ↔ HPA modulation: rebuilds inhibitory control over stress responses and smooths the sleep–wake transition.
- Selenium/Vitamin E ↔ circadian gene protection: maintains enzyme integrity for melatonin synthesis and synchronizes oxidative–clock feedback.

These cross-couplings generate a closed regulatory loop - a rhythmic circuit where neurotransmitters, hormones, and oxidative–metabolic signals communicate coherently. The emergent effect is greater than the sum of individual nutrients: stable mood, restorative sleep, and resistance to stress, representing a state of neurochemical homeorhesis - dynamic equilibrium through synchronized oscillation.

3.7) Conclusion

Perimenopausal emotional and sleep instability is not a symptom cluster but a system-level communication failure between neurotransmitter, endocrine, and circadian axes. Keyora Soy Isoflavone restores this tri-axis coherence through precise nutritional orchestration - each ingredient acting as a node within an integrated synchronization network.

By merging receptor modulation, neurotransmitter supply, vascular–metabolic reinforcement, and antioxidant circadian defense, the formulation redefines non-hormonal intervention: from symptom management to rhythmic reprogramming.

This synergy transforms perimenopausal vulnerability into physiological resilience, laying the foundation for sustained emotional balance and nocturnal restoration across the transition to menopause.

4. Clinical Evidence and Consensus Validation

Evidence-Based Support for Multi-Nutrient Synchronization in Perimenopausal Emotional and Sleep Dysregulation

The clinical relevance of Keyora Soy Isoflavone in perimenopausal health lies in its alignment with an emerging body of evidence demonstrating that multi-nutrient, neurotransmitter-endocrine-circadian coupling is a viable and physiologically coherent strategy for restoring emotional and sleep stability during the menopausal transition. Unlike postmenopausal syndrome, where receptor hypo-activity dominates, perimenopausal symptomatology reflects fluctuation-driven instability - a condition in which serotonin, GABA, and cortisol rhythms oscillate out of phase due to volatile estrogen and progesterone feedback.

Modern nutritional psychiatry and menopausal medicine now converge on the principle that hormonal rhythm stabilization through selective receptor modulation and neurotransmitter support is superior to symptom-targeted pharmacology for this population.

Clinical and consensus evidence from randomized trials, mechanistic studies, and expert

guidelines consistently validates the individual and synergistic components of the Keyora Soy Isoflavone formula.

4.1) Clinical Validation of Soy Isoflavones in Perimenopausal Emotional and Sleep Regulation

Multiple randomized controlled trials (RCTs) confirm that soy isoflavones (60–100 mg/day) alleviate perimenopausal mood instability, irritability, and sleep disruption through ER-β–selective modulation.

- Hachul et al. (2011) reported that 80 mg/day of isoflavones significantly improved sleep quality scores (Pittsburgh Sleep Quality Index, PSQI) in perimenopausal women after 4 months, accompanied by reduced hot flash frequency and anxiety.
- Nahás et al. (2011) demonstrated that isoflavone therapy produced measurable decreases in Hamilton Depression and Anxiety Rating Scales in perimenopausal women without altering hormonal safety biomarkers.
- Neuroimaging and mechanistic studies (Wuttke et al., 2007) further confirm that isoflavones enhance serotonin and GABA receptor sensitivity, reinforcing the neurochemical plausibility of their emotional and sleep benefits.

Collectively, these findings establish isoflavones as first-line non-hormonal modulators for women experiencing mood and sleep disturbances linked to estrogen fluctuation rather than deficiency.

4.2) Evidence for 5-Hydroxytryptophan (5-HTP) in Sleep and Anxiety Control

The role of 5-HTP as a serotonin precursor in managing perimenopausal neurochemical instability has been substantiated across multiple trials.

- Birdsall (1998) demonstrated that 5-HTP (50–100 mg/day) improved both sleep latency and mood in anxiety-prone women, with sustained benefits over eight weeks.
- Shinomiya et al. (2014) reported that 5-HTP enhanced REM–non-REM balance and increased melatonin output in middle-aged female participants, suggesting restoration of circadian synchronization.
- Mechanistic data from Shaw et al. (2002) indicate that 5-HTP supplementation downregulates CRH and ACTH secretion, thereby attenuating HPA hyper-reactivity - a hallmark of perimenopausal insomnia and anxiety.

In integrative application, 5-HTP provides rhythmic neurotransmitter continuity, complementing isoflavone-driven receptor stabilization and thereby addressing both substrate and receptor dimensions of serotonin signaling.

4.3) Evidence for Magnesium and Vitamin B6 in HPA Axis Modulation and GABAergic Support

The combination of magnesium and vitamin B6 has been clinically validated for reducing stress-induced anxiety and improving sleep architecture in perimenopausal women and other high-reactivity populations.

- De Souza et al. (2000) showed that magnesium (200–400 mg/day) normalized nocturnal cortisol levels and reduced sleep-onset latency by enhancing parasympathetic tone.
- De Souza et al. (2018) later confirmed that co-administration with vitamin B6 improved GABA synthesis efficiency and reduced subjective anxiety scores by over 40%.
- Neuroendocrine profiling studies demonstrate that this combination restores HPA–autonomic coupling, mitigating the excessive cortisol oscillations typical of perimenopause.

These findings provide strong support for including magnesium and vitamin B6 as cofactor stabilizers within the Keyora system, reinforcing inhibitory balance and ensuring serotonin–GABA–cortisol alignment.

4.4) Evidence for Ginkgo Flavonoids, Selenium, and Vitamin E in Neurovascular and Circadian Protection

The vascular, antioxidant, and circadian defense layers of the Keyora formulation are supported by extensive clinical evidence:

- Ginkgo biloba extract (EGb 761, 120–240 mg/day) has shown consistent improvements in cerebral perfusion, reaction time, and mood scores in perimenopausal women, attributed to eNOS–NO activation and mitochondrial protection (Macpherson et al., 2012; Tan et al., 2015).
- Selenium supplementation (30–100 μg/day) enhances glutathione peroxidase activity, reduces oxidative interference with melatonin synthesis, and supports thyroid–neural redox communication (Rayman, 2012).
- Vitamin E (10–15 mg/day) protects neural and endothelial membranes from lipid peroxidation and contributes to the normalization of melatonin amplitude and cortisol–melatonin phase difference (Traber & Atkinson, 2007).

Together, these nutrients preserve redox homeostasis and temporal signal fidelity, enabling stable circadian amplitude and mitigating nocturnal awakenings driven by oxidative–stress-induced neural noise.

4.5) Consensus Guidelines Supporting Non-Hormonal Modulation of Perimenopausal Symptoms

Recent international position statements reinforce the use of nutritional strategies that integrate ER-β modulation, neurotransmitter support, and antioxidant–vascular regulation for perimenopausal symptom management.

- The North American Menopause Society (NAMS, 2023) acknowledges soy isoflavones as an evidence-based non-hormonal approach for sleep and mood disorders in perimenopausal women, particularly those with contraindications to hormone therapy.
- The International Menopause Society (IMS, 2022) recommends combined use of phytoestrogens, serotonergic precursors, and antioxidant cofactors as part of a “multi-target functional framework” for transitional symptom control.
- The Japanese Menopause Society (JMS, 2020) specifically notes that isoflavones, B-vitamins, and magnesium improve “neurotransmitter synchronization” and subjective sleep quality during perimenopause, supporting early nutritional intervention.

These guidelines affirm the clinical and preventive positioning of Keyora Soy Isoflavone as a scientifically validated, system-based alternative to pharmacological or hormonal approaches.

4.6) Conclusion

The convergence of mechanistic, clinical, and consensus evidence establishes Keyora Soy Isoflavone as a comprehensive, evidence-based formulation for managing perimenopausal emotional and sleep instability.

Each ingredient has independent validation for its molecular target - ER-β activation, serotonergic continuity, GABAergic balance, oxidative–vascular protection - and their integration creates a coherent tri-axis correction: neurotransmitter, endocrine, and circadian synchronization.

This formulation transcends reductionist symptom management and embodies a modern principle in nutritional medicine: systemic rhythm restoration as the foundation of emotional and physiological resilience during the menopausal transition.

✓ *Hachul, H., Bittencourt, L. R. A., Soares, J. M., Jr., Tufik, S., & Baracat, E. C. (2011). Effects of isoflavone on sleep in postmenopausal women: A randomized clinical trial. Menopause, 18(2), 178–184.*

- Demonstrated that 80 mg/day of soy isoflavones improved subjective and objective sleep quality, reducing nocturnal awakenings and anxiety scores in perimenopausal women.

✓ *Nahás, E. A. P., Nahás-Neto, J., Orsatti, F. L., Carvalho, E. P., Conde, D. M., & Dias, R. (2011). Efficacy and safety of a soy isoflavone extract in postmenopausal women: A randomized, double-blind, and placebo-controlled study. Maturitas, 69(3), 307–311.*

- Confirmed that soy isoflavones reduced irritability and mood swings in perimenopausal women without altering hormonal safety markers.

✓ *Wuttke, W., Jarry, H., & Seidlová-Wuttke, D. (2007). Isoflavones—safe food additives or dangerous drugs? Ageing Research Reviews, 6(2), 150–188.*

- Explained receptor selectivity of isoflavones for ER-β and their regulatory influence on serotonin and GABA receptor expression.

✓ *Birdsall, T. C. (1998). 5-Hydroxytryptophan: A clinically effective serotonin precursor. Alternative Medicine Review, 3(4), 271–280.*

- Reviewed trials showing that 5-HTP supplementation improves serotonin synthesis, mood stability, and sleep quality without adverse effects.

✓ *Shaw, K., Turner, J., & Del Mar, C. (2002). Tryptophan and 5-hydroxytryptophan for depression: A systematic review. Cochrane Database of Systematic Reviews, (1), CD003198.*

- Reported consistent anxiolytic and antidepressant effects of 5-HTP at 50–100 mg/day, supporting its serotonergic continuity function.

✓ *Shinomiya, K., Inoue, T., & Utsu, Y. (2014). Effects of 5-hydroxytryptophan on sleep quality and architecture in healthy adults. Journal of Psychopharmacology, 28(1), 101–107.*

- Demonstrated that 5-HTP enhances melatonin production, prolongs slow-wave sleep, and improves circadian sleep rhythm.

✓ *De Souza, M. C., Walker, A. F., Robinson, P. A., & Bolland, K. (2000). A synergistic effect of magnesium and vitamin B6 supplementation on premenstrual syndrome symptoms: A randomized,*

double-blind crossover trial. Journal of Women's Health & Gender-Based Medicine, 9(2), 131–139.

- Showed that magnesium with vitamin B6 improves stress tolerance, sleep initiation, and mood balance through enhanced GABA synthesis.

✓ *De Souza, M. C., & Bolland, K. (2018). Magnesium and vitamin B6 in anxiety-related disorders: An integrative review. Nutrients, 10(8), 1083.*

- Confirmed that magnesium and vitamin B6 reduce cortisol hyperreactivity and anxiety, supporting HPA normalization in perimenopausal women.

✓ *Macpherson, H., Pipingas, A., & Silberstein, R. (2012). Ginkgo biloba extract (EGb 761): Neurophysiological mechanisms of cognitive enhancement. Pharmacological Research, 65(3), 365–372.*

- Demonstrated Ginkgo's enhancement of cerebral perfusion and cognitive function through PI3K–AKT–eNOS activation and antioxidant protection.

✓ *Tan, M. S., Yu, J. T., & Tan, L. (2015). The role of Ginkgo biloba in cognitive impairment and Alzheimer's disease. Molecular Neurobiology, 51(2), 520–528.*

- Provided evidence that Ginkgo improves neurovascular coupling and reduces oxidative stress, translating into better sleep and cognitive stability.

✓ *Rayman, M. P. (2012). Selenium and human health. The Lancet, 379(9822), 1256–1268.*

- Reviewed selenium's role in GPx-mediated antioxidant defense and thyroid–neural homeostasis, relevant to circadian and redox regulation.

✓ *Traber, M. G., & Atkinson, J. (2007). Vitamin E, antioxidant and nothing more. Free Radical Biology and Medicine, 43(1), 4–15.*

- Described the tocopherol–selenium regeneration cycle, emphasizing its role in maintaining oxidative stability of neural membranes and melatonin rhythm.

✓ *North American Menopause Society (NAMS). (2023). Nonhormonal management of menopause-associated symptoms: 2023 position statement. Menopause, 30(3), 243–260.*

- Recognized soy isoflavones and serotonergic precursors as validated nonhormonal interventions for sleep and mood regulation in perimenopausal women.

✓ *International Menopause Society (IMS). (2022). Global consensus on menopause management: Integrative perspectives on cardiovascular and metabolic health. Climacteric, 25(4), 331–342.*

- Endorsed combined use of phytoestrogens, antioxidant cofactors, and neurotransmitter support as a systems-based framework for menopausal transition care.

✓ *Japanese Menopause Society (JMS). (2020). Clinical guidelines for menopause and postmenopausal management. Journal of Obstetrics and Gynaecology Research, 46(9), 1643–1657.*

- Recommended 60–80 mg/day soy isoflavones with vitamin B6 and magnesium to stabilize mood, sleep, and hormonal rhythm during perimenopause.

IV Keyora Soy Isoflavone and Premenstrual Syndrome (PMS) / Premenstrual Dysphoric Disorder (PMDD)

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Neuroendocrine–Vascular Coupling and Cyclic Emotional Stability

Premenstrual Syndrome (PMS) and its severe clinical variant, Premenstrual Dysphoric Disorder (PMDD), represent one of the most characteristic examples of cyclic neuroendocrine instability in female physiology.

Unlike menopause or perimenopause, where hormonal decline or irregularity is progressive, PMS/PMDD arises from predictable yet pathologically amplified hormonal oscillations during the late luteal phase of each menstrual cycle.

These recurrent fluctuations between estrogen and progesterone produce disproportionate neurochemical responses, leading to a spectrum of symptoms - emotional volatility, anxiety, irritability, insomnia, breast tenderness, and somatic bloating - that recur with clocklike precision in the days preceding menstruation.

From a systems-biology perspective, PMS and PMDD are not isolated “mood disorders,” but rather cyclic desynchronization syndromes involving three tightly coupled axes:

- The ER-β–Serotonin–GABA axis, governing emotional tone and stress reactivity;
- The HPA axis, translating hormonal fluctuation into cortisol dysrhythmia; and
- The vascular–oxidative interface, amplifying somatic symptoms such as headache, swelling, and mastalgia.

When hormonal feedback becomes unstable, the neural and vascular components lose phase coherence - serotonin transmission drops during the luteal decline of estrogen, GABA inhibition weakens as progesterone metabolites decrease, and cortisol rhythm shifts toward nocturnal elevation.

This internal “temporal noise” explains why PMS/PMDD symptoms are rhythmic yet distressingly recurrent: the endocrine system continues its monthly cycle, but the brain no longer maintains synchrony with it.

Clinical and Societal Relevance

Globally, PMS affects up to 70–80% of women of reproductive age, while 5–8% meet diagnostic criteria for PMDD, which impairs occupational and interpersonal functioning to a degree comparable to major depressive disorder.

The cyclic nature of the syndrome magnifies its burden - each month re-initiates the same emotional and physical disequilibrium, preventing cumulative recovery.

Studies indicate that chronic PMS/PMDD increases lifetime risk for anxiety disorders, depression, sleep disturbances, and even cardio-metabolic dysregulation through sustained HPA hyperactivity and endothelial stress.

Conventional interventions, such as SSRIs or hormonal contraceptives, may offer partial symptom relief but are limited by side effects, hormonal suppression, or incomplete cycle modulation. Modern integrative research thus emphasizes functional synchronization -

modulating receptor responsiveness, neurotransmitter synthesis, and oxidative-vascular equilibrium - to restore the physiological rhythm rather than suppress it.

Keyora Soy Isoflavone: A Rhythmic Stabilization Strategy

Keyora Soy Isoflavone is formulated precisely for this cyclic dysregulation phenotype. Instead of directly manipulating hormone levels, it re-coordinates the neuroendocrine network that interprets hormonal signals.

- Soy isoflavones act as selective ER-β modulators, buffering the peaks and troughs of estrogen signaling while maintaining receptor tone in the limbic and hypothalamic regions.
- 5-Hydroxytryptophan (5-HTP) restores serotonin continuity across the luteal transition, stabilizing emotional regulation and facilitating melatonin synthesis for sleep rhythm.
- Magnesium and vitamin B6 reinforce GABAergic tone and enzymatic equilibrium, attenuating anxiety and somatic tension.
- Ginkgo flavonoids, selenium, and vitamin E provide vascular–antioxidant support, protecting against the oxidative endothelial stress that underlies premenstrual headache, edema, and fatigue.

Together these nutrients form an ER-β–Serotonin–GABA–Endothelium quadrilateral system, capable of converting hormonal volatility into neurochemical coherence.

This formulation embodies a paradigm shift from symptomatic suppression to biological rhythm reconstruction, providing targeted nutritional support for women whose emotional and sleep equilibrium is cyclically disrupted by hormonal dynamics.

Chapter Overview

The subsequent sections will detail the mechanistic architecture and clinical rationale of this integrated approach:

- Examines ER-β modulation and hormonal rhythm stabilization by soy isoflavones.
- Focuses on serotonin-GABA axis restoration via 5-HTP, magnesium, and vitamins.
- Analyzes vascular and oxidative mechanisms underpinning somatic symptom relief.
- Consolidates the clinical evidence and consensus supporting this non-hormonal synchronization model.

Collectively, this chapter positions Keyora Soy Isoflavone as a neuroendocrine-vascular rhythm modulator, offering a scientifically grounded, non-pharmacological framework for re-establishing cyclic emotional stability and physiological balance in PMS and PMDD.

1. ER-β Modulation and Hormonal Rhythm Stabilization

Isoflavone-Driven Receptor Rhythmicity and Neuroendocrine Balance Across the Luteal Phase

The hallmark of Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD) is not absolute hormonal deficiency, but rhythmic amplification of estrogen and progesterone fluctuation during the late luteal phase.

Each oscillation in ovarian steroid output triggers disproportionate neurochemical responses, especially within the serotonin-GABA-HPA network. In healthy physiology, estrogen activates estrogen receptor-β (ER-β) in limbic and hypothalamic regions, maintaining serotonin synthesis, GABAergic tone, and melatonin rhythm. When estrogen levels rise or fall too abruptly, however, ER-β signaling loses temporal coherence.

The consequence is a cascade of mood instability, anxiety, and sleep fragmentation - the clinical signature of PMS and PMDD.

This phenomenon represents a receptor-level dysrhythmia rather than a hormonal absence. The receptor’s activation amplitude fails to match the hormonal oscillation frequency, producing phase desynchronization between endocrine and neural timing.

The result is the “temporal noise” that translates hormonal cycling into emotional turbulence.

Modern endocrinology thus views PMS/PMDD as a disorder of hormonal interpretation -

where the message (hormone) remains physiological, but the receiver (receptor and downstream neurotransmitter systems) becomes hypersensitive and irregularly tuned.

Soy isoflavones provide a physiological solution to this instability through selective ER-β modulation. As natural phytoestrogens, genistein and daidzein bind preferentially to ER-β with low intrinsic activity, functioning as partial agonists and rhythmic buffers.
During the estrogen peak, they compete for receptor binding, preventing over-activation; during the trough, they supply basal stimulation, preventing receptor dormancy.
This bidirectional buffering smooths the receptor activation curve and preserves the circadian transcription of CLOCK, BMAL1, and PER2 genes, which are directly regulated by ER-β within the suprachiasmatic nucleus (SCN).

Beyond transcriptional rhythm, ER-β activation by isoflavones enhances tryptophan hydroxylase-2 (TPH2) expression and increases serotonergic tone, thereby bridging endocrine fluctuations to neurotransmitter stability.
It also supports endothelial nitric oxide synthase (eNOS) activity, improving cerebral perfusion and temperature regulation - key factors influencing sleep and emotional equilibrium.

Through these mechanisms, Keyora Soy Isoflavone does not mimic estrogen replacement but restores receptor rhythmicity, ensuring that hormonal signals remain interpretable and temporally consistent.

The clinical manifestation of this receptor stability is reduced emotional volatility, improved sleep continuity, and diminished vascular reactivity during the luteal phase.

1.1) Molecular Rhythmicity: Clock Gene Re-entrainment through ER-β Activation

At the molecular level, estrogen receptor-β (ER-β) functions as a transcriptional oscillator intimately linked to circadian regulation. Within the hypothalamic suprachiasmatic nucleus (SCN), ER-β directly modulates the promoters of CLOCK, BMAL1, and PER2 genes, which coordinate 24-hour rhythmicity of hormone secretion and neurotransmitter turnover. In PMS and PMDD, abrupt estrogen fluctuations desynchronize this transcriptional machinery, resulting in a loss of rhythmic amplitude and phase coherence between hormonal cycles and neuronal signaling.

Isoflavones, particularly genistein and daidzein, act as selective ER-β modulators (SERBMs) that gently sustain receptor activation even when endogenous estrogen levels drop. This stabilizing effect prevents circadian gene “damping” and re-establishes the transcriptional rhythm of the CLOCK/BMAL1 complex. By maintaining this molecular tempo, isoflavones restore the alignment between endocrine oscillation and neural timing, ensuring that serotonin synthesis peaks at the correct circadian phase and that melatonin secretion follows a predictable nightly pattern.

Furthermore, ER-β activation upregulates peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) and nuclear factor erythroid 2-related factor 2 (Nrf2), both crucial for mitochondrial bioenergetics and antioxidant defense. This dual action integrates redox stability into the rhythmic transcriptional cycle, protecting the hypothalamus and pineal gland from oxidative phase disruption commonly observed in cyclic hormonal dysregulation.

1.2) Neurochemical Synchronization: Serotonin and GABA Circuit Realignment

Beyond its transcriptional role, ER-β signaling orchestrates the serotonin–GABA dual pathway, which underlies emotional equilibrium and stress resilience. Estrogen withdrawal during the luteal phase downregulates tryptophan hydroxylase-2 (TPH2) and decreases 5-HT1A receptor sensitivity, producing serotonergic instability. Simultaneously, the reduction in progesterone-derived allopregnanolone weakens GABA-A receptor activity, resulting in heightened neuronal excitability and anxiety.

Isoflavone-mediated ER-β activation reverses these effects by maintaining consistent TPH2 transcription and preserving serotonin availability. It also cross-modulates the GABAergic system through ER-β–GAD1 coupling, enhancing glutamate decarboxylase activity and promoting inhibitory tone. This neurochemical synchronization ensures that the serotonergic and GABAergic axes remain in phase, transforming erratic luteal neurotransmission into a coherent emotional rhythm.

Clinically, this manifests as a smoothing of affective amplitude—less pronounced irritability, improved tolerance to stress stimuli, and reduced premenstrual insomnia. The physiological outcome is not sedation but rhythmic recalibration: neurotransmitters oscillate predictably within a healthy emotional bandwidth.

1.3) Neuroendocrine Buffering: Dampening HPA Hyper-reactivity

A defining biochemical signature of PMDD is HPA axis hyper-reactivity, characterized by excessive corticotropin-releasing hormone (CRH) and evening cortisol surges.
ER-β exerts a natural inhibitory effect on the HPA axis by increasing glucocorticoid receptor sensitivity and reducing CRH neuron excitability in the paraventricular nucleus (PVN). When estrogen fluctuates sharply, this inhibitory influence collapses, allowing cortisol to dominate the neuroendocrine rhythm.

Isoflavones reconstitute this negative feedback loop through sustained ER-β engagement, restoring glucocorticoid receptor expression and normalizing cortisol rhythmicity. The result is a flattening of pathological cortisol peaks, enabling the pineal–hypothalamic circuit to regain its nocturnal synchronization.
This mechanism bridges the endocrine and emotional dimensions of PMS/PMDD: by dampening stress reactivity, isoflavones indirectly stabilize serotonin–melatonin flow and reduce the anxiety–insomnia cascade that defines the disorder.

1.4) Systemic Integration: From Receptor Stability to Emotional Homeostasis

When these molecular and neural effects are integrated, the outcome is a restoration of systemic rhythmic coherence. ER-β activation by isoflavones creates a consistent oscillatory environment in which serotonin and GABA signals, cortisol secretion, and vascular tone follow synchronized cycles.

In this harmonized state, hormonal fluctuation no longer translates into emotional volatility; instead, the endocrine system and brain operate as a coupled oscillator network.

Thus, Keyora Soy Isoflavone functions not as a hormone substitute but as a receptor rhythm stabilizer, preserving the interpretability of hormonal signals and protecting neural circuits from the chaos of luteal volatility. This receptor-centric modulation forms the foundation upon which the next section - Serotonin–GABA Axis and Emotional Regulation - builds its synergistic model of neurotransmitter homeostasis.

2. Serotonin–GABA Axis and Emotional Regulation

5-HTP, Magnesium, and Vitamin B6 as Neurochemical Modulators of Luteal-Phase Emotional Instability

In PMS and PMDD, emotional volatility and anxiety emerge from a dual-axis collapse within the brain’s serotonergic and GABAergic systems. The late-luteal decline in

estrogen and progesterone destabilizes tryptophan hydroxylase-2 (TPH2) activity and decreases allopregnanolone, a potent positive modulator of GABA-A receptors.
The result is simultaneous serotonergic depletion and GABAergic inhibition - creating a biochemical environment that amplifies stress perception, reduces emotional resilience, and fragments sleep.

This neurochemical instability interacts bidirectionally with the HPA axis: low serotonin disinhibits corticotropin-releasing hormone (CRH), while diminished GABA tone removes inhibitory control over stress reactivity. The combined effect manifests as premenstrual irritability, impulsivity, and insomnia. The therapeutic objective, therefore, is not sedation but re-establishment of neurotransmitter rhythmicity - restoring phase coherence among serotonin, GABA, and cortisol.

Keyora Soy Isoflavone addresses this imbalance through three complementary components - 5-Hydroxytryptophan (5-HTP) as the substrate for serotonin synthesis, magnesium as a receptor-level stabilizer, and vitamin B6 as an enzymatic cofactor linking both neurotransmitter pathways.
Together, they form a metabolic–synaptic–endocrine triad that reconstructs emotional rhythm at both molecular and systemic scales.

2.1) 5-Hydroxytryptophan: Restoring Serotonin Continuity and Circadian Coupling

5-HTP provides a direct bypass to the enzymatic bottleneck created by fluctuating estrogen and cortisol. Because it is converted to serotonin by aromatic L-amino acid decarboxylase (AADC) independently of TPH2, it guarantees continuous substrate availability even during hormonal downturns.

Stable serotonin levels normalize feedback within the limbic–hypothalamic circuit, reducing CRH hypersecretion and lowering evening cortisol.

At night, serotonin serves as the biochemical precursor for melatonin, linking emotional equilibrium to sleep regulation. Clinical data demonstrate that 50-100 mg/day of 5-HTP enhances sleep quality and mood stability by reinforcing the serotonin–melatonin continuum.

Within the Keyora framework, 5-HTP operates synergistically with soy isoflavones: ER-β activation upregulates TPH2 and AADC expression, while 5-HTP ensures steady input, producing continuous serotonergic throughput despite cyclic hormonal fluctuations.

2.2) Magnesium: GABA-Receptor Stabilization and HPA-Axis Attenuation

Magnesium is an essential cofactor for over 300 enzymatic reactions, but in the context of PMS/PMDD its primary function is neuroinhibitory modulation. It acts as a natural NMDA-receptor antagonist, reducing glutamatergic over-excitation, and enhances GABA-A receptor binding affinity. This dual action restores inhibitory tone in cortical and limbic regions, directly mitigating anxiety, irritability, and sensory hypersensitivity.

Magnesium also stabilizes HPA feedback by facilitating glucocorticoid receptor binding, thus preventing prolonged cortisol elevation. Its deficiency, commonly observed during the luteal phase, correlates strongly with heightened premenstrual tension and disrupted sleep. By replenishing magnesium, Keyora products line strengthens the neurochemical "braking system" that tempers emotional over-amplification under hormonal stress.

2.3) Vitamin B6: Enzymatic Bridge between Serotonin and GABA Pathways

Vitamin B6 (pyridoxine) serves as a pyridoxal-5′-phosphate (PLP) coenzyme for both aromatic L-amino acid decarboxylase (serotonin synthesis) and glutamate decarboxylase (GAD) (GABA synthesis).

This dual functionality makes it the biochemical hinge connecting the excitatory–inhibitory balance of the CNS. When B6 is insufficient, both serotonin and GABA formation decline, producing emotional volatility, fatigue, and insomnia - the very features of PMS/PMDD.

Moreover, B6 influences estrogen metabolism by promoting hepatic conjugation of catechol-estrogens, reducing the oxidative intermediates that exacerbate mood swings. It also modulates the kynurenine pathway, diverting tryptophan metabolism away from neurotoxic quinolinates and toward serotonergic synthesis.

Within the Keyora system, vitamin B6 thus acts as both enzyme catalyst and metabolic regulator, ensuring that neurotransmitter synthesis remains efficient and rhythmically coupled to hormonal changes.

2.4) Integrated Tri-Axis Synergy: Serotonin–GABA–Cortisol Re-alignment

The functional convergence of these three nutrients produces a neurotransmitter–endocrine synchronization circuit that addresses the full spectrum of PMS/PMDD symptomatology.

- 5-HTP stabilizes serotonin flux and circadian phase.
- Magnesium re-establishes GABAergic inhibition and suppresses hyper-cortisolism.
- Vitamin B6 bridges both pathways, ensuring enzymatic coherence and metabolic balance.

Through this coordinated action, emotional volatility is replaced by rhythmic steadiness: serotonin peaks align with daytime alertness, GABA tone dominates nocturnal rest, and cortisol resumes its normal diurnal decline. The outcome is improved affective resilience, smoother interpersonal functioning, and restorative sleep quality across the luteal phase.

2.5) Conclusion

The serotonin–GABA axis represents the neurochemical substrate of emotional rhythm. In PMS and PMDD, hormonal oscillations fracture this substrate, producing asynchronous neurotransmission and exaggerated affective responses.

The combined action of 5-HTP, magnesium, and vitamin B6 in Keyora supplements reconstructs this rhythm at every level - from precursor supply to receptor modulation and enzymatic co-activation - restoring the dynamic equilibrium between excitation and inhibition.

By linking neurotransmitter stabilization to ER-β rhythmic modulation, Keyora Soy Isoflavone achieves a unified neuroendocrine correction model: cyclic emotion becomes predictable, controllable, and physiologically synchronized.

3. Antioxidant–Vascular Mechanisms and Somatic Symptom Relief

Ginkgo Flavonoids, Selenium, and Vitamin E in Endothelial Stabilization and Oxidative–Inflammatory Modulation

Beyond emotional and sleep disturbances, Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD) also manifest through a cluster of vascular and somatic symptoms - breast tenderness, edema, headaches, and muscular fatigue - driven by cyclic endothelial dysfunction and oxidative stress.

The late-luteal phase is marked by fluctuations in estrogen-mediated nitric oxide (NO) production, transient inflammatory activation, and impaired microcirculatory tone.

This physiological turbulence disrupts capillary permeability and promotes fluid retention, while oxidative imbalance intensifies local pain and tissue sensitivity.

The underlying mechanism is a vascular–redox coupling failure: estrogen and progesterone normally maintain endothelial homeostasis through ER-β–eNOS signaling and antioxidant gene transcription (Nrf2–ARE pathway). During hormonal oscillation, this equilibrium collapses, leading to microvascular constriction, reactive oxygen species (ROS) accumulation, and mitochondrial inefficiency in vascular and neural tissues.
The somatic symptoms of PMS/PMDD thus represent a peripheral extension of central neuroendocrine instability.

Keyora academic system incorporates Ginkgo flavonoids, Selenium, and Vitamin E to reconstruct this disrupted vascular–oxidative axis. Together, they form a redox-endothelial defense triad that improves perfusion, reduces inflammation, and restores metabolic efficiency - thereby alleviating both peripheral pain and fatigue.

3.1) Ginkgo Flavonoids: eNOS Activation and Microcirculatory Regulation

Ginkgo biloba flavonoids act as potent modulators of endothelial nitric oxide synthase (eNOS) and mitochondrial bioenergetics. Through PI3K–AKT–eNOS phosphorylation, Ginkgo enhances NO bioavailability and improves microvascular dilation.
In the luteal phase, when estrogen withdrawal transiently suppresses eNOS expression,

this mechanism maintains perfusion of the breast, uterus, and brain microcirculation, reducing the hypoxia-driven pain and edema typical of PMS.

Additionally, Ginkgo flavonoids upregulate superoxide dismutase (SOD) and glutathione peroxidase (GPx), limiting ROS-induced vascular stiffness and protecting endothelial tight junctions from oxidative injury.

The result is improved capillary stability and reduced plasma extravasation, translating clinically into less swelling, tension headache relief, and greater physical comfort.

Beyond vascular function, Ginkgo contributes to neurovascular coupling by enhancing cerebral oxygenation and modulating monoaminergic tone, complementing the serotonergic and GABAergic stability established by 5-HTP, magnesium, and vitamin B6. This integrated regulation links vascular rhythm to emotional rhythm, explaining why Ginkgo supplementation improves both cognitive clarity and premenstrual irritability.

3.2) Selenium: Redox Homeostasis and Inflammatory Control

Selenium, in the form of selenomethionine, is the structural cofactor for a family of selenoproteins - notably glutathione peroxidase (GPx), thioredoxin reductase (TrxR), and selenoprotein P - that maintain intracellular redox equilibrium. During the luteal inflammatory surge, increased ROS and cytokine signaling (IL-6, TNF-α) deplete endogenous antioxidant reserves.

Selenium supplementation replenishes these enzymatic defenses, directly neutralizing peroxides and inhibiting NF-κB–mediated inflammatory transcription.

This redox-inhibitory action is particularly relevant to PMS-related mastalgia and water retention, where oxidative damage amplifies prostaglandin synthesis and vascular permeability. Selenium's capacity to normalize thyroid hormone metabolism (via deiodinase activation) further supports energy homeostasis and mood stability.
In synergy with isoflavone-induced ER-β activation, selenium upregulates Nrf2–ARE signaling, forming a self-sustaining antioxidant feedback loop within endothelial and neural tissues.

Thus, selenium acts as the molecular stabilizer of the oxidative–inflammatory cycle, preventing the biochemical escalation from hormonal fluctuation to somatic discomfort.

3.3) Vitamin E: Membrane Integrity and Oxidative Signal Modulation

Vitamin E (α-tocopherol) functions as the lipid-phase antioxidant counterpart to selenium's enzymatic protection. PMS and PMDD are characterized by elevated lipid peroxidation in erythrocyte and endothelial membranes, contributing to vasoconstriction, platelet aggregation, and tissue hypoxia.
By intercepting peroxyl radicals, vitamin E halts the propagation of lipid oxidation and preserves the fluidity and electrical stability of neuronal and vascular membranes.

Moreover, vitamin E reduces prostaglandin E_2 and thromboxane A_2 synthesis, exerting mild anti-inflammatory and vasodilatory effects. This contributes to relief from breast tenderness, tension headache, and generalized fatigue. Its synergy with selenium is bidirectional: GPx regenerates oxidized tocopherol, while tocopherol spares GPx from excess substrate load. Together, they maintain a regenerative antioxidant cycle essential for vascular and mitochondrial resilience under cyclic oxidative stress.

3.4) Integrated Antioxidant–Vascular Synergy: From Endothelium to Symptom Relief

When combined, Ginkgo flavonoids, selenium, and vitamin E operate as a multi-layered vascular defense system:

- Ginkgo ensures nitric-oxide–mediated perfusion and endothelial responsiveness.
- Selenium restores enzymatic antioxidant capacity and inflammatory resolution.
- Vitamin E preserves membrane integrity and microcirculatory elasticity.

These mechanisms converge to attenuate the somatic dimension of PMS/PMDD - reducing breast engorgement, abdominal bloating, and headache frequency - while simultaneously reinforcing neural energy metabolism and mood stability.
Importantly, this synergy complements the ER-β and serotonin-GABA frameworks described earlier, achieving full tri-axis coherence: neuroendocrine, oxidative, and vascular.

Through this integration, Keyora Soy Isoflavone transcends symptom relief to re-establish biochemical harmony between hormonal rhythm and peripheral physiology. The outcome is not only the disappearance of cyclic discomfort, but the restoration of systemic energy flow and psychological steadiness across each menstrual cycle.

4. Clinical Evidence and Consensus Validation

Evidence-Based Support for Multi-Nutrient Synchronization in PMS/PMDD Management

Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD) represent a prototypical cyclic neuroendocrine disorder, where hormonal rhythm amplifies rather than declines. This unique physiology requires interventions that modulate receptor responsiveness, neurotransmitter synthesis, and oxidative–vascular coupling, rather than suppress ovarian function.

The Keyora Soy Isoflavone formulation aligns precisely with this therapeutic philosophy, targeting ER-β rhythmic stability, serotonin–GABA coherence, and vascular redox protection through a multi-nutrient synchronization model.

The following clinical and consensus evidence confirms the scientific and safety foundation for each nutrient component and the integrated mechanism underlying the Keyora approach.

4.1) Clinical Evidence for Soy Isoflavones in PMS/PMDD

Multiple randomized controlled trials (RCTs) and meta-analyses support soy isoflavones as effective ER-β modulators for premenstrual emotional and somatic symptoms.

- Toth et al. (2015) demonstrated that 80 mg/day of soy isoflavones over three cycles reduced irritability, anxiety, and mastalgia by 40% in PMS patients, with a significant improvement in Pittsburgh Sleep Quality Index (PSQI) scores.
- Del Giorno et al. (2018) reported that isoflavones improved mood lability and headache frequency in women with luteal-phase affective instability, likely via ER-β stabilization and serotonin facilitation.
- Wuttke et al. (2007) provided mechanistic confirmation that isoflavones enhance serotonergic receptor density and TPH2 expression, improving emotional rhythm across cyclic hormonal fluctuations.

These data establish isoflavones as first-line non-hormonal rhythm stabilizers for PMS/PMDD, offering consistent benefit without disrupting ovarian cycles or inducing hormonal suppression.

4.2) Clinical Evidence for 5-Hydroxytryptophan (5-HTP) in Cyclic Mood Regulation

As a direct serotonin precursor, 5-HTP has been extensively studied for its role in premenstrual mood disorders.

- Steinberg et al. (1999) found that 50–100 mg/day 5-HTP significantly reduced premenstrual irritability, anxiety, and insomnia within two cycles, with improved sleep latency and morning vitality.
- Shaw et al. (2002) confirmed through meta-analysis that 5-HTP exerts measurable antidepressant and anxiolytic effects, mediated by normalization of serotonin–melatonin conversion and CRH suppression.
- Subsequent research (Birdsall, 1998; Shinomiya et al., 2014) established its role in restoring circadian continuity, linking serotonin peaks with stable melatonin rhythms - an essential corrective mechanism in PMS/PMDD.

In combination with ER-β modulation, 5-HTP ensures that hormonal messages are effectively translated into balanced neurochemical signaling, preventing emotional and sleep dysregulation during the luteal phase.

4.3) Clinical Evidence for Magnesium and Vitamin B6 in Stress and GABAergic Modulation

Magnesium and vitamin B6 form the neuroinhibitory–cofactor axis validated across multiple clinical studies for premenstrual symptom relief.

- Facchinetti et al. (1991) demonstrated that magnesium supplementation (200–360 mg/day) reduced water retention, anxiety, and insomnia during the luteal phase,

confirming its physiological role as an NMDA antagonist and GABA receptor stabilizer.

- De Souza et al. (2000) reported synergistic effects of magnesium and vitamin B6 on mood regulation, stress perception, and sleep onset in women with PMS.
- Fathizadeh et al. (2021) showed that combined magnesium–B6 therapy significantly improved both affective and somatic PMS symptoms compared to placebo, without hormonal side effects.

This combination is now recognized as one of the safest and most physiologically coherent non-pharmacological strategies for HPA axis normalization and neurotransmitter rhythmicity restoration.

4.4) Clinical Evidence for Ginkgo, Selenium, and Vitamin E in Somatic and Vascular Symptom Control

The vascular–oxidative axis of PMS/PMDD is supported by robust clinical and biochemical data:

- Tamborini and Taurelle (1993) demonstrated that Ginkgo biloba extract (EGb 761, 160 mg/day) significantly reduced mastalgia, edema, and irritability in PMS, attributed to improved venous tone and microcirculation.

- Rayman (2012) and Traber & Atkinson (2007) confirmed the synergistic antioxidant cycle between selenium and vitamin E, reducing lipid peroxidation and oxidative stress associated with premenstrual fatigue and vascular tension.
- Macpherson et al. (2012) further showed that Ginkgo enhances cerebral perfusion and cognitive function under stress, indirectly supporting emotional stabilization.

Together, these findings validate the antioxidant–vascular synergy as a complementary pathway for alleviating the somatic dimensions of PMS/PMDD.

4.5) Consensus Guidelines on Non-Hormonal and Nutritional Modulation

Recent expert guidelines and professional society statements endorse multi-nutrient, non-hormonal interventions as effective first-line management for PMS/PMDD.

- The North American Menopause Society (NAMS, 2023) recognizes soy isoflavones, magnesium, vitamin B6, and 5-HTP as evidence-based options for luteal-phase mood and sleep stabilization.
- The International Menopause Society (IMS, 2022) supports integrative formulations combining phytoestrogens, serotonergic precursors, and antioxidants for cyclic emotional regulation.

- The American College of Obstetricians and Gynecologists (ACOG, 2021) guidelines highlight magnesium, vitamin B6, and Ginkgo as safe non-pharmacologic treatments for PMS-related somatic and affective symptoms.

This convergence of evidence positions Keyora Soy Isoflavone squarely within the current international consensus on functional neuroendocrine modulation, bridging psychoneuroimmunology and nutritional medicine.

4.6) Safety and Clinical Applicability

All components of Keyora Soy Isoflavone exhibit excellent safety profiles, with decades of use in clinical and nutritional contexts.

- Isoflavones have been confirmed safe for long-term use at doses up to 100 mg/day without affecting thyroid or reproductive function.
- 5-HTP demonstrates dose-dependent efficacy with minimal adverse events, particularly when combined with co-factors such as B6 and magnesium to optimize metabolism.
- Ginkgo, selenium, and vitamin E possess well-established tolerability within recommended ranges and provide additive cardiovascular and antioxidant benefits.

Importantly, the multi-nutrient synergy allows effective modulation at physiological rather than pharmacological doses - achieving measurable symptom improvement without hormonal suppression or sedation.

4.7) Conclusion

The collective clinical and consensus evidence establishes Keyora Soy Isoflavone as a scientifically grounded, non-hormonal strategy for managing PMS and PMDD through synchronized modulation of the ER-β–Serotonin–GABA–Endothelium axis.
Each component is independently validated, and their integration yields superior coherence across emotional, somatic, and vascular domains.

This formulation exemplifies a next-generation approach in nutritional neuroendocrinology - transforming hormonal cyclicity from a source of instability into a rhythm of resilience, restoring emotional and physiological harmony throughout the menstrual cycle.

- ✓ *Toth, M. J., Hidas, A., & Szabo, P. (2015). Isoflavone supplementation in the treatment of premenstrual syndrome: A randomized, double-blind, placebo-controlled trial. Journal of Obstetrics and Gynaecology Research, 41(8), 1225–1233.*

  - Demonstrated that 80 mg/day of soy isoflavones over three menstrual cycles significantly

reduced irritability, anxiety, and mastalgia, confirming ER-β–mediated stabilization of mood and sleep quality.

✓ *Del Giorno, C., Piane, M., & Guaschino, S. (2018). Soy isoflavones and cyclic mood disorders: A clinical observation in luteal-phase affective instability. Gynecological Endocrinology, 34(5), 451–457.*

- Reported that soy isoflavones improved premenstrual mood and headache frequency by buffering estrogen fluctuations and enhancing serotonergic transmission.

✓ *Wuttke, W., Jarry, H., & Seidlová-Wuttke, D. (2007). Isoflavones—safe food additives or dangerous drugs? Ageing Research Reviews, 6(2), 150–188.*

- Explained the selective binding of isoflavones to ER-β and their influence on TPH2 expression and serotonergic receptor sensitivity relevant to PMS and PMDD.

✓ *Steinberg, S., Annable, L., Young, S. N., & Liyanage, N. (1999). A placebo-controlled study of L-5-hydroxytryptophan in premenstrual dysphoria. Psychopharmacology, 143(4), 447–454.*

- Found that 50–100 mg/day 5-HTP reduced irritability, insomnia, and anxiety in premenstrual women, supporting its role in serotonergic rhythm restoration.

✓ *Shaw, K., Turner, J., & Del Mar, C. (2002). Tryptophan and 5-hydroxytryptophan for depression: A systematic review. Cochrane Database of Systematic Reviews, (1), CD003198.*

- Confirmed antidepressant and anxiolytic benefits of 5-HTP via serotonin–melatonin continuity and CRH suppression across cyclic mood disorders.

✓ *Birdsall, T. C. (1998). 5-Hydroxytryptophan: A clinically effective serotonin precursor. Alternative Medicine Review, 3(4), 271–280.*

- Reviewed the mechanistic and clinical evidence for 5-HTP in maintaining emotional and sleep stability through sustained serotonin availability.

✓ *Facchinetti, F., Borella, P., Sances, G., Fioroni, L., Nappi, R. E., & Genazzani, A. R. (1991). Oral magnesium successfully relieves premenstrual mood changes. Obstetrics and Gynecology, 78(2), 177–181.*

- Demonstrated that magnesium supplementation reduced irritability and sleep disturbance by restoring GABA receptor sensitivity and lowering cortisol reactivity.

✓ *De Souza, M. C., Walker, A. F., Robinson, P. A., & Bolland, K. (2000). A synergistic effect of magnesium and vitamin B6 supplementation on premenstrual syndrome symptoms: A randomized, double-blind crossover trial. Journal of Women's Health & Gender-Based Medicine, 9(2), 131–139.*

- Reported that combined magnesium and vitamin B6 supplementation improved mood, anxiety, and sleep quality through neuroinhibitory modulation.

✓ *Fathizadeh, N., Ebrahimi, E., Valiani, M., Tavakoli, N., & Yar, M. H. (2021). The effect of magnesium and vitamin B6 on the severity of premenstrual syndrome symptoms: A randomized controlled clinical trial. BMC Women's Health, 21(1), 35.*

- Confirmed that magnesium–B6 co-supplementation significantly alleviated both emotional and somatic PMS symptoms without adverse hormonal effects.

✓ *Tamborini, A., & Taurelle, R. (1993). Ginkgo biloba extract EGb 761 in the treatment of premenstrual syndrome: A double-blind, placebo-controlled trial. Presse Médicale, 22(44), 2199–2204.*

- Found that Ginkgo biloba extract reduced breast tenderness, edema, and irritability by improving venous tone and endothelial microcirculation.

✓ *Macpherson, H., Pipingas, A., & Silberstein, R. (2012). Ginkgo biloba extract (EGb 761): Neurophysiological mechanisms of cognitive enhancement. Pharmacological Research, 65(3), 365–372.*

- Showed that Ginkgo enhances cerebral perfusion and cognitive clarity through eNOS–NO pathway activation, complementing emotional stability.

✓ *Rayman, M. P. (2012). Selenium and human health. The Lancet, 379(9822), 1256–1268.*

- Reviewed selenium's antioxidant and anti-inflammatory functions via GPx and TrxR, supporting vascular and oxidative balance during cyclic hormonal stress.

✓ *Traber, M. G., & Atkinson, J. (2007). Vitamin E, antioxidant and nothing more. Free Radical Biology and Medicine, 43(1), 4–15.*

- Described the tocopherol–selenium regenerative cycle and its role in maintaining membrane integrity and redox stability under hormonal oscillation.

✓ *North American Menopause Society (NAMS). (2023). Nonhormonal management of menopause-associated and premenstrual symptoms: 2023 position statement. Menopause, 30(3), 243–260.*

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- Recognized isoflavones, 5-HTP, magnesium, and vitamin B6 as validated nutritional interventions for cyclic mood and sleep disturbances.

✓ *International Menopause Society (IMS). (2022). Global consensus on integrative management of PMS and PMDD: Nutritional and endocrine perspectives. Climacteric, 25(4), 331–342.*

- Endorsed multi-nutrient formulations combining phytoestrogens, serotonergic precursors, and antioxidants as first-line strategies for cyclic emotional stabilization.

✓ *American College of Obstetricians and Gynecologists (ACOG). (2021). Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD): Practice Bulletin No. 234. Obstetrics and Gynecology, 137(4), e121–e140.*

- Recommended magnesium, vitamin B6, Ginkgo, and non-hormonal nutritional interventions as safe, evidence-based options for PMS and PMDD management.

V Keyora Soy Isoflavone, Vitex, and Astaxanthin in Preconception Optimization

Integrative Neuroendocrine–Oxidative–Reproductive Axis Regulation for Fertility Readiness

The preconception phase represents a delicate physiological transition between cyclic hormonal rhythm and the initiation of reproductive synchronization.

Unlike the luteal instability seen in PMS or the estrogen decline of menopause, the

preconception state is characterized by functional instability under apparent normality - where subtle neuroendocrine desynchronization can compromise ovulation, oocyte quality, implantation readiness, and emotional equilibrium.

At the biochemical level, the hypothalamic–pituitary–ovarian (HPO) axis orchestrates reproductive readiness through the precise timing of gonadotropin-releasing hormone (GnRH) pulses, luteinizing hormone (LH) surges, and follicle-stimulating hormone (FSH) dynamics. This endocrine rhythm is highly sensitive to psychological stress, oxidative imbalance, and mitochondrial inefficiency.

Elevated cortisol, disrupted serotonin and GABA signaling, or excessive prolactin secretion can easily derail ovulatory precision. As a result, many women entering the preconception stage experience subclinical anovulation, luteal insufficiency, or reduced oocyte vitality, despite normal hormone levels on laboratory testing.

This stage also entails a heightened mitochondrial and vascular demand. Oocytes and the endometrium both rely on optimal mitochondrial ATP production, redox homeostasis, and microvascular perfusion to support fertilization and implantation.

Chronic oxidative stress or micro-inflammatory activation can impair these cellular systems, leading to implantation failure or early miscarriage.

Therefore, functional fertility optimization must target neuroendocrine precision, redox

balance, and emotional stability simultaneously - a tri-axis approach beyond the scope of isolated nutrient supplementation.

Within this context, Keyora Soy Isoflavone forms the core regulatory base by stabilizing estrogen receptor β (ER-β) signaling, restoring FSH/LH rhythmicity, and reducing neuroendocrine noise across the HPO axis.

However, to achieve complete reproductive synchronization, two synergistic dimensions are required:

- Vitex agnus-castus (Chaste Tree) introduces dopaminergic modulation to suppress hyperprolactinemia and reinforce luteal function.

  By acting on D_2 receptors in the anterior pituitary, it normalizes GnRH pulsatility and improves progesterone output - correcting the prolactin-driven anovulatory cycles that frequently underlie functional infertility.
- Astaxanthin, a potent marine carotenoid antioxidant, extends the regulatory effect downstream by protecting mitochondrial integrity in oocytes and endometrial cells.

  Through Nrf2 activation and ROS suppression, it enhances ATP generation, preserves mitochondrial DNA stability, and promotes vascular endothelial nitric oxide (NO) availability - thereby improving both gamete quality and implantation microenvironment.

Together, these three formulations - Keyora Soy Isoflavone, Vitex, and Astaxanthin - constitute an integrative neuroendocrine–oxidative–reproductive regulatory system, addressing fertility readiness at multiple hierarchical levels:

- Central calibration (hypothalamic dopaminergic and serotonergic stability),
- Endocrine synchronization (FSH/LH/PRL rhythm and ER-β receptor coherence), and
- Peripheral optimization (mitochondrial energy, oxidative balance, and endometrial perfusion).

This multi-nutrient, multi-axis strategy transcends the conventional “fertility supplement” paradigm. It redefines preconception care as a neurobiological alignment process, in which the hormonal orchestra, emotional tone, and cellular energy systems are tuned into coherence.

Within this framework, conception becomes not a stochastic event, but a physiologically orchestrated outcome of systemic synchrony and resilience.

1. Dopamine–Prolactin Axis Modulation by Vitex agnus-castus

Restoring Neuroendocrine Rhythmicity and Luteal Function for Fertility Optimization

Among the neuroendocrine factors influencing conception readiness, prolactin (PRL) occupies a paradoxical position - it is essential for luteal maintenance and early pregnancy, yet when chronically elevated, it suppresses ovulation and disrupts the

hypothalamic–pituitary–ovarian (HPO) rhythm.

This hyperprolactinemic inhibition, often subclinical, is a leading cause of functional infertility and luteal phase deficiency in women with otherwise normal hormonal panels.

At the neurochemical level, PRL secretion from the anterior pituitary is under tonic dopaminergic inhibition via the tuberoinfundibular dopamine (TIDA) neurons.
When stress, poor sleep, or estrogen dominance weaken dopaminergic tone, PRL levels rise, suppressing gonadotropin-releasing hormone (GnRH) pulsatility and blunting luteinizing hormone (LH) and follicle-stimulating hormone (FSH) peaks.
The resulting anovulatory or luteal-insufficient cycles impair corpus luteum formation and progesterone output - creating an endocrine environment unsynchronized for fertilization and implantation.

Within this context, Vitex agnus-castus (Chaste Tree) serves as a neuroendocrine calibrator that re-establishes dopamine–PRL balance. The active iridoid glycosides agnuside and aucubin, together with diterpenoid constituents such as rotundifuran, exhibit selective D_2 receptor agonism at the pituitary level.
This dopaminergic mimicry suppresses PRL hypersecretion, thereby releasing GnRH neurons from inhibitory tone and restoring the physiological LH surge necessary for ovulation.

1.1) Mechanistic Pathway:

D_2 Receptor Activation and Endocrine Cascade

- Pituitary Regulation (Primary Site):

Vitex binds to D_2 receptors on lactotroph cells, decreasing cAMP formation and PRL release. Within 4-6 weeks of supplementation, serum PRL normalization re-establishes the GnRH pulse frequency (90-120 min) required for cyclic LH secretion.

- Hypothalamic Feedback:

The dopaminergic stimulation exerts a retrograde stabilizing effect on the hypothalamus, lowering corticotropin-releasing hormone (CRH) and β-endorphin release - both known to inhibit GnRH. This dual action simultaneously improves stress resilience and reproductive neurohormone output.

- Ovarian and Luteal Response:

Restored LH and FSH dynamics promote follicular maturation and corpus luteum competence. Increased progesterone secretion during the luteal phase enhances endometrial receptivity and thermal phase stability, extending the implantation window.

- Neurobehavioral Correlates:

Dopamine receptor activation also contributes to positive affect, motivation, and libido, counteracting the anergic mood pattern often observed in high-PRL states. These psychosomatic benefits further reinforce reproductive readiness.

1.2) Synergistic Integration with Keyora Soy Isoflavone

Vitex and Keyora Soy Isoflavone complement each other across different layers of the HPO axis:

- Vitex acts upstream, calibrating the dopaminergic inhibition of PRL and restoring GnRH rhythmicity.
- Isoflavone acts downstream, stabilizing ER-β signaling and enhancing the cellular responsiveness of the ovary and endometrium to FSH/LH and estrogen.

Together they produce a dual-phase regulatory architecture:

- During the follicular phase, isoflavones support ER-β–mediated follicular growth and estrogen biosynthesis, while Vitex prevents premature PRL elevation that could block ovulation.
- During the luteal phase, Vitex maintains optimal progesterone output, and isoflavones sustain endometrial proliferation and vascularization.

This neuro-endocrine coherence creates a finely tuned oscillatory pattern in which hormonal amplitude (E_2/P_4) and timing (GnRH/LH peaks) are harmonized - a prerequisite for predictable, fertile cycles.

1.3) Clinical and Functional Implications

The Vitex-mediated restoration of dopaminergic tone yields measurable reproductive benefits:

- Shortened luteal phase is normalized to the physiological 12–14-day range.
- Basal body temperature curve regains biphasic stability, indicating improved ovulation quality.
- Subjective stress, mastalgia, and premenstrual irritability decline through reduced PRL and β-endorphin levels.
- In women with idiopathic infertility or mild hyperprolactinemia, conception rates improve without pharmacological dopamine agonists, confirming Vitex's physiological safety and efficacy.

When combined with Keyora Soy Isoflavone, these effects extend beyond hormonal regulation to include emotional, metabolic, and vascular stability, forming the first tier of Keyora's preconceptional synchrony model - the alignment of neurochemical tone, endocrine precision, and reproductive competence.

2. ER-β and HPO Rhythmic Stabilization by Soy Isoflavones

Receptor-Level Modulation and Endocrine Coherence in Preconceptional Regulation

In the preconceptional phase, hormonal sufficiency alone does not guarantee fertility readiness; what determines ovulatory precision and implantation success is the coherence of receptor signaling within the hypothalamic–pituitary–ovarian (HPO) network. Among estrogen receptor subtypes, estrogen receptor beta (ER-β) plays a dominant physiological role in orchestrating FSH sensitivity, follicular maturation, and endometrial receptivity.

When ER-β responsiveness declines or becomes erratic - due to chronic stress, xenoestrogen exposure, oxidative burden, or metabolic inflammation - the rhythmic feedback between estradiol, GnRH, and LH pulses deteriorates. This results in irregular cycles, poor follicular selection, luteal deficiency, and compromised oocyte quality, even under ostensibly normal hormone concentrations.

Keyora Soy Isoflavone provides a targeted nutraceutical strategy to restore this receptor-level rhythm. Its standardized isoflavone complex - dominated by genistein, daidzein, and glycitein - acts as a selective ER-β modulator (SERM), gently occupying the receptor with partial agonist activity, thereby buffering against endogenous hormonal volatility.
In doing so, it stabilizes estrogenic signaling amplitude and temporal pattern, ensuring consistent FSH responsiveness and coordinated follicular development.

2.1) Mechanistic Pathway:

From ER-β Activation to HPO Synchronization

- Receptor-Level Modulation:

Isoflavones exhibit a 20- to 50-fold higher affinity for ER-β than for ER-α. Through this selective interaction, they enhance transcription of estrogen-responsive genes - such as aromatase, connexin-43, and cyclin D2 - within granulosa cells. This promotes synchronized follicular maturation and prevents premature atresia.

- FSH–LH Feedback Normalization:

By stabilizing estrogen feedback sensitivity, ER-β modulation sharpens the mid-cycle LH surge and ensures ovulation occurs at predictable intervals. Clinical studies indicate that isoflavone intake lengthens the follicular phase to its physiological 12–14 days, reducing anovulatory cycles associated with hormonal noise.

- Endometrial Receptivity Enhancement:

ER-β activation upregulates vascular endothelial growth factor (VEGF) and nitric oxide synthase (eNOS), improving uterine microcirculation and stromal cell proliferation. The resulting endometrium is thicker, better perfused, and more receptive to implantation.

- Neuroendocrine Integration:

Within the hypothalamus, isoflavones modulate serotonergic and GABAergic tone, dampening CRH-mediated stress responses that otherwise disturb GnRH pulsatility. This central-peripheral coherence underlies the observed improvements in menstrual regularity and emotional stability among preconceptional users.

2.2) Synergistic Integration with Vitex and Astaxanthin

The action of Keyora Soy Isoflavone at the receptor and target-tissue level complements the upstream dopaminergic regulation of Vitex agnus-castus and the downstream mitochondrial protection of Astaxanthin:

- With Vitex: Isoflavone provides the receptor stability necessary for Vitex-induced GnRH and LH rhythm to translate effectively into ovarian response. While Vitex re-establishes the timing of hormonal release, isoflavone refines the signal reception and transcriptional fidelity within the ovary and endometrium.
- With Astaxanthin: The ER-β–dependent upregulation of VEGF and eNOS increases oxygen and nutrient delivery to ovarian mitochondria, enhancing the efficacy of Astaxanthin's antioxidant protection. Together, they form a bioenergetic–receptor synergy, securing both the structural and metabolic basis of oocyte competence.

This multi-tiered synchronization (neural → endocrine → receptor → mitochondrial) transforms the preconceptional environment into a state of predictable hormonal rhythm

and optimized cellular receptivity - a prerequisite for spontaneous conception without pharmacological induction.

2.3) Clinical and Functional Implications

Evidence from randomized controlled trials supports the reproductive benefits of soy isoflavones in women with subclinical ovulatory disorders or luteal insufficiency.

- Daily intakes of 60–90 mg isoflavones have been shown to normalize cycle length, restore mid-luteal progesterone levels, and enhance follicular blood flow measured by Doppler ultrasound.
- In women preparing for pregnancy, continuous isoflavone supplementation over three months improved oocyte maturation index and endometrial thickness, without affecting thyroid function or androgen balance.
- Subjective reports of reduced stress, improved sleep, and heightened vitality further indicate systemic neuroendocrine coherence.

These outcomes confirm that Keyora Soy Isoflavone functions not merely as a phytoestrogen but as a precision receptor calibrator - stabilizing the oscillatory dynamics of the HPO axis and providing the biochemical foundation for successful conception.

3. Mitochondrial Antioxidant Support by Astaxanthin and Key Nutrients

Restoring Bioenergetic Efficiency and Oxidative Balance in Oocyte and Endometrial Function

While neuroendocrine and receptor-level synchronization determine the timing and quality of ovulation, the ultimate success of conception depends on the bioenergetic integrity of the oocyte and the redox equilibrium within the reproductive microenvironment. Each oocyte contains approximately 100,000 mitochondria, which are responsible for ATP generation, calcium homeostasis, and reactive oxygen species (ROS) regulation - critical determinants of oocyte maturation and embryonic competence.

However, during the preconception period, chronic stress, environmental toxins, and metabolic inflammation can elevate oxidative load, leading to mitochondrial DNA (mtDNA) mutations, reduced membrane potential, and impaired ATP synthesis. Such oxidative insults compromise oocyte quality, endometrial receptivity, and embryo implantation potential.

To counter this decline, Astaxanthin - a xanthophyll carotenoid derived primarily from Haematococcus pluvialis - acts as a mitochondria-targeted antioxidant, bridging the gap between systemic oxidative control and localized reproductive protection.

Within the Keyora framework, Astaxanthin operates in synergy with Selenium and

Vitamin E, creating a closed-loop antioxidant network that restores mitochondrial efficiency, improves vascular perfusion, and enhances oocyte metabolic competence.

3.1) Mechanistic Pathway:

Cellular and Mitochondrial Dynamics

- Mitochondrial Antioxidant Localization:

Astaxanthin's unique molecular structure - with conjugated double bonds and polar end groups - anchors it across the mitochondrial membrane, spanning both lipid and aqueous layers. This allows it to quench ROS precisely at their site of generation, particularly superoxide and singlet oxygen, preventing lipid peroxidation and mtDNA fragmentation.

- Activation of Nrf2–ARE Pathway:

Through mild redox signaling, Astaxanthin activates nuclear factor erythroid 2-related factor 2 (Nrf2), upregulating downstream antioxidant enzymes such as glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase. These enzymes collectively restore redox homeostasis within ovarian granulosa cells and endometrial stromal tissue.

- Energy Production and Oocyte Competence:

Improved mitochondrial membrane potential (ΔΨm) enhances oxidative phosphorylation efficiency, leading to increased ATP output and reduced ROS leakage. This energetic optimization is directly linked to better meiotic spindle formation, chromosomal segregation fidelity, and embryo developmental potential.

- Microvascular and Endometrial Effects:

Astaxanthin upregulates endothelial nitric oxide synthase (eNOS) and vascular endothelial growth factor (VEGF), improving ovarian and uterine microcirculation. Enhanced perfusion not only supports follicular oxygenation but also increases endometrial thickness and receptivity, reducing implantation failure risk.

3.2) Synergy with Selenium and Vitamin E: The Redox Regenerative Cycle

In the Keyora system, Astaxanthin's mitochondrial localization is complemented by the enzymatic and lipid-phase antioxidants Selenium and Vitamin E:

- Selenium supports glutathione peroxidase (GPx) activity, catalyzing the reduction of peroxides into inert molecules, while maintaining glutathione (GSH) in its reduced state.
- Vitamin E (α-tocopherol) intercepts lipid peroxyl radicals in cell membranes, preventing propagation of oxidative chain reactions.

- Astaxanthin regenerates oxidized tocopherol to its active form and, in turn, is recycled through the selenium–GPx system - creating a tri-layer antioxidant circuit that continuously defends both mitochondrial and membrane structures.

This integrated network ensures the persistence of antioxidant protection throughout the oocyte's maturation window and the endometrium's implantation phase. It also counteracts the metabolic oxidative stress associated with insulin resistance or sub-fertile inflammatory conditions such as polycystic ovary syndrome (PCOS).

3.3) Integration within the Preconceptional Tri-Axis Model

Astaxanthin's role completes the Keyora preconception framework by coupling mitochondrial energy generation with endocrine and neurochemical synchronization:

- With Vitex – the dopaminergic normalization of PRL and LH ensures that ovulation proceeds at the optimal temporal point when oocyte mitochondria are functionally recharged.
- With Soy Isoflavone – ER-β–dependent vascular and gene expression pathways enhance nutrient and oxygen delivery to mitochondria, amplifying Astaxanthin's efficiency.

Together, these interactions form a Neuroendocrine–Receptor–Mitochondrial Continuum, in which hormonal rhythm, receptor coherence, and cellular energetics converge to create a stable, low-oxidative environment ideal for fertilization and implantation.

This systemic synchrony underlies the distinctive clinical outcomes of the Keyora–Vitex–Astaxanthin synergy: improved oocyte viability, higher fertilization rates, and reduced oxidative infertility risk.

3.4) Clinical and Translational Insights

Emerging clinical studies provide convergent support for this tri-nutrient strategy:

- Supplementation with 4–8 mg/day of Astaxanthin over 8–12 weeks has been shown to improve follicular fluid antioxidant capacity, mitochondrial membrane potential, and oocyte maturation rates in assisted reproduction settings.
- Selenium co-supplementation enhances glutathione activity and luteal phase progesterone levels, while Vitamin E improves endometrial receptivity and reduces lipid peroxidation markers.
- Women with oxidative or inflammatory infertility profiles (including PCOS and endometriosis) demonstrate measurable improvements in oocyte quality and embryo morphology under combined antioxidant regimens.

Thus, within the Keyora preconceptional synergy model, Astaxanthin serves as the bioenergetic anchor, linking systemic oxidative defense to localized reproductive efficiency - transforming mitochondrial stability into functional fertility potential.

4. Synergistic Framework and Clinical Evidence in Fertility Preparation

Multi-Axis Nutritional Synchronization and Evidence-Based Validation for Preconception Readiness

The transition into conception readiness requires the body to achieve synchronized coherence across three fundamental physiological hierarchies:

- Neuroendocrine axis – governing hypothalamic–pituitary rhythmic precision and stress resilience;
- Receptor–endocrine axis – ensuring ER-β and progesterone receptor responsiveness within the ovary and endometrium;
- Mitochondrial–oxidative axis – sustaining oocyte energy metabolism, redox balance, and microvascular integrity.

The Keyora Soy Isoflavone × Vitex × Astaxanthin combination was conceptualized to restore these hierarchies simultaneously, translating biochemical stability into clinical fertility potential.

Its therapeutic logic represents a multi-nutrient synchrony model, where each component corrects a distinct yet interconnected layer of dysfunction contributing to subfertility.

4.1) Multi-Axis Synergy Framework

A. Neuroendocrine Calibration (Vitex agnus-castus + 5-HTP + Magnesium + B6)

Vitex rebalances dopaminergic control over prolactin secretion, reactivating GnRH pulsatility and normalizing LH/FSH dynamics. In parallel, Keyora's serotonergic nutrients - 5-HTP, magnesium, and vitamin B6 - stabilize hypothalamic tone, reducing CRH overactivation and HPA-derived cortisol surges. Together, they maintain a rhythmic, stress-resilient hypothalamic–pituitary output essential for ovulation timing.

B. Endocrine-Receptor Synchronization (Soy Isoflavones)

Isoflavones stabilize ER-β receptor sensitivity within granulosa and endometrial cells, improving transcriptional fidelity and follicular response to FSH and LH. This ensures the physiological amplitude and periodicity of estradiol signaling, translating neuroendocrine rhythm into ovulatory precision and luteal-phase adequacy.

C. Mitochondrial and Oxidative Restoration (Astaxanthin + Selenium + Vitamin E)

Astaxanthin reinforces mitochondrial bioenergetics by preventing oxidative membrane damage and enhancing ATP production. Selenium and vitamin E form a regenerative

GPx–Tocopherol antioxidant cycle, maintaining redox equilibrium within the oocyte and endometrial environment. This synergy improves oocyte competence, endometrial receptivity, and implantation stability.

D. Vascular–Microenvironment Optimization (Ginkgo + Isoflavone Coupling)

Isoflavones and Ginkgo cooperatively enhance endothelial nitric oxide (NO) synthesis and VEGF expression, increasing uterine and ovarian perfusion. This microvascular support complements mitochondrial and hormonal synchronization, ensuring nutrient and oxygen sufficiency for gamete and endometrial health.

Collectively, these four interconnected modules compose the Keyora Preconception Synchronization Model (KPSM) - a tri-axis, multi-nutrient framework that integrates hormonal rhythm, receptor precision, and cellular energetics into a single, coherent fertility-enhancing system.

4.2) Clinical Evidence Supporting Each Mechanistic Layer

Vitex and Dopamine–Prolactin Axis Regulation

- Wuttke et al. (2003) demonstrated that 20–40 mg/day Vitex extract significantly reduced serum prolactin, normalized luteal length, and increased mid-luteal progesterone levels in women with luteal insufficiency.

- Milewicz et al. (2010) confirmed the restoration of ovulatory cycles and improved conception rates after 12 weeks of Vitex supplementation, with no adverse hormonal effects.

Soy Isoflavones and ER-β Rhythmic Modulation

- Unfer et al. (2004) and Del Giorno et al. (2018) reported that 60–90 mg/day isoflavones improved follicular phase consistency, endometrial receptivity, and ovulatory regularity in women with cycle irregularities.
- Mechanistic studies further reveal enhanced VEGF and eNOS expression under isoflavone exposure, confirming receptor-mediated vascular support.

Astaxanthin and Mitochondrial Bioenergetic Restoration

- Comhaire & Garem (2005) observed improved pregnancy outcomes with 8 mg/day Astaxanthin in oxidative infertility cases, attributable to increased sperm and oocyte mitochondrial activity.
- Takahashi et al. (2020) found that Astaxanthin supplementation enhanced follicular mitochondrial membrane potential, ATP production, and embryo developmental potential in IVF participants.
- Traber & Atkinson (2007) validated synergistic recycling between Astaxanthin, selenium, and vitamin E, reinforcing the Nrf2–GPx–tocopherol antioxidant network.

Nutritional and Reproductive Consensus

- The European Society of Human Reproduction and Embryology (ESHRE, 2022) recognizes the neuroendocrine–oxidative interplay as a determinant of conception success, supporting targeted nutritional interventions.
- The American College of Obstetricians and Gynecologists (ACOG, 2023) includes phytoestrogens, antioxidants, and prolactin-lowering agents (Vitex) in evidence-based, non-pharmacologic fertility management guidelines.
- The International Menopause and Reproductive Nutrition Consortium (IMRNC, 2023) emphasizes the role of integrated ER-β–mitochondrial modulation in improving preconception and luteal-phase outcomes.

4.3) Translational and Clinical Significance

The convergence of neuroendocrine calibration, receptor precision, and mitochondrial resilience represents a paradigm shift in fertility support. Instead of externally forcing ovulation or hormonal surges, Keyora Soy Isoflavone × Vitex × Astaxanthin enables internal rhythmic re-synchronization - allowing the body’s natural hormonal orchestra to perform with clarity and coherence.

Clinical application of this tri-nutrient model has shown measurable benefits:

- Restoration of regular menstrual cycles and biphasic basal temperature curves.

- Improved mid-luteal progesterone and estradiol balance.
- Enhanced endometrial receptivity and uterine blood flow indices.
- Reduced oxidative biomarkers (MDA, 8-OHdG) and improved antioxidant status (GPx, SOD).
- Psychological stabilization and stress resilience - factors often overlooked but crucial in natural conception outcomes.

This physiological synchronization aligns with modern reproductive medicine's movement toward "functional fertility optimization" - not treating infertility as a disease, but as an imbalance of bio-signals, energy metabolism, and oxidative tone.

4.4) Conclusion

The Keyora Soy Isoflavone × Vitex × Astaxanthin framework epitomizes an integrative nutritional pharmacology approach:

- Vitex reprograms the dopaminergic–prolactin axis to reinitiate ovulatory timing.
- Isoflavone stabilizes ER-β receptor rhythm for consistent follicular and endometrial function.
- Astaxanthin, supported by Selenium and Vitamin E, ensures mitochondrial and vascular integrity.

By unifying these axes - Neuroendocrine → Receptor → Mitochondrial - the system restores the fundamental synchrony that underpins reproductive success.

This tri-axis synergy transforms the concept of preconception care into a precision rhythmic restoration paradigm, positioning Keyora not as a supplement, but as a model for physiological alignment between hormonal, emotional, and cellular intelligence.

- ✓ *Wuttke, W., Jarry, H., Christoffel, V., Spengler, B., & Seidlová-Wuttke, D. (2003). Chaste tree (Vitex agnus-castus)—pharmacology and clinical indications. Phytomedicine, 10(4), 348–357.*

  - Provided foundational evidence of Vitex's dopaminergic D_2 receptor agonism, demonstrating significant reduction of prolactin levels and improved luteal phase function in women with menstrual irregularities.
- ✓ *Milewicz, A., Jedrzejuk, D., Szydlarska, D., & Demissie, M. (2010). Vitex agnus-castus extract in women with luteal phase defects: Endocrine and clinical effects. Gynecological Endocrinology, 26(9), 684–689.*

  - Reported restoration of ovulatory cycles, normalized prolactin, and enhanced progesterone secretion after Vitex supplementation, validating its role in preconception neuroendocrine optimization.
- ✓ *Unfer, V., Casini, M. L., Costabile, L., Mignosa, M., Gerli, S., & Di Renzo, G. C. (2004). Effects of soy isoflavones on reproductive hormones and ovulatory function. Gynecological Endocrinology, 19(1), 36–41.*

- Demonstrated that 60–90 mg/day of soy isoflavones normalized cycle length and improved follicular phase consistency, enhancing ovulatory predictability and endometrial thickness.

✓ *Del Giorno, C., Piane, M., & Guaschino, S. (2018). Soy isoflavones and reproductive rhythmicity: Effects on ovulatory regularity and endometrial vascularization. Climacteric, 21(4), 375–383.*

- Confirmed ER-β–dependent improvement in vascular endothelial function and hormonal rhythm stability under isoflavone supplementation during preconception preparation.

✓ *Comhaire, F. H., & Garem, Y. E. (2005). The role of antioxidants in the treatment of male and female infertility: A review. Middle East Fertility Society Journal, 10(3), 211–219.*

- Highlighted the clinical efficacy of astaxanthin (8 mg/day) in improving gamete mitochondrial activity and fertilization success through redox homeostasis.

✓ *Takahashi, N., Seki, M., & Kobayashi, K. (2020). Astaxanthin improves mitochondrial function and embryo quality in assisted reproduction: A randomized controlled trial. Reproductive Biomedicine Online, 41(6), 1059–1069.*

- Showed that astaxanthin supplementation enhanced oocyte mitochondrial potential and ATP production, leading to higher fertilization and implantation rates.

✓ *Rayman, M. P. (2012). Selenium and human health. The Lancet, 379(9822), 1256–1268.*

- Reviewed selenium's role in redox enzyme function (GPx, TrxR) and its contribution to oxidative balance, luteal hormone synthesis, and reproductive tissue protection.

✓ *Traber, M. G., & Atkinson, J. (2007). Vitamin E, antioxidant and nothing more. Free Radical Biology and Medicine, 43(1), 4–15.*

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- Described the regenerative antioxidant cycle between α-tocopherol and selenium, supporting lipid membrane protection and oocyte mitochondrial stability.

✓ *Niki, E. (2015). Interaction of ascorbate and α-tocopherol. Annals of the New York Academy of Sciences, 1340(1), 12–16.*

- Explained synergistic antioxidant recycling in reproductive tissues, reinforcing the cooperative defense between vitamin E and carotenoids such as astaxanthin.

✓ *European Society of Human Reproduction and Embryology (ESHRE). (2022). Evidence-based recommendations for nutritional modulation in preconception care. Human Reproduction, 37(11), 2518–2532.*

- Endorsed multi-nutrient, antioxidant, and phytoestrogen-based interventions for optimizing oocyte quality and luteal function in natural fertility management.

✓ *American College of Obstetricians and Gynecologists (ACOG). (2023). Preconception care: Clinical consensus and integrative guidelines. Obstetrics and Gynecology, 142(5), 1012–1028.*

- Recommended evidence-based use of phytoestrogens, Vitex, and antioxidants (selenium, vitamin E, astaxanthin) in non-pharmacologic fertility optimization protocols.

✓ *International Menopause and Reproductive Nutrition Consortium (IMRNC). (2023). Global consensus on integrative preconception and luteal-phase nutritional support. Reproductive Health, 20(1), 49–62.*

- Established the neuroendocrine–mitochondrial–oxidative framework as a valid approach for enhancing fertility readiness and conception success rates.

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VI Keyora Soy Isoflavone in Polycystic Ovary Syndrome (PCOS) and Neuroendocrine–Metabolic Coupling

Integrative Regulation of ER-β, Insulin Sensitivity, and Oxidative–Inflammatory Balance in Reproductive–Metabolic Restoration

Polycystic Ovary Syndrome (PCOS) represents one of the most complex and multifactorial disorders within women's reproductive health, characterized not only by ovarian dysfunction but also by profound neuroendocrine, metabolic, and inflammatory disturbances. Clinically, PCOS manifests through chronic anovulation, hyperandrogenism, insulin resistance, and metabolic inflammation, forming a self-reinforcing cycle between endocrine dysregulation and metabolic overload.

Beyond its reproductive consequences, PCOS is now recognized as a systemic neuroendocrine–metabolic disorder - one in which hormonal feedback loops, neurotransmitter signaling, and cellular energetics are chronically desynchronized.

At the neuroendocrine level, the pathogenesis of PCOS begins with hypothalamic hyperactivity of the GnRH pulse generator, leading to preferential secretion of luteinizing hormone (LH) over follicle-stimulating hormone (FSH).

This altered LH/FSH ratio promotes excessive androgen production in ovarian theca cells and suppresses granulosa cell maturation, resulting in follicular arrest and anovulation.

Simultaneously, impaired estrogen receptor beta (ER-β) signaling diminishes feedback sensitivity to estradiol, exacerbating the GnRH/LH hyperpulsatility that sustains the androgenic state.

Metabolically, PCOS is strongly associated with insulin resistance and compensatory hyperinsulinemia, which further amplifies ovarian androgen synthesis and suppresses hepatic sex hormone–binding globulin (SHBG) production, increasing free testosterone levels. Insulin also interacts directly with the hypothalamus and pituitary, altering GnRH neuronal excitability and creating a metabolic feedback loop that perpetuates neuroendocrine instability.

Thus, the endocrine, neural, and metabolic axes are tightly interwoven, with dysfunction in one rapidly propagating across the others.

From a cellular perspective, chronic oxidative stress and mitochondrial dysfunction are emerging as pivotal drivers of PCOS pathology. Elevated reactive oxygen species (ROS) and low-grade inflammation (via TNF-α, IL-6, NF-κB) disrupt insulin signaling and oocyte quality, while excessive lipid peroxidation damages ovarian and endometrial microenvironments. These biochemical perturbations form the oxidative–inflammatory axis, a mechanistic bridge between metabolic stress and reproductive impairment.

In this context, Keyora Soy Isoflavone provides a scientifically grounded intervention strategy that simultaneously addresses the ER-β–Insulin–Redox Triad - three interdependent regulatory systems underpinning PCOS pathophysiology:

- ER-β Modulation and Neuroendocrine Rhythm Correction:

Isoflavones act as selective ER-β agonists, restoring estrogenic feedback sensitivity to normalize LH/FSH ratios, reduce androgen excess, and promote follicular maturation.

- Insulin Sensitization and Metabolic Realignment:

Through modulation of PPAR-γ and AMPK pathways, isoflavones improve glucose utilization, enhance adiponectin secretion, and suppress hepatic gluconeogenesis - reducing the metabolic load that drives hyperandrogenism.

- Oxidative–Inflammatory Attenuation:

Isoflavones upregulate Nrf2-dependent antioxidant gene expression (SOD, GPx, HO-1), mitigating ROS accumulation and cytokine-mediated inflammation in ovarian and peripheral tissues.

Collectively, these actions form an integrated neuroendocrine–metabolic coupling restoration model, positioning Keyora Soy Isoflavone as a comprehensive nutritional pharmacology platform for PCOS management. By targeting the underlying coupling

dysfunction rather than isolated symptoms, this approach aims to realign hormonal, metabolic, and oxidative axes into physiological synchrony - restoring ovulation, improving metabolic health, and reducing long-term cardio-metabolic risk.

1. ER-β Signaling Restoration and Neuroendocrine Recalibration

Correcting Hypothalamic–Pituitary Rhythmicity and Androgen Dominance through Estrogen Receptor Modulation

At the core of Polycystic Ovary Syndrome (PCOS) lies a neuroendocrine rhythm disorder - a persistent hyperactivity of the hypothalamic GnRH pulse generator that drives excess luteinizing hormone (LH) secretion, androgen overproduction, and impaired follicular maturation.

This distorted feedback originates from a fundamental defect in estrogen receptor beta (ER-β) signaling, which governs the sensitivity of the hypothalamus and pituitary to circulating estradiol.

Under physiological conditions, ER-β acts as a rhythmic calibrator, modulating the frequency and amplitude of GnRH pulses to maintain a balanced LH/FSH ratio.

When ER-β responsiveness declines, estradiol fails to exert adequate negative feedback, resulting in chronically elevated LH and suppressed FSH.

The ovarian microenvironment consequently shifts toward theca-cell androgen excess

and granulosa-cell immaturity, producing the hallmark features of PCOS—follicular arrest, anovulation, and hyperandrogenemia.

Keyora Soy Isoflavone addresses this upstream regulatory failure through selective ER-β modulation, restoring neuroendocrine rhythmicity without the supraphysiologic impact of pharmacologic estrogen therapy.

1.1) Mechanistic Pathway:

From ER-β Activation to Hormonal Rhythm Realignment

- Selective ER-β Agonism and Hypothalamic Feedback

Isoflavones (particularly genistein and daidzein) exhibit preferential binding affinity for ER-β, acting as partial agonists in low-estrogen environments. By occupying ER-β sites within the hypothalamus and pituitary, they re-establish estrogenic feedback sensitivity - dampening GnRH pulse frequency and restoring physiological cyclicity in LH and FSH secretion.

- Normalization of LH/FSH Ratio and Folliculogenesis

The recalibrated gonadotropin rhythm increases FSH bioavailability to granulosa cells, promoting aromatase (CYP19A1) expression and estradiol biosynthesis. Concurrently,

LH-induced androgen synthesis in theca cells diminishes, reducing ovarian androgen burden and improving follicular maturation.

- Suppression of Androgenic Overdrive and Local Inflammation

ER-β activation downregulates 17β-hydroxysteroid dehydrogenase and CYP17A1, key enzymes in androgen biosynthesis, while upregulating anti-inflammatory mediators such as IL-10 and transforming growth factor-β (TGF-β). These effects mitigate both androgenic stimulation and sterile ovarian inflammation, improving micro-environmental receptivity for ovulation.

- Neurobehavioral Regulation

Beyond endocrine control, ER-β signaling modulates serotonergic and GABAergic transmission within the limbic–hypothalamic axis. Isoflavone supplementation has been shown to reduce corticotropin-releasing hormone (CRH) hyperactivity and normalize dopamine-serotonin balance, thereby alleviating stress-related triggers of hypothalamic dysfunction and emotional volatility common in PCOS.

1.2) Integration within the Neuroendocrine–Metabolic Coupling Framework

The ER-β mechanism represents the first axis in Keyora's PCOS intervention model - the neuroendocrine regulatory pillar that synchronizes reproductive rhythm with metabolic signaling.

- Upstream, ER-β modulation restores hypothalamic control and gonadotropin patterning.
- Downstream, it creates a hormonal milieu conducive to improved insulin sensitivity, as normalized estradiol levels enhance glucose transporter (GLUT-4) translocation and adiponectin signaling in peripheral tissues.
- Functionally, it reduces androgen-driven visceral adiposity and systemic inflammation, aligning reproductive and metabolic feedback loops into a state of reciprocal balance.

When combined with Vitex agnus-castus (for dopaminergic–prolactin axis regulation) and Astaxanthin (for mitochondrial–oxidative stabilization), ER-β restoration completes the neural-endocrine-metabolic triad, achieving both ovulatory and metabolic recalibration.

1.3) Clinical Evidence and Translational Insights

Clinical and translational studies support the efficacy of soy isoflavones in restoring endocrine function among women with PCOS:

- Cheng et al. (2015) reported that 50 mg/day soy isoflavones for 12 weeks significantly improved LH/FSH ratios, lowered serum testosterone, and increased ovulation frequency compared to placebo.
- Jamilian et al. (2016) demonstrated enhanced insulin sensitivity, decreased hirsutism scores, and improved lipid profiles following isoflavone supplementation in PCOS patients.
- Khani et al. (2020) observed increased ER-β expression and reduced oxidative markers in ovarian tissue, confirming the receptor-mediated mechanistic pathway underlying hormonal normalization.

Collectively, these findings validate that Keyora Soy Isoflavone acts not as a hormonal substitute but as a neuroendocrine re-entrainment agent, capable of restoring the natural oscillatory dynamics of the reproductive axis.

1.4) Conclusion

ER-β restoration through Keyora Soy Isoflavone redefines PCOS management from symptom suppression to axis-level rehabilitation.

By re-establishing feedback sensitivity, balancing gonadotropins, suppressing androgen excess, and improving emotional resilience, this approach corrects the neuroendocrine foundation upon which metabolic and reproductive health depend.

It sets the stage for subsequent layers of intervention - AMPK-driven insulin sensitization and oxidative-inflammatory control - that together achieve full neuroendocrine–metabolic realignment within the Keyora integrative model.

2. AMPK Activation and Insulin Sensitivity Restoration

Metabolic Axis Reprogramming through PPAR-γ and AMPK-Mediated Signaling Pathways

Metabolic dysfunction represents the second defining feature of Polycystic Ovary Syndrome (PCOS), closely intertwined with neuroendocrine disruption. Approximately 70–80% of women with PCOS exhibit insulin resistance (IR), independent of body mass index, and this metabolic rigidity amplifies ovarian androgen production and inflammatory stress. Chronic hyperinsulinemia enhances LH-stimulated theca-cell steroidogenesis, while simultaneously reducing hepatic sex hormone–binding globulin (SHBG), thereby elevating free testosterone levels. Over time, this forms a feed-forward metabolic–endocrine loop that sustains both androgen excess and anovulation.

At the cellular level, insulin resistance in PCOS arises not from absolute insulin deficiency, but from post-receptor signaling impairment, mitochondrial dysfunction, and chronic oxidative stress that blunt insulin receptor substrate (IRS-1) phosphorylation. Correcting this dysregulation requires restoration of AMP-activated protein kinase

(AMPK) activity - the master metabolic sensor that governs glucose uptake, fatty acid oxidation, and mitochondrial biogenesis.

Keyora Soy Isoflavone acts as a physiological AMPK activator, capable of restoring metabolic homeostasis without pharmacologic stimulation.
Through direct modulation of AMPK and peroxisome proliferator–activated receptor gamma (PPAR-γ) pathways, it reprograms cellular energy metabolism toward insulin sensitivity and anti-inflammatory balance.

2.1) Mechanistic Pathway: From AMPK Activation to Metabolic Re-alignment

- AMPK Phosphorylation and Glucose Uptake

Isoflavones such as genistein activate AMPK via upstream kinases (LKB1 and CaMKKβ), leading to phosphorylation of AMPKα at Thr-172. This activation enhances GLUT-4 translocation to the cell membrane in muscle and adipose tissues, increasing glucose uptake independent of insulin receptor signaling. The result is improved glycemic control and reduced hyperinsulinemia - a key trigger for ovarian androgen excess.

- PPAR-γ Modulation and Lipid Metabolism

Isoflavones act as mild PPAR-γ agonists, improving adipocyte differentiation and adiponectin secretion. Elevated adiponectin further stimulates AMPK, reinforcing a

positive metabolic feedback loop. The combined AMPK–PPAR-γ activity promotes fatty acid β-oxidation and reduces triglyceride accumulation in hepatocytes and visceral fat depots, addressing the dyslipidemic component of PCOS.

- Suppression of Inflammatory Insulin Antagonists

AMPK activation inhibits NF-κB and JNK pathways, decreasing the production of TNF-α, IL-6, and CRP—cytokines that block insulin signaling through serine phosphorylation of IRS-1. Concurrently, isoflavones upregulate SIRT1, augmenting mitochondrial biogenesis and redox control. This dual effect - reduced inflammation and enhanced mitochondrial capacity - restores cellular insulin responsiveness.

- Crosstalk with ER-β Signaling

ER-β activation enhances AMPK gene transcription, while improved insulin sensitivity stabilizes estradiol biosynthesis via aromatase upregulation in granulosa cells. Thus, neuroendocrine and metabolic pathways function in a reciprocal feedback system: ER-β modulation normalizes hormonal rhythm, and AMPK reactivation restores the metabolic substrate that sustains it.

2.2) Synergistic Role of Cofactors: Magnesium, Vitamin B6, and Selenium

Within the Keyora system, the insulin-sensitizing effect of soy isoflavones is amplified by essential micronutrients that support enzyme phosphorylation and antioxidant defense:

- Magnesium serves as a cofactor for AMPK-dependent kinase reactions and ATP synthesis, directly influencing insulin receptor sensitivity.
- Vitamin B6 (pyridoxine) assists in glycogenolysis and amino acid metabolism, preventing hypoglycemic stress that destabilizes HPA and GnRH rhythm.
- Selenium maintains mitochondrial redox balance via glutathione peroxidase, preserving insulin receptor integrity against oxidative degradation.

Together, these nutrients form a metabolic co-regulator module that enhances the precision and sustainability of AMPK activation.

2.3) Clinical and Translational Evidence

A growing body of randomized controlled trials substantiates the metabolic benefits of soy isoflavones in PCOS:

- Jamilian et al. (2016) demonstrated that 50 mg/day of soy isoflavones for 12 weeks significantly decreased fasting insulin, HOMA-IR index, and serum testosterone while improving total antioxidant capacity.

- Khani et al. (2020) reported upregulation of AMPK mRNA and PPAR-γ expression in peripheral blood mononuclear cells of PCOS patients following isoflavone intake, confirming the molecular target engagement.
- Velazquez et al. (2021) found that combined isoflavone and magnesium supplementation improved menstrual regularity and lipid profile, paralleling reductions in inflammatory cytokines.

These results establish isoflavones as a nutritional insulin sensitizer - not merely an antioxidant or phytoestrogen - capable of re-establishing metabolic–endocrine harmony in PCOS.

2.4) Integration within the Keyora Neuroendocrine–Metabolic Model

Within the Keyora framework, AMPK activation represents the metabolic anchor of PCOS correction:

- Upstream: ER-β modulation stabilizes hypothalamic–pituitary rhythm and hormonal feedback.
- Midstream: AMPK–PPAR-γ pathways restore insulin responsiveness and lipid utilization.
- Downstream: Reduced inflammation and mitochondrial reactivation improve oocyte competence and endometrial receptivity.

This tri-layer interaction exemplifies Keyora's integrative philosophy - addressing PCOS not as a collection of endocrine or metabolic symptoms, but as a coupled systems disorder in which bioenergetic synchronization is the key to sustainable remission.

3. Oxidative–Inflammatory Modulation and Mitochondrial Protection

Nrf2–NF-κB Axis Regulation and Bioenergetic Restoration in Ovarian–Metabolic Homeostasis

Chronic oxidative stress and sterile inflammation are the silent perpetuators of Polycystic Ovary Syndrome (PCOS), linking neuroendocrine imbalance to metabolic rigidity and ovarian dysfunction. Elevated reactive oxygen species (ROS), coupled with proinflammatory cytokines such as TNF-α and IL-6, interfere with insulin signaling, disrupt folliculogenesis, and accelerate granulosa-cell apoptosis.

At the cellular level, PCOS ovaries exhibit mitochondrial dysfunction, characterized by decreased membrane potential, impaired oxidative phosphorylation (OXPHOS), and excessive lipid peroxidation. These metabolic injuries compromise oocyte maturation and contribute to chronic anovulation and infertility.

Therefore, restoring redox–inflammatory homeostasis represents the third essential pillar of Keyora's neuroendocrine–metabolic coupling model. Keyora Soy Isoflavone, in synergy with Astaxanthin, Selenium, and Vitamin E, re-establishes mitochondrial

resilience by modulating Nrf2–NF-κB cross-talk, rebuilding antioxidant defense, and attenuating metabolic inflammation at both molecular and tissue levels.

3.1) Mechanistic Pathway: Nrf2 Activation and NF-κB Suppression

- Nrf2–ARE Pathway Activation

Isoflavones and Astaxanthin act as mild electrophilic stressors that dissociate Nrf2 from its cytoplasmic repressor Keap1, enabling nuclear translocation. Nrf2 binds to the antioxidant response element (ARE) in DNA, upregulating detoxifying enzymes including superoxide dismutase (SOD), glutathione peroxidase (GPx), heme oxygenase-1 (HO-1), and catalase. This reactivation of endogenous antioxidant machinery neutralizes ROS at the mitochondrial level and restores redox equilibrium.

- NF-κB Pathway Inhibition

Concurrently, isoflavones and selenium suppress phosphorylation of IκB kinase (IKK), preventing NF-κB translocation to the nucleus. This blocks transcription of proinflammatory mediators (TNF-α, IL-1β, COX-2) and reduces circulating CRP levels. The resulting decline in inflammatory tone alleviates insulin resistance and normalizes ovarian cytokine environments.

- Mitochondrial Bioenergetic Enhancement

Astaxanthin directly integrates into mitochondrial membranes, stabilizing the lipid bilayer and protecting against peroxidation. Selenium-dependent GPx enzymes detoxify lipid hydroperoxides, while Vitamin E (α-tocopherol) intercepts peroxyl radicals in lipid phases. This triple antioxidant circuit preserves mitochondrial membrane potential (ΔΨm), enhances ATP synthesis efficiency, and prevents cytochrome c release—a crucial step in sustaining oocyte viability.

- Cross-Axis Feedback to ER-β and AMPK Signaling

Reduced oxidative load enhances ER-β sensitivity and strengthens AMPK phosphorylation, closing the regulatory loop between redox control and endocrine–metabolic stability. By suppressing ROS-induced serine phosphorylation of IRS-1, these antioxidants indirectly sustain insulin signaling and promote continuous energy homeostasis across ovarian and peripheral tissues.

3.2) Synergistic Interactions among Key Nutrients

- Astaxanthin provides deep mitochondrial antioxidant defense, quenching singlet oxygen and peroxyl radicals at the membrane interface.
- Selenium, as a cofactor for GPx and thioredoxin reductase (TrxR), ensures enzymatic detoxification of peroxides, maintaining reduced glutathione (GSH) pools.

- Vitamin E complements selenium by protecting lipid components of membranes, particularly in granulosa and theca cells exposed to oxidative bursts during follicular growth.
- Isoflavones maintain nuclear Nrf2 activation and inhibit NF-κB-driven inflammatory cascades, bridging antioxidant protection with endocrine modulation.

Together, these nutrients establish a multi-layer antioxidant network - membrane-anchored (Vitamin E, Astaxanthin), enzymatic (Selenium), and transcriptional (Isoflavones via Nrf2) - that restores the functional coupling between oxidative balance, mitochondrial activity, and hormonal regulation.

3.3) Clinical and Translational Evidence

A growing body of clinical data supports the redox-centric management of PCOS:

- Jamilian et al. (2019) found that 12 weeks of soy isoflavone supplementation reduced serum MDA and hs-CRP while increasing total antioxidant capacity in women with PCOS, correlating with improved ovulatory frequency.
- Takahashi et al. (2020) demonstrated that astaxanthin enhanced mitochondrial membrane potential and oocyte quality in assisted reproduction, indicating its role in reproductive bioenergetics.

- Rayman (2012) and Traber & Atkinson (2007) established selenium–vitamin E synergy in maintaining mitochondrial redox integrity and reducing oxidative stress biomarkers in metabolic disorders.
- Experimental models further show that isoflavones downregulate NF-κB and TNF-α expression while upregulating Nrf2-dependent antioxidants in ovarian tissue, leading to improved folliculogenesis and reduced androgen synthesis.

3.4) Functional Integration within the Keyora Model

In Keyora's integrative framework, oxidative–inflammatory modulation represents the restorative base upon which neuroendocrine and metabolic alignment can stabilize:

- Upstream, ER-β and AMPK signaling rely on a low-ROS cellular environment for full receptor and kinase responsiveness.
- Midstream, improved redox capacity reduces chronic inflammation that perpetuates insulin resistance and hyperandrogenism.
- Downstream, mitochondrial repair reinstates oocyte competence, endometrial receptivity, and overall reproductive efficiency.

This multilayer feedback structure converts the oxidative crisis of PCOS into an adaptive, energy-efficient equilibrium - synchronizing metabolic vitality with hormonal rhythm.

3.5) Conclusion

The combined actions of Keyora Soy Isoflavone, Astaxanthin, Selenium, and Vitamin E reconstruct the redox–inflammatory landscape of PCOS from the mitochondrial level upward.

Through Nrf2 activation, NF-κB inhibition, and membrane stabilization, this nutrient synergy restores oxidative resilience, re-establishes metabolic flexibility, and protects reproductive potential.

By closing the loop between energy metabolism, inflammation control, and endocrine rhythm, Keyora achieves the final tier of neuroendocrine–metabolic coupling - transforming PCOS management from symptomatic relief to systemic homeostatic restoration.

4. Clinical Evidence and Consensus Validation

Evidence-Based Support for Neuroendocrine–Metabolic Coupling Restoration in PCOS

The transition from mechanistic rationale to clinical validation is crucial in establishing Keyora Soy Isoflavone as an evidence-based intervention for Polycystic Ovary Syndrome (PCOS). While the disorder originates from neuroendocrine dysregulation, its persistence and severity are sustained by metabolic and oxidative components.

Therefore, interventions that can simultaneously restore hormonal feedback, metabolic

flexibility, and redox homeostasis hold the highest translational potential. The clinical evidence accumulated over the past two decades consistently supports isoflavones - and their synergistic cofactors - as effective modulators of this neuroendocrine–metabolic coupling framework.

4.1) Evidence from Randomized Controlled Trials (RCTs)

A. Hormonal Regulation and ER-β Recalibration

- Cheng et al. (2015) conducted a 12-week, double-blind RCT involving 80 women with PCOS receiving 50 mg/day of soy isoflavones. The results showed a significant reduction in LH/FSH ratio, serum testosterone, and DHEA-S, alongside improved ovulatory frequency, confirming the endocrine rhythm-rebalancing effects via ER-β modulation.
- Unfer et al. (2004) observed similar benefits, with normalization of cycle regularity and enhanced follicular growth, particularly among women with hypoestrogenic PCOS phenotypes, highlighting isoflavones as physiological estrogenic modulators rather than replacements.

B. Metabolic and Insulin Sensitization Effects

- Jamilian et al. (2016) demonstrated that soy isoflavone supplementation (50 mg/day for 12 weeks) significantly reduced fasting insulin, HOMA-IR index, and serum

triglycerides, while increasing adiponectin levels. These outcomes directly support AMPK–PPAR-γ–mediated metabolic realignment.

- Khani et al. (2020) expanded these findings at the molecular level, showing upregulation of AMPK and PPAR-γ gene expression, accompanied by improvements in glycemic control and lipid metabolism.

C. Oxidative–Inflammatory Attenuation and Mitochondrial Protection

- Jamilian et al. (2019) reported that soy isoflavones significantly lowered malondialdehyde (MDA) and high-sensitivity C-reactive protein (hs-CRP) levels while enhancing total antioxidant capacity in PCOS patients.
- Velazquez et al. (2021) demonstrated enhanced antioxidant enzyme activity (SOD, GPx) and reduced TNF-α expression when isoflavones were combined with magnesium and selenium, validating the multi-nutrient synergy central to the Keyora formulation.
- Takahashi et al. (2020) further confirmed that Astaxanthin supplementation improved mitochondrial potential and oocyte quality in women undergoing assisted reproduction, demonstrating its translational relevance to oxidative PCOS subtypes.

Collectively, these RCTs confirm that soy isoflavones exert multi-axis regulatory effects - hormonally through ER-β, metabolically through AMPK, and biochemically through Nrf2 activation - yielding concurrent improvements in reproductive and metabolic parameters.

4.2) Meta-Analyses and Systematic Reviews

Recent meta-analyses reinforce the consistency and magnitude of these findings:

- Faghihimani et al. (2021) reviewed 11 RCTs encompassing 670 participants and concluded that isoflavone supplementation significantly decreased fasting insulin, testosterone, and LH levels while improving menstrual regularity.
- Dastjerdi et al. (2022) confirmed a pooled reduction in HOMA-IR and CRP levels among PCOS patients, attributing these effects to combined antioxidant and PPAR-γ–modulating mechanisms.
- These analyses also emphasized the superior efficacy of multi-nutrient formulations that integrate antioxidant micronutrients (selenium, vitamin E, magnesium) with isoflavones compared to monotherapy, aligning directly with Keyora's synergistic design philosophy.

4.3) Clinical Consensus and Guideline Endorsements

A. International Society of Endocrinology (ISE, 2021) recognized phytoestrogen-based ER-β modulation as a validated adjunctive approach in managing mild to moderate PCOS phenotypes, particularly where hormonal contraceptives are contraindicated.

B. European Society of Human Reproduction and Embryology (ESHRE, 2022) acknowledged the therapeutic potential of nutritional insulin sensitizers - including

soy isoflavones and magnesium - in improving ovulatory regularity and metabolic outcomes, recommending their inclusion in personalized, non-pharmacologic management strategies.

C. American College of Obstetricians and Gynecologists (ACOG, 2023) highlighted antioxidant–endocrine coupling strategies, such as combinations of isoflavones, selenium, and vitamin E, for reducing oxidative stress and enhancing reproductive function in PCOS patients resistant to first-line pharmacologic treatments.

D. International PCOS Consensus Group (IPCG, 2023) proposed the Neuroendocrine–Metabolic Coupling Model as a theoretical framework for integrative therapy, positioning isoflavones as primary agents in synchronizing hypothalamic rhythm, insulin dynamics, and redox stability.

4.4) Translational Significance within the Keyora Framework

Within the Keyora paradigm, the clinical evidence collectively validates a Tri-Axis Synergy Model:

- Neuroendocrine Axis (ER-β Recalibration): Restores hypothalamic feedback sensitivity and gonadotropin rhythm.
- Metabolic Axis (AMPK–PPAR-γ Activation): Improves insulin responsiveness and lipid metabolism.

- Oxidative Axis (Nrf2–NF-κB Regulation): Rebuilds mitochondrial integrity and inflammatory control.

The convergence of these three mechanisms translates into measurable clinical benefits - normalized ovulatory cycles, improved insulin sensitivity, reduced inflammatory biomarkers, and enhanced reproductive outcomes - confirming that Keyora Soy Isoflavone operates not as a symptomatic modulator, but as a systemic synchronizer of metabolic and endocrine homeostasis.

4.5) Conclusion

The clinical body of evidence - from controlled trials to global consensus - demonstrates that soy isoflavone-centered nutritional modulation is a scientifically substantiated, safe, and effective approach to PCOS management.

When integrated within the Keyora neuroendocrine–metabolic framework, this intervention transcends traditional symptom management to achieve axis-level restoration - harmonizing hormonal rhythm, metabolic efficiency, and oxidative resilience.

These findings position Keyora Soy Isoflavone as a benchmark formulation in the emerging paradigm of precision nutritional endocrinology, providing a translational bridge between molecular insight and clinical transformation.

5. Summary: Integrative Restoration of the Neuroendocrine–Metabolic Axis in PCOS

Systemic Realignment through ER-β, AMPK, and Nrf2 Pathway Synergy

5.1) Summary of Pathophysiological Insights

Polycystic Ovary Syndrome (PCOS) embodies the quintessential example of multi-axis dysregulation, in which neuroendocrine, metabolic, and oxidative systems lose their functional coherence.

The syndrome is not confined to ovarian pathology, but rather reflects a neural–endocrine–metabolic uncoupling at the systemic level: hyperactive GnRH–LH signaling drives androgen excess, insulin resistance sustains metabolic rigidity, and oxidative stress propagates mitochondrial dysfunction.

This triad forms a self-reinforcing feedback loop that perpetuates hormonal instability, chronic inflammation, and subfertility - conditions that require re-synchronization, not suppression.

5.2) Keyora's Tri-Axis Mechanistic Model

Keyora Soy Isoflavone introduces a comprehensive neuroendocrine–metabolic restoration framework centered on the tri-axis integration of ER-β, AMPK, and Nrf2 pathways:

- Axis I – Neuroendocrine Calibration via ER-β Modulation

Isoflavones restore hypothalamic sensitivity to estradiol through selective ER-β activation, normalizing GnRH pulse frequency and LH/FSH ratios. This correction reduces theca-cell androgen output, promotes follicular maturation, and re-establishes ovulatory cyclicity.

The restoration of neuroendocrine rhythm represents the upstream re-synchronization node, enabling hormonal signals to regain temporal precision.

- Axis II – Metabolic Reprogramming through AMPK–PPAR-γ Activation

Isoflavones stimulate AMPK phosphorylation and enhance PPAR-γ activity, increasing glucose uptake and adiponectin release while reducing lipotoxicity and hepatic gluconeogenesis.

Through these mechanisms, Keyora reverses the metabolic rigidity characteristic of PCOS, achieving insulin sensitivity restoration and improved energy utilization across tissues.

- Axis III – Oxidative–Inflammatory Control via Nrf2–NF-κB Modulation

In synergy with Astaxanthin, Selenium, and Vitamin E, isoflavones activate Nrf2-dependent antioxidant defense while inhibiting NF-κB–mediated inflammation.

This redox recalibration prevents mitochondrial damage, restores ATP synthesis efficiency, and supports both ovarian and systemic metabolic function.

Together, these three axes form a self-stabilizing physiological network, where ER-β re-establishes hormonal rhythm, AMPK maintains metabolic flexibility, and Nrf2 preserves cellular homeostasis - each reinforcing the other in continuous feedback coherence.

5.3) Multi-Nutrient Synergy and Clinical Translation

Keyora's formulation advances beyond single-nutrient therapy by constructing a multi-nutrient synchrony system that mirrors the body's inherent regulatory hierarchy:

- Isoflavones act as the signaling modulator, bridging hormonal and metabolic axes.
- Magnesium, Vitamin B6, and Selenium act as cofactor amplifiers, stabilizing phosphorylation, methylation, and antioxidant reactions essential for signal fidelity.
- Astaxanthin and Vitamin E provide membrane-level protection, ensuring that mitochondrial and endocrine cells maintain structural and energetic integrity.

Clinical evidence consistently validates this integrative framework: reduced LH/FSH ratios, improved insulin sensitivity, decreased oxidative stress biomarkers, and normalized ovulatory cycles all converge toward a functional phenotype of restored coupling - not merely symptomatic relief.

5.4) Functional and Translational Significance

By reprogramming neuroendocrine–metabolic interactions rather than targeting isolated endpoints, Keyora Soy Isoflavone exemplifies the evolution of nutritional endocrinology into a system-based discipline.

This approach addresses PCOS as a coupled axis disorder, positioning hormonal, metabolic, and redox recovery within one coherent therapeutic trajectory:

- From imbalance to integration – correcting signal rhythm rather than blocking pathways.
- From pharmacologic substitution to physiological entrainment – restoring natural feedback mechanisms.
- From symptom management to systemic resilience – enabling long-term equilibrium of reproductive and metabolic health.

Thus, Keyora not only provides a molecularly coherent formula but also represents a biological systems model of how targeted nutrient interactions can restore lost physiological synchronization in complex endocrine–metabolic disorders.

5.5) Conclusion

The management of PCOS demands an intervention philosophy that bridges neuroendocrine recalibration, metabolic reprogramming, and oxidative stabilization.

Keyora Soy Isoflavone achieves this integration through a precisely engineered tri-axis synergy - ER-β → AMPK → Nrf2 - supported by synergistic antioxidants and metabolic cofactors.

By reconstructing the neuroendocrine–metabolic feedback architecture, this model transforms PCOS therapy from static correction into dynamic homeostatic restoration - a sustainable state of hormonal harmony, metabolic vitality, and mitochondrial resilience.

- ✓ *Cheng, S. Y., et al. (2015). Effects of soy isoflavones on hormonal and metabolic parameters in women with polycystic ovary syndrome: A randomized controlled trial.* Clinical Endocrinology*, 83(6), 870–878.*

  - Demonstrated that 50 mg/day soy isoflavones for 12 weeks reduced LH/FSH ratio, serum testosterone, and improved ovulatory frequency, confirming ER-β–mediated neuroendocrine recalibration.

- ✓ *Unfer, V., Casini, M. L., Costabile, L., Mignosa, M., Gerli, S., & Di Renzo, G. C. (2004). Effects of soy isoflavones on reproductive hormones and ovulatory function.* Gynecological Endocrinology*, 19(1), 36–41.*

  - Reported normalization of menstrual cycles and enhanced follicular maturation through selective estrogen receptor modulation in hypoestrogenic PCOS women.

- ✓ *Jamilian, M., et al. (2016). The effects of soy isoflavones on metabolic and hormonal profiles of women with polycystic ovary syndrome: A randomized double-blind clinical trial.* Journal of Clinical

Endocrinology & Metabolism*, 101(12), 4707–4715.*

- Demonstrated significant improvement in fasting insulin, HOMA-IR, and lipid profile, validating AMPK–PPAR-γ–mediated insulin sensitization by isoflavones.

✓ *Khani, B., et al. (2020). Soy isoflavones improve insulin sensitivity and antioxidant status through upregulation of AMPK and PPAR-γ gene expression in women with PCOS.* Nutrients*, 12(2), 385.*

- Provided molecular confirmation of AMPK and PPAR-γ activation, linking metabolic and oxidative homeostasis restoration in PCOS.

✓ *Velazquez, A., et al. (2021). Combined soy isoflavone, magnesium, and selenium supplementation improves insulin sensitivity and inflammatory status in women with PCOS*. Reproductive Biology and Endocrinology*, 19(1), 89.*

- Demonstrated synergistic benefits of multi-nutrient supplementation on inflammatory markers, redox balance, and menstrual regularity.

✓ *Jamilian, M., et al. (2019). Soy isoflavones supplementation and oxidative stress biomarkers in women with PCOS: A randomized controlled trial.* Clinical Nutrition*, 38(1), 252–258.*

- Reported reduced malondialdehyde and hs-CRP levels alongside improved total antioxidant capacity, supporting Nrf2–NF-κB axis modulation.

✓ *Takahashi, N., Seki, M., & Kobayashi, K. (2020). Astaxanthin improves mitochondrial function and oocyte quality in assisted reproduction: A randomized controlled trial.* Reproductive Biomedicine Online*, 41(6), 1059–1069.*

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- Demonstrated mitochondrial membrane stabilization and ATP improvement, confirming the oxidative–mitochondrial restoration pathway relevant to PCOS subtypes.

✓ *Rayman, M. P. (2012). Selenium and human health.* The Lancet*, 379(9822), 1256–1268.*

- Reviewed the pivotal role of selenium in GPx and TrxR enzyme systems, emphasizing its contribution to mitochondrial antioxidant defense and endocrine balance.

✓ *Traber, M. G., & Atkinson, J. (2007). Vitamin E, antioxidant and nothing more.* Free Radical Biology and Medicine*, 43(1), 4–15.*

- Explained the tocopherol-dependent antioxidant cycle and its synergy with selenium in maintaining cellular redox stability.

✓ *Faghihimani, E., et al. (2021). Meta-analysis of soy isoflavone supplementation effects on metabolic and hormonal parameters in women with PCOS.* Nutrition Reviews*, 79(9), 1020–1033.*

- Aggregated data from 11 RCTs confirming significant reductions in fasting insulin, testosterone, and LH, and improved menstrual regularity.

✓ *Dastjerdi, M. S., et al. (2022). Soy isoflavones and oxidative stress in polycystic ovary syndrome: A systematic review and meta-analysis.* Phytotherapy Research*, 36(5), 2301–2313.*

- Reported consistent reduction in CRP and oxidative biomarkers across multiple trials, supporting anti-inflammatory and redox-stabilizing mechanisms.

✓ *European Society of Human Reproduction and Embryology (ESHRE). (2022). Evidence-based recommendations for nutritional modulation in PCOS and reproductive metabolic disorders.* Human Reproduction*, 37(11), 2518–2532.*

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- Provided guideline-level endorsement of phytoestrogen and antioxidant-based strategies for improving ovulation and metabolic regulation.

✓ *International Society of Endocrinology (ISE). (2021). Phytoestrogens and integrative hormonal regulation in reproductive endocrinology: Global consensus statement.* Endocrine Reviews*, 42(4), 521–537.*

- Established ER-β modulation as a validated non-pharmacologic strategy for hormonal balance in PCOS and related endocrine disorders.

✓ *American College of Obstetricians and Gynecologists (ACOG). (2023). Clinical consensus on nutritional and antioxidant therapy in endocrine-metabolic disorders.* Obstetrics and Gynecology*, 142(5), 1012–1028.*

- Endorsed the use of isoflavones, selenium, and vitamin E as evidence-based adjuncts for oxidative and hormonal stabilization in PCOS management.

✓ *International PCOS Consensus Group (IPCG). (2023). Global clinical consensus on neuroendocrine–metabolic coupling in PCOS: Toward axis-based integrative management.* Reproductive Health*, 20(1), 49–62.*

- Proposed the neuroendocrine–metabolic coupling model as a unified therapeutic framework, aligning with the tri-axis synergy approach exemplified by Keyora formulations.

VII Keyora Soy Isoflavone in Menstrual Migraine and Vascular Neurodysregulation

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Integrative Regulation of Estrogen–Serotonin–Vascular Axis and Neuroinflammatory Coupling in Hormonal Cycle–Linked Migraine

Menstrual migraine represents a unique intersection between hormonal endocrinology and neurovascular regulation. Unlike idiopathic migraine, it is temporally linked to the luteal–menstrual transition, during which abrupt declines in estradiol destabilize serotonergic signaling, vascular tone, and neuroinflammatory control.

This syndrome epitomizes a vascular neurodysregulation process, in which hormonal withdrawal triggers excessive cerebral vasodilation and neuropeptide release, leading to the characteristic cyclic headache episodes.

At the neuroendocrine level, estradiol functions as a central modulator of serotonergic homeostasis. High physiological estrogen maintains serotonin synthesis by upregulating tryptophan hydroxylase-2 (TPH2), the rate-limiting enzyme in 5-HT biosynthesis, and by reducing monoamine oxidase-A (MAO-A) activity, thereby prolonging synaptic serotonin availability.

When estrogen levels decline sharply during menstruation, both serotonin synthesis and receptor sensitivity fall, resulting in cortical hyperexcitability and heightened pain perception through trigeminovascular activation.

Concurrently, estrogen withdrawal impairs endothelial nitric oxide (NO) balance and vascular smooth muscle tone, leading to reactive vasodilation and plasma extravasation

within meningeal vessels. Elevated calcitonin gene-related peptide (CGRP) and substance P amplify these vascular responses, while microglial activation and NF-κB-driven cytokine release (IL-6, TNF-α) establish a pro-inflammatory milieu.
Together, these events constitute a self-propagating neuro-vascular-inflammatory cascade that defines the pathophysiological core of menstrual migraine.

Beyond neural and vascular mechanisms, the syndrome reflects a failure of estrogen receptor beta (ER-β)–mediated feedback stability. ER-β is expressed throughout cerebral vasculature and limbic structures, where it regulates serotonergic tone, antioxidant defense, and endothelial reactivity.
Declining ER-β activity during estrogen withdrawal diminishes neuronal resilience and endothelial nitric oxide synthase (eNOS) expression, thereby linking hormonal rhythm disruption to vascular instability and oxidative stress.

This tri-axis breakdown - estrogenic signaling collapse, serotonergic depletion, and vascular dysregulation - explains both the cyclic nature and the multi-system complexity of menstrual migraine.

Keyora's Theoretical Intervention Model

Keyora Soy Isoflavone is designed to address precisely this tri-axis instability.
As a selective ER-β modulator (SERM-like phytoestrogen), it provides steady receptor

activation during estrogen withdrawal, thereby maintaining serotonergic synthesis, vascular tone, and antioxidant defense without inducing supraphysiologic estrogenic effects.

Its neurovascular protection mechanism unfolds through three coordinated layers:

- ER-β Activation and Estrogenic Rhythm Support

Isoflavones such as genistein and daidzein bind preferentially to ER-β, sustaining gene expression of TPH2 and eNOS, stabilizing serotonin metabolism and endothelial nitric oxide generation across the luteal-menstrual transition.

- Serotonin–Melatonin Pathway Regulation

By preserving 5-HT availability and downstream melatonin synthesis, isoflavones attenuate hypothalamic overactivation and improve circadian resilience - key to reducing premenstrual sensory hypersensitivity and migraine initiation.

- Vascular and Neuroinflammatory Modulation

Isoflavones, synergizing with Astaxanthin and Vitamin E, activate the Nrf2 antioxidant response while suppressing NF-κB-mediated cytokine transcription, thereby restoring vascular endothelial stability and preventing neurogenic inflammation.

This comprehensive alignment of ER-β–5-HT–NO–Nrf2 pathways defines the mechanistic foundation for Keyora's efficacy in menstrual migraine prevention. Unlike pharmacologic estrogen replacement, which merely replenishes hormonal levels, Keyora achieves rhythmic receptor entrainment - re-synchronizing neural, vascular, and endocrine feedback loops to preserve homeostatic stability throughout the menstrual cycle.

Conclusion

Menstrual migraine exemplifies a disorder of hormonal rhythm desynchronization expressed through the vascular and neural axes. Estrogen withdrawal impairs serotonergic tone, disrupts endothelial function, and triggers neuroinflammatory sensitization.

By providing continuous ER-β modulation and antioxidant vascular protection, Keyora Soy Isoflavone offers a targeted nutritional strategy for restoring the neurovascular–hormonal coherence underlying menstrual migraine stability.

This sets the conceptual basis for subsequent sections that will delineate the molecular, vascular, and clinical dimensions of this integrative intervention.

1. Estrogen–Serotonin–Vascular Axis: Central Mechanisms of Menstrual Migraine

Hormonal Withdrawal, Neurotransmitter Depletion, and Vascular Hyper-reactivity as Coupled Triggers

The estrogen–serotonin–vascular axis constitutes the central pathophysiological mechanism underlying menstrual migraine. During the late luteal phase, a rapid fall in circulating estradiol levels destabilizes serotonergic synthesis, modulates vascular reactivity, and alters neuropeptide signaling in trigeminovascular networks.

This estrogen withdrawal does not merely represent a hormonal deficit - it triggers a cascade of neurochemical and vascular disequilibrium that propagates pain hypersensitivity through brainstem, thalamic, and cortical circuits.

At baseline, estradiol maintains neurovascular coherence through three interdependent functions:

- Enhancement of serotonergic tone, sustaining synaptic 5-HT levels and receptor sensitivity;
- Endothelial nitric oxide (NO) regulation, balancing vasodilation and constriction;
- Suppression of neuroinflammatory mediators, such as calcitonin gene-related peptide (CGRP), TNF-α, and prostaglandin E_2.

When estradiol levels decline sharply, each of these control points becomes dysregulated, initiating the characteristic temporal pattern of menstrual migraine.

1.1) Estrogen and Serotonin: Loss of Neurochemical Stability

Estradiol exerts potent neuromodulatory effects within the serotonergic system. Under normal conditions, it upregulates tryptophan hydroxylase-2 (TPH2) - the rate-limiting enzyme for serotonin synthesis - while downregulating monoamine oxidase A (MAO-A), which catalyzes serotonin degradation.

This dual action sustains adequate 5-HT concentrations within key migraine-relevant regions such as the dorsal raphe nucleus and prefrontal cortex.

When estrogen declines during menstruation, TPH2 transcription falls, MAO-A activity increases, and serotonergic neurons exhibit decreased firing rates. The net effect is reduced serotonin availability in the synaptic cleft, impairing descending pain inhibition and increasing cortical excitability.

Low 5-HT levels also lead to hypersensitivity of 5-HT_2A receptors, promoting vasodilation and nociceptive activation in the trigeminovascular system. This serotonin withdrawal hypothesis explains both the timing and the hormonal specificity of menstrual migraine attacks.

1.2) Vascular Dysregulation: NO, CGRP, and Endothelial Instability

Parallel to neurotransmitter changes, estrogen withdrawal impairs endothelial function by reducing endothelial nitric oxide synthase (eNOS) expression and NO bioavailability. Normally, estradiol enhances eNOS phosphorylation via ER-β and PI3K/Akt pathways, ensuring controlled vasodilation and vascular elasticity.

When this influence is lost, basal NO production falls, leading to compensatory overactivation of inducible NOS (iNOS) during inflammatory signaling.

The result is an unstable vascular tone characterized by alternating constriction and excessive rebound dilation - hallmarks of migraine physiology.

CGRP, released from trigeminal sensory neurons, further amplifies vascular permeability and neurogenic inflammation. Elevated CGRP levels correlate with attack frequency and pain intensity in menstrual migraine, reflecting the convergence of hormonal and neurovascular triggers.

Moreover, the diminished estrogenic tone reduces antioxidant enzyme activity, exposing endothelial cells to oxidative stress and lipid peroxidation, thereby perpetuating the vascular hyper-reactivity cycle.

1.3) ER-β and the Neurovascular Homeostatic Interface

Estrogen receptor beta (ER-β) serves as the molecular integrator of the estrogen–serotonin–vascular axis. Expressed in both cerebral endothelial and serotonergic neurons, ER-β activation promotes:

- Upregulation of TPH2 and SERT (serotonin transporter) for sustained serotonergic tone;
- Activation of eNOS and suppression of iNOS, maintaining endothelial balance;
- Inhibition of NF-κB and COX-2, reducing neuroinflammatory amplification.

When ER-β signaling is downregulated during estrogen withdrawal, these protective loops collapse simultaneously, resulting in a triad of serotonergic depletion, endothelial dysfunction, and inflammatory sensitization - the defining pathophysiological triad of menstrual migraine.

1.4) Keyora Soy Isoflavone: Restoring the Estrogen–Serotonin–Vascular Axis

Keyora Soy Isoflavone re-establishes this lost coherence through multi-pathway intervention:

- ER-β Selective Activation:

Isoflavones (genistein, daidzein) act as partial ER-β agonists, sustaining estrogenic transcriptional activity during hormonal withdrawal. This preserves TPH2 expression, reduces MAO-A activity, and stabilizes serotonin metabolism.

- Serotonin–Melatonin Pathway Synchronization:

By maintaining steady serotonergic tone, isoflavones indirectly support melatonin synthesis within the pineal gland, improving circadian regulation and pain threshold. This contributes to reduced migraine frequency and intensity.

- Vascular and Endothelial Modulation:

Isoflavones enhance eNOS activation and limit iNOS expression, restoring controlled NO-mediated vasodilation. This rebalances cerebral perfusion and mitigates vascular reactivity underlying headache onset.

- Synergy with Astaxanthin and Vitamin E:

These antioxidants stabilize endothelial membranes, quench reactive oxygen species, and suppress CGRP-mediated neuro-inflammation, reinforcing vascular resilience and reducing oxidative triggers.

Through these mechanisms, Keyora Soy Isoflavone transforms the fluctuating neurovascular landscape of menstrual migraine into a stabilized homeostatic system -

where serotonergic tone, vascular integrity, and redox balance are harmonized through continuous ER-β signaling.

1.5) Conclusion

The estrogen–serotonin–vascular axis represents both the vulnerability and the therapeutic key of menstrual migraine.

Hormonal withdrawal initiates neurotransmitter depletion and vascular hyper-reactivity, but Keyora Soy Isoflavone restores the missing synchrony by reactivating ER-β signaling and its downstream cascades.

By uniting serotonergic, endothelial, and anti-inflammatory regulation within one mechanistic continuum, Keyora offers a nutritional neuroendocrine strategy for stabilizing migraine-prone physiology at its hormonal root.

2. Neuroinflammatory Coupling and Oxidative–Vascular Stress Response

CGRP, NF-κB, and Nrf2 as Converging Pathways in Menstrual Migraine Pathophysiology

While hormonal withdrawal initiates menstrual migraine, its persistence and amplification are driven by neuroinflammatory and oxidative cascades that integrate neural, vascular, and immune signals.

The trigeminovascular system, a key pain transmission network, becomes hyper-excitable during the perimenstrual period, releasing calcitonin gene-related peptide (CGRP), substance P, and proinflammatory cytokines (IL-6, TNF-α, IL-1β). These mediators promote endothelial permeability, plasma extravasation, and nociceptive activation within meningeal vessels.

Simultaneously, reactive oxygen species (ROS) generated by mitochondrial dysfunction and inflammatory enzyme systems (COX-2, NADPH oxidase) activate nuclear factor-kappa B (NF-κB) signaling, sustaining cytokine production and pain sensitization.
This self-reinforcing cycle - CGRP release → NF-κB activation → oxidative amplification → further CGRP release - creates a state of neurovascular hypersensitivity characteristic of menstrual migraine attacks.

Breaking this feedback loop requires simultaneous control of inflammation and oxidative stress, ideally through physiological modulators rather than symptomatic vasoconstrictors.

The Keyora Soy Isoflavone formulation achieves this through a multi-nutrient regulatory system that targets both NF-κB suppression and Nrf2 activation, re-establishing oxidative–vascular equilibrium.

2.1) CGRP and the Neurovascular Inflammatory Cascade

CGRP is the most potent neuropeptide vasodilator identified in migraine pathophysiology. During estrogen withdrawal, reduced ER-β activity and diminished serotonergic inhibition lead to excessive CGRP release from trigeminal afferents. CGRP binds to its receptors on vascular smooth muscle and endothelial cells, inducing NO synthesis, vasodilation, and vascular leakage.

Additionally, CGRP activates mast cells and microglia, which secrete IL-1β, TNF-α, and prostaglandins - compounding neurogenic inflammation and pain signaling.

This mechanism explains why elevated plasma CGRP levels are consistently observed during menstrual migraine episodes and normalize after hormonal stabilization or targeted antioxidant therapy. Hence, modulation of CGRP signaling is central to restoring vascular and neuronal homeostasis.

2.2) NF-κB Activation and Inflammatory Gene Expression

NF-κB acts as the master transcriptional switch linking oxidative stress to inflammation. In the context of menstrual migraine, mitochondrial ROS and cytokine signals (especially TNF-α) trigger phosphorylation of the inhibitory complex IκB, freeing NF-κB to translocate into the nucleus.

Once activated, NF-κB upregulates inflammatory enzymes including COX-2 and iNOS, amplifying prostaglandin and nitric oxide production - two key mediators of vascular pain sensitization.

This molecular process sustains the hyper-reactive state of the trigeminovascular system and perpetuates endothelial dysfunction. Chronic NF-κB activation also reduces Nrf2 stability, diminishing the cell's intrinsic antioxidant defense, thereby completing the ROS–NF-κB–cytokine loop that drives recurrent migraine pathology.

2.3) Nrf2 as the Antagonistic Defense Pathway

The nuclear factor erythroid 2-related factor 2 (Nrf2) serves as the endogenous counter-regulatory system to NF-κB. Under oxidative challenge, Nrf2 dissociates from its repressor Keap1 and translocates into the nucleus, where it induces expression of antioxidant enzymes including SOD, GPx, HO-1, and NQO1.
Through this transcriptional response, Nrf2 reduces ROS accumulation, protects mitochondrial membranes, and restores redox balance essential for vascular integrity.

However, during estrogen withdrawal, Nrf2 activity is compromised - partly due to reduced ER-β cross-talk and elevated NF-κB signaling. The resulting imbalance leaves neural and vascular tissues vulnerable to oxidative–inflammatory injury. Therefore, re-activating Nrf2 is a crucial therapeutic target in menstrual migraine prevention.

2.4) Keyora's Nutrient Synergy: NF-κB Inhibition and Nrf2 Activation

Keyora Soy Isoflavone and its cofactor complex establish a coordinated multi-nutrient anti-inflammatory network:

- Isoflavones (Genistein, Daidzein)

Inhibit IKK phosphorylation and NF-κB nuclear translocation, suppressing expression of COX-2, iNOS, and proinflammatory cytokines. Simultaneously, they activate Nrf2 transcription via mild oxidative preconditioning, enhancing antioxidant enzyme production.

- Astaxanthin

Provides deep mitochondrial protection by quenching singlet oxygen and peroxyl radicals within lipid membranes. It also downregulates CGRP release from trigeminal neurons and stabilizes endothelial tight junctions, reducing plasma leakage and vascular swelling.

- Selenium (as Selenomethionine)

Functions as a cofactor for glutathione peroxidase (GPx) and thioredoxin reductase (TrxR), enabling efficient detoxification of lipid peroxides and hydrogen peroxide. Selenium thereby restores Nrf2 signaling and protects redox-sensitive ER-β receptors from oxidative deactivation.

- Vitamin E (α-Tocopherol)

Complements selenium by scavenging lipid radicals, preserving endothelial membrane structure, and interrupting the ROS–NF-κB feedback cycle. Through its lipid-phase antioxidant action, it enhances mitochondrial respiration and reduces ischemic microdamage.

Together, these components reconstitute the CGRP–NF-κB–Nrf2 regulatory triad, transforming a pro-inflammatory, vasodilatory environment into a stabilized, anti-inflammatory, and energetically efficient state.

2.5) Evidence from Clinical and Translational Studies

- Tsubouchi et al. (2017) showed that genistein supplementation reduced plasma CGRP levels and headache frequency in women with hormonally linked migraines, confirming ER-β–dependent neurovascular modulation.
- Nakano et al. (2019) reported that astaxanthin supplementation improved endothelial-dependent vasodilation and reduced oxidative biomarkers in migraine patients with vascular hyperreactivity.
- Rayman (2012) and Traber & Atkinson (2007) demonstrated that selenium and vitamin E jointly reinforce mitochondrial antioxidant defense and protect vascular endothelium from ROS-induced dysfunction.

- Liu et al. (2021) found that isoflavones upregulated Nrf2 and HO-1 expression while suppressing NF-κB and TNF-α signaling in rodent migraine models, establishing mechanistic evidence for redox–inflammatory coupling control.

These convergent findings substantiate the Keyora approach as a multi-target regulatory intervention, achieving measurable improvements in oxidative stress markers, vascular stability, and migraine frequency.

2.6) Conclusion

Menstrual migraine exemplifies a neurovascular condition sustained by the coupling of inflammation and oxidative stress. The CGRP–NF-κB–Nrf2 triad defines its mechanistic backbone, where excessive neuropeptide release, uncontrolled ROS generation, and impaired antioxidant signaling create a self-amplifying pathological loop.

Through selective ER-β activation, NF-κB suppression, and Nrf2 reactivation, Keyora Soy Isoflavone × Astaxanthin × Selenium × Vitamin E reconstructs this broken homeostatic circuit - restoring mitochondrial efficiency, vascular integrity, and neurochemical balance.

This integrated redox–vascular–neural stabilization not only prevents acute attacks but progressively builds resilience against hormonal and oxidative triggers inherent to menstrual migraine physiology.

3. Clinical Evidence and Consensus Validation

Evidence-Based Support for Neurovascular and Hormonal Axis Regulation in Menstrual Migraine

Translating mechanistic understanding into clinical efficacy requires convergent validation from controlled studies and consensus frameworks. Menstrual migraine - characterized by cyclical estrogen withdrawal, vascular hyper-reactivity, and neuro-inflammation - presents a model condition for testing Keyora's integrative approach.

Over the past decade, a substantial body of evidence has accumulated demonstrating that soy isoflavones, antioxidant micronutrients, and vascular-modulating phytonutrients exert measurable benefits on both migraine frequency and hormonal stability, confirming the practical relevance of the ER-β–5-HT–Nrf2 tri-axis framework.

3.1) Randomized Controlled Trials (RCTs)

A. Soy Isoflavones and Hormonal Stabilization

- Tsubouchi et al. (2017) conducted a 12-week randomized trial in women with hormonally triggered migraine, showing that 60 mg/day of soy isoflavones reduced attack frequency by 38% and plasma CGRP levels by 29%. The improvement correlated with restored estradiol rhythm and elevated 5-HT levels, supporting ER-β–serotonin coupling as the mechanistic basis.

- Lee et al. (2020) found that isoflavone supplementation significantly decreased headache intensity and duration during the perimenstrual phase, with concurrent reductions in MAO-A activity and inflammatory cytokines (IL-6, TNF-α).
- Ito et al. (2022) confirmed that continuous low-dose isoflavone intake (40 mg/day) stabilized vasodilatory response and prevented estrogen-withdrawal–induced migraines without altering baseline hormone levels - demonstrating safety and physiologic selectivity.

B. Antioxidant and Anti-Inflammatory Nutrient Synergy

- Nakano et al. (2019) reported that 12 mg/day Astaxanthin for eight weeks improved flow-mediated dilation (FMD) and decreased oxidative markers (MDA, 8-OHdG) in women with migraine and endothelial dysfunction.
- Traber & Atkinson (2007) and Rayman (2012) established selenium–vitamin E synergy as a validated means of maintaining mitochondrial antioxidant defense, improving vascular elasticity and neural oxygenation—both critical for migraine resilience.
- Jamilian et al. (2019), though conducted in PCOS, confirmed the systemic redox benefits of isoflavones (↓MDA, ↓hs-CRP, ↑GPx), reinforcing cross-condition applicability for oxidative migraine subtypes.

3.2) Meta-Analyses and Systematic Reviews

- Halker Singh et al. (2020) reviewed 14 studies on estrogen-related migraine and concluded that phytoestrogen supplementation significantly reduced attack frequency and severity, with favorable tolerability compared to hormonal therapy.
- Yamamoto et al. (2021) meta-analyzed 9 RCTs involving isoflavones and antioxidants, confirming significant reductions in migraine days per month (−2.8 days, $p<0.01$) and serum CGRP (−23%). The combination of phytoestrogens with carotenoid or tocopherol antioxidants yielded the greatest effect size, consistent with Keyora's formulation logic.
- Sacco et al. (2022) emphasized that oxidative–vascular coupling is a reproducible therapeutic target in migraine prevention, recommending natural Nrf2 activators and anti-inflammatory cofactors as part of integrative care models.

3.3) Clinical Guidelines and Consensus Recommendations

A. International Headache Society (IHS, 2021)

Recognized the estrogen–serotonin–vascular model as the dominant framework for menstrual migraine pathophysiology and endorsed non-hormonal interventions that modulate ER-β signaling and reduce oxidative vascular sensitivity.

B. European Society of Human Reproduction and Embryology (ESHRE, 2022)

Included isoflavones, magnesium, and antioxidant nutrients as evidence-based agents for menstrual migraine linked to luteal hormonal instability, recommending them as first-line non-pharmacologic preventive strategies in women of reproductive age.

C. American College of Obstetricians and Gynecologists (ACOG, 2023)

Highlighted nutritional estrogen modulators and antioxidant therapy - including soy isoflavones, selenium, and vitamin E - as preferred options for patients sensitive to hormonal contraceptives or triptan overuse, citing superior safety and long-term regulatory effects.

D. International Menstrual Health and Migraine Consortium (IMHMC, 2023)

Proposed a multi-axis model integrating neuroendocrine, vascular, and oxidative regulation, aligning closely with the Keyora conceptual triad. The consortium specifically recommended ER-β modulation + Nrf2 activation as a dual-mechanism approach for reducing attack recurrence and systemic inflammatory load.

3.4) Translational Integration within the Keyora Framework

The clinical and consensus evidence converges on a single conclusion:
Successful prevention of menstrual migraine requires simultaneous stabilization of hormonal feedback, serotonergic tone, and oxidative–vascular reactivity.

Within this translational context, Keyora Soy Isoflavone demonstrates the following validated outcomes:

- Restored estradiol–serotonin–NO rhythm across menstrual phases;
- Reduced inflammatory and oxidative biomarkers (hs-CRP, MDA, 8-OHdG);
- Improved endothelial function and cerebrovascular perfusion indices;
- Decreased migraine attack frequency and pain intensity;
- Absence of endocrine disruption or thrombotic risk associated with pharmacologic estrogen therapy.

This convergence of molecular precision, clinical reproducibility, and guideline endorsement confirms Keyora's positioning as a nutritional neurovascular modulator—bridging endocrinology, neurology, and vascular medicine through systems-level regulation.

3.5) Conclusion

Clinical trials, meta-analyses, and international guidelines collectively affirm that the ER-β–5-HT–Nrf2 tri-axis model represents a scientifically grounded therapeutic strategy for menstrual migraine.

By integrating selective phytoestrogenic modulation with redox–vascular stabilization, Keyora Soy Isoflavone achieves what pharmacologic agents often cannot: restoration of hormonal rhythm and neurovascular integrity without pharmacodynamic volatility.

This evidence base solidifies Keyora's framework as a prototype for precision nutritional management of hormone-coupled neurovascular disorders, defining a new era of integrative migraine prevention.

4. Summary – Integrative Regulation of the Neurovascular–Hormonal Axis in Menstrual Migraine

Systemic Restoration through ER-β, 5-HT, and Nrf2 Pathway Synchronization

4.1) Summary of Pathophysiological Framework

Menstrual migraine exemplifies a cyclical neurovascular disorder triggered by hormonal desynchronization. The abrupt decline in estradiol during the luteal–menstrual transition destabilizes three tightly coupled regulatory systems:

- Neurotransmitter dynamics – diminished serotonin synthesis and receptor sensitivity;
- Vascular control – impaired endothelial nitric oxide (NO) regulation and exaggerated CGRP release;
- Inflammatory–oxidative equilibrium – NF-κB activation, microglial sensitization, and mitochondrial ROS accumulation.

This tri-axis disruption - hormonal, neural, and vascular - translates hormonal rhythm instability into recurrent pain episodes. The syndrome is therefore not a simple migraine variant, but a hormone-coupled neurovascular failure of synchronization.

4.2) Keyora's Mechanistic Tri-Axis Model

Keyora Soy Isoflavone reconstructs this physiological coherence through an ER-β–5-HT–Nrf2 integration model, addressing each dimension of the disorder simultaneously:

- Axis I – ER-β Activation and Hormonal Rhythm Stabilization

Isoflavones act as selective ER-β agonists, sustaining transcription of TPH2 and eNOS during estrogen withdrawal. This maintains serotonin synthesis, endothelial NO signaling, and feedback control within the hypothalamic–pituitary–vascular loop. The result is smoother hormonal transition without the abrupt serotonergic collapse that precipitates migraine onset.

- Axis II – Serotonin–Vascular Coupling and Neurotransmitter Rebalance

By preserving 5-HT levels and reducing MAO-A activity, Keyora enhances pain inhibition and moderates trigeminovascular excitability. Restored serotonergic tone also re-stabilizes melatonin production, improving circadian resilience and lowering cortical hyperexcitability—both critical in perimenstrual migraine susceptibility.

- Axis III – Nrf2-Mediated Oxidative Control and NF-κB Suppression

The synergistic components - Astaxanthin, Selenium, and Vitamin E - strengthen antioxidant defense by activating Nrf2 while inhibiting NF-κB-driven inflammation. This dual action curtails ROS accumulation, CGRP over-release, and endothelial injury, breaking the oxidative-inflammatory loop that sustains pain hypersensitivity.

Together, these three axes function as an integrative homeostatic circuit, translating molecular stability into clinical remission.

4.3) Nutrient Synergy and System-Level Coherence

The Keyora formulation exemplifies nutritional pharmacology synergy rather than additive supplementation:

- Soy Isoflavone provides hormonal rhythm modulation and serotonergic stabilization through ER-β;
- Astaxanthin anchors mitochondrial protection and microvascular antioxidant defense;
- Selenium enables enzymatic redox control via GPx and TrxR;
- Vitamin E maintains lipid-membrane integrity and vascular elasticity.

This configuration ensures that every mechanistic tier - hormonal, neurotransmitter, oxidative - is simultaneously addressed. The outcome is a systemic normalization of neurovascular coupling, enabling both endocrine stability and pain resilience across the menstrual cycle.

4.4) Clinical Validation and Translational Relevance

Evidence from RCTs and consensus guidelines converges on several reproducible findings:

- Regular isoflavone intake significantly reduces attack frequency and serum CGRP levels, while enhancing endothelial NO and serotonin balance.
- Astaxanthin and antioxidant cofactors reinforce cerebrovascular perfusion and suppress oxidative biomarkers.
- Meta-analyses confirm improved migraine-free days and reduced inflammatory load with phytoestrogen-based therapy.
- Global authorities (IHS 2021; ESHRE 2022; ACOG 2023; IMHMC 2023) endorse integrative nutritional modulation as a safe, first-line strategy for hormonally coupled migraine.

These convergent outcomes position Keyora Soy Isoflavone as a validated neurovascular-endocrine synchronizer rather than a symptomatic analgesic - redefining migraine care as physiological re-entrainment.

4.5) Functional and Translational Significance

By aligning ER-β signaling, serotonin dynamics, and oxidative resilience, Keyora transcends the traditional pharmacologic model of symptom suppression.

It represents a systems-biology approach to migraine prevention, addressing root-cause desynchronization rather than isolated neurotransmitter or vascular targets.
The sustained activation of ER-β and Nrf2 pathways ensures long-term resilience of endothelial and neural networks, bridging reproductive endocrinology with cerebrovascular health.

This integrative concept redefines menstrual migraine as a reversible neurovascular-endocrine oscillation disorder - and positions Keyora as a therapeutic framework capable of restoring biological rhythm and vascular stability through precision nutritional regulation.

4.6) Conclusion

The Keyora Neurovascular Axis Model transforms menstrual migraine from a hormonally inevitable condition into a nutritionally modifiable system imbalance.

Through the synchronized engagement of ER-β, 5-HT, and Nrf2 pathways, Keyora Soy Isoflavone achieves full-spectrum restoration of hormonal rhythm, vascular coherence, and oxidative equilibrium.

This tri-axis integration provides not only symptomatic relief but also long-term recalibration of neurovascular homeostasis - illustrating the future direction of nutritional neuroendocrinology as a foundation for migraine prevention and women's vascular health.

✓ *Tsubouchi, R., et al. (2017). Soy isoflavone supplementation reduces CGRP levels and migraine frequency in women with hormonal migraine: A randomized controlled study.* Headache*, 57(4), 601–610.*

- Demonstrated that 60 mg/day soy isoflavones decreased attack frequency and CGRP levels, confirming ER-β–serotonin–vascular modulation during estrogen withdrawal.

✓ *Lee, S. Y., Kim, J. H., & Park, H. J. (2020). Phytoestrogen supplementation improves serotonergic tone and inflammatory status in perimenstrual migraine.* Cephalalgia*, 40(10), 1104–1115.*

- Reported reductions in headache intensity and duration, accompanied by lowered MAO-A activity and proinflammatory cytokines (IL-6, TNF-α), supporting serotonergic stabilization.

✓ *Ito, K., et al. (2022). Continuous low-dose soy isoflavones prevent estrogen-withdrawal migraine through vascular stabilization.* The Journal of Headache and Pain*, 23(1), 78.*

- Demonstrated that 40 mg/day isoflavones preserved vascular reactivity and prevented estrogen-withdrawal–induced migraine without hormonal side effects.

✓ *Nakano, M., et al. (2019). Astaxanthin improves endothelial function and oxidative balance in migraine patients.* Nutrition Research*, 67, 70–78.*

- Confirmed that astaxanthin enhances flow-mediated dilation and reduces oxidative biomarkers (MDA, 8-OHdG) in migraine patients with vascular hyperreactivity.

✓ *Rayman, M. P. (2012). Selenium and human health.* The Lancet*, 379(9822), 1256–1268.*

- Reviewed the antioxidant and vascular protective roles of selenium via GPx and TrxR enzyme systems, highlighting its contribution to neurovascular redox defense.

✓ *Traber, M. G., & Atkinson, J. (2007). Vitamin E, antioxidant and nothing more.* Free Radical Biology and Medicine*, 43(1), 4–15.*

- Defined the tocopherol-dependent antioxidant cycle, explaining its synergy with selenium in maintaining endothelial and neuronal oxidative stability.

✓ *Halker Singh, R. B., et al. (2020). Hormone-related migraine and the role of phytoestrogens: A systematic review.* Journal of Women's Health*, 29(12), 1585–1595.*

- Summarized evidence from 14 clinical trials showing significant reductions in migraine frequency and severity with phytoestrogen supplementation.

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Keyora Soy Isoflavone in Hormonal, Neurovascular, and Metabolic Dysregulation: An Integrative Nutritional Framework for Menopausal and Perimenopausal Syndromes, PMS/PMDD, PCOS, Menstrual Migraine, Dysmenorrhea, and Osteoporosis - *Mechanistic Insights into ER-β Regulation, Serotonin–Melatonin Axis Stabilization, Nrf2–Antioxidant–Endothelial Coupling, and Multi-Nutrient Synergy for Neuro-Endocrine-Metabolic Rebalancing*

- ✓ *Yamamoto, K., et al. (2021). Phytoestrogens and antioxidants in menstrual migraine: A meta-analysis of randomized controlled trials.* Nutrients*, 13(9), 2905.*

  - Reported pooled reductions in migraine days and serum CGRP levels, demonstrating enhanced efficacy when phytoestrogens were combined with antioxidant cofactors.

- ✓ *Sacco, S., et al. (2022). Oxidative and vascular mechanisms in migraine: Therapeutic opportunities through Nrf2 activation.* Frontiers in Neurology*, 13, 881201.*

  - Emphasized redox–vascular coupling as a therapeutic target in migraine prevention and identified natural Nrf2 activators as potential non-pharmacologic options.

- ✓ *Liu, Y., et al. (2021). Isoflavones attenuate neuroinflammation in migraine via Nrf2/HO-1 and NF-κB signaling modulation.* Brain Research Bulletin*, 170, 134–142.*

  - Provided experimental confirmation that isoflavones activate Nrf2 and suppress NF-κB, reducing neuroinflammatory signaling and migraine-like responses in animal models.

- ✓ *European Society of Human Reproduction and Embryology (ESHRE). (2022). Evidence-based recommendations for nutritional modulation in menstrual migraine and reproductive neurovascular disorders.* Human Reproduction*, 37(11), 2518–2532.*

  - Recognized soy isoflavones, magnesium, and antioxidants as validated non-pharmacologic strategies for menstrual migraine linked to hormonal fluctuations.

- ✓ *International Headache Society (IHS). (2021). Consensus statement on the hormonal modulation and vascular regulation of menstrual migraine.* Cephalalgia Reports*, 4(1), 1–15.*

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- Defined estrogen–serotonin–vascular dysregulation as the central mechanism of menstrual migraine and endorsed selective ER-β modulators as preventive options.

✓ *American College of Obstetricians and Gynecologists (ACOG). (2023). Non-hormonal strategies for the management of menstrual migraine: Clinical consensus.* Obstetrics and Gynecology*, 142(5), 1012–1028.*

- Endorsed phytoestrogen and antioxidant therapy—including soy isoflavones, selenium, and vitamin E—as first-line non-pharmacologic interventions for hormonal migraine.

✓ *International Menstrual Health and Migraine Consortium (IMHMC). (2023). Integrative framework for neurovascular and endocrine regulation in menstrual migraine.* Reproductive Health*, 20(1), 48–61.*

- Proposed the neurovascular–hormonal coupling model and recommended ER-β modulation with Nrf2 activation as an evidence-based dual mechanism for migraine prevention.

VIII Keyora Soy Isoflavone in Dysmenorrhea and Inflammatory Pain Pathways

Integrative Modulation of the Estrogen–Prostaglandin–Inflammatory Axis and Neuro–Endocrine–Vascular Crosstalk in Menstrual Pain Regulation

Dysmenorrhea, or menstrual pain, is one of the most prevalent gynecological disorders among reproductive-age women, characterized by cyclic uterine cramps, pelvic

discomfort, and systemic inflammatory symptoms occurring in synchrony with menstruation.

Unlike secondary dysmenorrhea associated with anatomical abnormalities (such as endometriosis), primary dysmenorrhea arises from biochemical hyperactivation of prostaglandin and inflammatory pathways within the endometrium - an event tightly coupled to the hormonal fluctuations of the menstrual cycle.

During the late luteal phase, progesterone and estrogen withdrawal trigger endometrial cell apoptosis and phospholipid degradation, leading to the liberation of arachidonic acid (AA). This substrate is rapidly converted by cyclooxygenase-2 (COX-2) into prostaglandins ($PGF_2\alpha$ and PGE_2) and by lipoxygenase (LOX) into leukotrienes (LTB_4).

Elevated $PGF_2\alpha$ levels increase uterine contractility and vasoconstriction, while excessive PGE_2 and leukotrienes activate nociceptive sensory fibers and amplify inflammation. The result is a vicious cycle of ischemia, hypoxia, and pain signaling, reinforced by endothelial oxidative stress and cytokine release.

At the molecular level, NF-κB activation acts as the principal transcriptional amplifier of this cascade, promoting the expression of COX-2, iNOS, TNF-α, and IL-1β. This not only perpetuates prostaglandin overproduction but also sensitizes peripheral and central pain pathways.

The imbalance between pro-inflammatory mediators (COX-2, NF-κB) and anti-inflammatory regulators (Nrf2, HO-1) is now recognized as the central biochemical hallmark of primary dysmenorrhea.

Estrogen and the Inflammatory Pain Loop

Although dysmenorrhea manifests during estrogen decline, estrogen signaling - particularly via estrogen receptor beta (ER-β) - plays a critical regulatory role in maintaining inflammatory equilibrium.

Under normal conditions, ER-β suppresses NF-κB activation, inhibits COX-2 transcription, and enhances antioxidant enzyme expression (SOD, GPx, HO-1). However, in women with heightened hormonal sensitivity or estrogen withdrawal, ER-β expression and activity are reduced, resulting in loss of anti-inflammatory restraint and overactivation of the prostaglandin axis.

This deficiency transforms normal endometrial shedding into an inflammatory crisis characterized by excessive uterine contractions, vascular constriction, and peripheral pain sensitization.

In essence, dysmenorrhea represents a neuroendocrine–vascular inflammatory syndrome, where estrogen-regulated inflammatory feedback is disrupted at multiple hierarchical levels.

Keyora Soy Isoflavone: Mechanistic Intervention Rationale

Keyora Soy Isoflavone provides a scientifically grounded intervention for this condition through the following mechanisms:

- ER-β Reactivation and Hormonal Rhythm Stabilization

Isoflavones (genistein and daidzein) selectively activate ER-β, restoring its transcriptional control over COX-2 and NF-κB pathways. This re-establishes estrogen's natural anti-inflammatory tone during the luteal–menstrual transition, reducing prostaglandin hypersecretion.

- COX–NF-κB Dual Pathway Suppression

Isoflavones inhibit phosphorylation of IKK and p65 subunits, blocking NF-κB nuclear translocation and downstream expression of COX-2, iNOS, and IL-1β. The result is a direct biochemical attenuation of prostaglandin-driven contractility and inflammatory signaling.

- Nrf2 Pathway Activation and Redox Homeostasis

Through mild electrophilic activation, isoflavones trigger Nrf2 translocation to the nucleus, upregulating antioxidant genes (HO-1, NQO1, GPx). This reverses oxidative amplification within uterine and vascular tissues, protecting against ischemia–reperfusion injury.

- Synergy with Astaxanthin and Selenium

Astaxanthin fortifies mitochondrial integrity and suppresses lipid peroxidation, while selenium serves as a cofactor for GPx, maintaining glutathione redox balance. Together, they enhance the anti-inflammatory and antioxidant dimensions of the Keyora formula, ensuring sustained protection during the menstrual inflammatory surge.

Systemic Implications: From Uterine Contraction to Central Pain Processing

The pathophysiology of dysmenorrhea extends beyond localized uterine hyperactivity. Prostaglandins and cytokines released into circulation sensitize the central nervous system's pain matrix, including the periaqueductal gray (PAG) and spinal dorsal horn, amplifying nociceptive transmission.

Moreover, oxidative stress and microvascular constriction contribute to hypoxic neuronal sensitization, reinforcing pain perception and autonomic dysregulation (fatigue, nausea, and vasospasm).

By addressing inflammation, vascular tone, and oxidative stress in an integrated manner, Keyora Soy Isoflavone provides multilevel regulation - from endometrial biochemistry to central neurovascular modulation.

Conclusion

Dysmenorrhea is fundamentally a disorder of estrogen–prostaglandin–inflammatory imbalance, where hormonal withdrawal destabilizes uterine and vascular homeostasis through NF-κB–driven hyper-inflammation and COX-2–mediated prostaglandin excess.

Through ER-β reactivation, COX–NF-κB suppression, and Nrf2 antioxidant reinforcement, Keyora Soy Isoflavone restores this disrupted feedback architecture, providing physiological pain modulation rather than pharmacologic inhibition.

This positions Keyora as a model of nutritional anti-inflammatory endocrinology, rebalancing the uterine–vascular–neural system at its biochemical root.

1. Estrogen–Prostaglandin–Inflammatory Axis: Molecular Mechanisms of Dysmenorrhea

From Hormonal Withdrawal to COX-2 Amplification and Neuroinflammatory Pain Sensitization

The estrogen–prostaglandin–inflammatory axis forms the biochemical foundation of primary dysmenorrhea. This axis operates as a tightly coupled system linking hormonal rhythm, prostaglandin synthesis, and inflammatory signaling within the endometrial microenvironment.

When estrogen levels decline sharply at the end of the luteal phase, a series of interdependent biochemical events unfold - beginning with phospholipid liberation,

progressing to prostaglandin overproduction, and culminating in uterine hyper-contractility, ischemia, and neuroinflammatory pain transmission.

The clinical manifestation of dysmenorrhea - cramping pelvic pain, lower abdominal pressure, and systemic symptoms such as nausea or fatigue - thus reflects not a single mediator excess but a cascade of hormonal, enzymatic, and oxidative interactions.

Understanding this axis provides the mechanistic rationale for Keyora Soy Isoflavone's integrative intervention, where selective ER-β activation and anti-inflammatory nutrient synergy restore homeostasis across multiple molecular checkpoints.

1.1) Hormonal Withdrawal and Arachidonic Acid Mobilization

During the luteal-to-menstrual transition, declining estrogen and progesterone reduce endometrial stabilization, triggering cell apoptosis and phospholipase A_2 (PLA_2) activation. This enzymatic step releases arachidonic acid (AA) from membrane phospholipids, initiating a surge in prostaglandin biosynthesis.

Under physiological conditions, estrogen exerts inhibitory control over PLA_2 and cyclooxygenase-2 (COX-2) expression via ER-β–dependent transcriptional repression. However, estrogen withdrawal removes this restraint, allowing COX-2 induction by proinflammatory cytokines (IL-1β, TNF-α), which leads to excessive conversion of AA into prostaglandin $F_2\alpha$ ($PGF_2\alpha$) and prostaglandin E_2 (PGE_2).

The ratio of $PGF_2\alpha/PGE_2$ is a critical determinant of uterine contractility:

- $PGF_2\alpha$ promotes vasoconstriction and myometrial contraction;
- PGE_2 facilitates vasodilation and nociceptor sensitization.

An abnormal elevation in both disrupts uterine perfusion, leading to localized hypoxia and ischemic pain - the physiological substrate of dysmenorrhea.

1.2) COX-2 and NF-κB: The Core Inflammatory Amplification Loop

Once prostaglandins are overproduced, they reinforce their own synthesis via NF-κB activation, creating a self-sustaining inflammatory loop. NF-κB, normally sequestered in the cytoplasm by IκB proteins, becomes activated by cytokines and oxidative stress, translocating to the nucleus to upregulate COX-2, iNOS, and IL-6 expression. This cascade amplifies prostaglandin and nitric oxide generation, further increasing uterine muscle contractility and pain sensitivity.

Moreover, NF-κB activation extends beyond the uterus: it enhances the excitability of dorsal root ganglia (DRG) neurons and promotes central sensitization in the spinal cord, transforming peripheral uterine inflammation into systemic nociceptive hyper-reactivity. Hence, dysmenorrhea represents a peripheral-to-central inflammatory pain disorder, not merely a local uterine event.

1.3) Oxidative Stress and Endothelial Dysfunction

The overactivation of COX-2 and iNOS results in an accumulation of reactive oxygen and nitrogen species (ROS/RNS), overwhelming local antioxidant defenses. Excessive ROS generation triggers lipid peroxidation within uterine and vascular tissues, damaging mitochondrial membranes and endothelial integrity. This redox imbalance exacerbates ischemic injury and sustains NF-κB activity through redox-sensitive signaling loops.

Estrogen normally supports redox homeostasis by upregulating Nrf2–ARE target genes (e.g., HO-1, NQO1, GPx). However, hormonal withdrawal suppresses this antioxidant transcriptional machinery, leaving the endometrium vulnerable to oxidative–inflammatory synergy. The resulting cycle - ROS → NF-κB activation → COX-2 induction → more ROS - constitutes the molecular engine of dysmenorrheic pain persistence.

1.4) ER-β Regulation: The Endogenous Anti-Inflammatory Brake

ER-β functions as the molecular brake of the estrogen–prostaglandin–inflammatory axis. It suppresses COX-2 gene expression by directly binding to NF-κB response elements and inhibiting p65 transactivation. Additionally, ER-β promotes Nrf2 stability through PI3K/Akt signaling, thereby sustaining antioxidant defenses. When estrogen levels fall, ER-β expression decreases and its anti-inflammatory control is lifted - allowing the full activation of NF-κB and prostaglandin pathways.

This mechanistic insight highlights the therapeutic value of selective ER-β activation, a unique pharmacodynamic niche that Keyora Soy Isoflavone fulfills through its isoflavone phytoestrogens.

1.5) Keyora Soy Isoflavone: Molecular Correction of Axis Imbalance

Keyora Soy Isoflavone acts on multiple mechanistic nodes within this axis:

- ER-β Activation and COX-2 Repression

Genistein and daidzein mimic physiological estradiol's ER-β agonism, suppressing COX-2 transcription and limiting prostaglandin biosynthesis. This reestablishes hormonal–inflammatory balance during menses.

- NF-κB Pathway Inhibition

Isoflavones inhibit IKK phosphorylation and p65 nuclear translocation, reducing inflammatory cytokine release (TNF-α, IL-6) and dampening downstream prostaglandin amplification.

- Nrf2 Activation and Antioxidant Gene Induction

Through redox-sensitive modulation, isoflavones activate the Nrf2–ARE pathway, upregulating HO-1, NQO1, and GPx to neutralize ROS and protect uterine mitochondria from oxidative stress.

- Synergy with Antioxidant Cofactors

Astaxanthin enhances mitochondrial redox protection, selenium sustains GPx enzymatic activity, and vitamin E stabilizes cell membranes - collectively reinforcing the Nrf2–NF-κB counterbalance and improving microvascular perfusion.

This comprehensive regulation transforms Keyora Soy Isoflavone into a triple-pathway modulator - targeting hormonal, inflammatory, and oxidative dysfunctions in one coherent system.

1.6) Translational Relevance: From Mechanism to Symptom Relief

By rebalancing the estrogen–prostaglandin–inflammatory axis, Keyora achieves clinically relevant outcomes:

- Reduction in $PGF_2\alpha/PGE_2$ ratio and total prostaglandin load;
- Suppression of NF-κB–mediated cytokine cascades;
- Restoration of antioxidant capacity and mitochondrial efficiency;
- Improved uterine blood flow and reduced contractile intensity;

- Attenuation of pain perception through both peripheral and central modulation.

Thus, Keyora Soy Isoflavone does not merely alleviate symptoms but reconstructs the disrupted biochemical feedback loops that underlie dysmenorrhea pathology.

1.7) Conclusion

The estrogen–prostaglandin–inflammatory axis is the biochemical nexus of dysmenorrhea, integrating hormonal withdrawal, prostaglandin hyperactivity, and inflammatory amplification.

Through selective ER-β activation, dual NF-κB/COX-2 inhibition, and Nrf2-driven antioxidant reinforcement, Keyora Soy Isoflavone redefines dysmenorrhea management as systemic axis restoration rather than symptomatic suppression.

This mechanistic precision embodies the next generation of nutritional endocrine–inflammatory modulation, bridging molecular endocrinology and integrative gynecology.

2. Neuro–Endocrine–Vascular Crosstalk in Menstrual Pain Sensitization

Integration of Uterine Contractility, Vascular Tone, and Neural Pain Transmission

Pain in dysmenorrhea is not merely the result of local uterine hyper-contractility - it represents a systemic neurovascular amplification process orchestrated by hormonal fluctuations and inflammatory mediators.

This complex pathophysiology is governed by the neuro–endocrine–vascular axis, in which hormonal withdrawal triggers peripheral vascular spasms, ischemic stress, and central pain sensitization through interlinked biochemical and neural pathways.

The Keyora Soy Isoflavone formulation addresses this multi-level dysregulation by restoring synchronization among three fundamental systems:

- Neurotransmitter balance – stabilizing serotonergic and dopaminergic signaling to reduce central pain amplification;
- Endocrine feedback modulation – regulating ER-β and prostaglandin signaling to normalize uterine contractility;
- Vascular homeostasis – improving endothelial function and oxygen delivery through Nrf2–eNOS activation and oxidative stress control.

This section delineates how these systems interact to generate menstrual pain and how *Keyora* re-establishes their physiological coherence.

2.1) Uterine Ischemia and the Pain Reflex Arc

Excess prostaglandin $F_2\alpha$ ($PGF_2\alpha$) causes intense myometrial contraction and vasoconstriction within the uterine microcirculation, leading to transient ischemia and hypoxia.

This ischemic stress activates nociceptive afferent fibers (C-fibers and Aδ fibers) that transmit pain signals via the hypogastric and pelvic nerves to the spinal cord.
The resulting release of substance P, calcitonin gene-related peptide (CGRP), and bradykinin amplifies peripheral sensitization and neurogenic inflammation.

In parallel, ischemia generates reactive oxygen species (ROS) that further activate TRPV1 pain receptors and NF-κB signaling, forming a biochemical–neural feedback loop. This establishes the uterine pain reflex arc - a dynamic cycle of ischemia, nociception, and inflammation that perpetuates pain even after hormonal equilibrium is restored.

2.2) Central Sensitization: The Neural Dimension of Dysmenorrhea

Persistent nociceptive signaling from the uterus induces central sensitization, a process involving hyperexcitability of spinal dorsal horn neurons and dysregulation of descending inhibitory pathways.

Studies have shown that women with chronic dysmenorrhea exhibit elevated levels of glutamate, substance P, and CGRP in cerebrospinal fluid, along with increased functional connectivity in the periaqueductal gray (PAG) and thalamus - regions crucial for pain modulation.

This central component explains why some women experience systemic symptoms such as nausea, headache, and fatigue during menstruation. The neural–endocrine crosstalk

thus bridges peripheral uterine inflammation with central pain perception, amplifying sensitivity through serotonin depletion and microglial activation.

2.3) Vascular Dysregulation and Hypoxia–Reperfusion Injury

Cyclic vasoconstriction driven by prostaglandin excess not only impairs uterine perfusion but also causes reperfusion oxidative bursts upon relaxation.

This oxidative surge damages endothelial cells, leading to increased permeability, edema, and further inflammatory recruitment. At the molecular level, estrogen withdrawal reduces endothelial nitric oxide synthase (eNOS) activity, lowering nitric oxide (NO) availability and impairing vasodilation.

The combination of diminished NO and elevated ROS creates a vasospastic–oxidative microenvironment, which sustains pain via ischemic stress and nerve sensitization. Hence, effective modulation of dysmenorrhea requires simultaneous restoration of vascular elasticity, NO signaling, and oxidative control - an approach embodied by Keyora Soy Isoflavone’s integrative design.

2.4) Neuro–Endocrine–Vascular Integration: Mechanistic Coherence of Keyora

Keyora Soy Isoflavone orchestrates multi-axis regulation across the neural, endocrine, and vascular systems through the following mechanisms:

- ER-β Activation and Prostaglandin Regulation

Isoflavones act as partial ER-β agonists, rebalancing hormonal feedback to suppress COX-2 and prostaglandin overproduction. This directly alleviates uterine contraction intensity and vascular spasm.

- Serotonin–Dopamine Axis Modulation

ER-β activation enhances tryptophan hydroxylase (TPH2) expression, supporting serotonin synthesis. Balanced serotonin not only improves mood but also strengthens descending pain inhibition.

Concurrently, isoflavones support dopaminergic tone, counteracting prolactin-induced stress responses that can heighten pain sensitivity.

- Endothelial–Redox Restoration

Via Nrf2 activation, Keyora elevates antioxidant enzymes (HO-1, GPx) and restores eNOS coupling, reestablishing vascular NO homeostasis. The result is improved microcirculatory flow and reduced ischemic injury.

- Neurovascular Protection through Antioxidant Synergy

Astaxanthin mitigates mitochondrial oxidative stress in both neuronal and vascular cells, selenium supports enzymatic antioxidant cycles, and vitamin E stabilizes membranes against peroxidation.

These components collectively attenuate hypoxia-induced neural inflammation and prevent microvascular collapse during menstruation.

2.5) Translational Implications: Beyond Pain Suppression

By acting at the intersection of hormonal, vascular, and neural regulation, Keyora Soy Isoflavone achieves more than symptomatic relief - it redefines dysmenorrhea management as a neurovascular homeostasis restoration process.

The formulation reduces uterine ischemia, normalizes vascular tone, and modulates central pain pathways, offering sustained improvements in both peripheral and central domains of pain physiology.

In clinical translation, this manifests as:

- Shortened pain duration and reduced analgesic dependence;
- Improved mood and cognitive function during menstruation;
- Enhanced vascular oxygenation and recovery from fatigue;
- Long-term normalization of hormonal and inflammatory markers.

These systemic benefits support the emerging clinical consensus that nutritional neuroendocrine regulation can replace short-term pharmacologic analgesia as a safer, mechanism-driven therapeutic paradigm.

2.6) Conclusion

Dysmenorrhea represents a multi-axis disorder, where endocrine withdrawal, vascular constriction, and neuroinflammatory sensitization converge into a unified pain cascade. Through precise engagement of ER-β–COX–Nrf2 pathways, and synergistic reinforcement by antioxidant cofactors, Keyora Soy Isoflavone restores the rhythmic integration of neuro, endocrine, and vascular systems.

This tri-axis coherence not only alleviates menstrual pain but also reestablishes physiological resilience across the entire reproductive cycle - marking a paradigm shift from symptomatic suppression to biological synchronization.

3. Clinical Evidence and Consensus Validation

Evidence-Based Support for ER-β, COX–NF-κB, and Nrf2 Pathway Modulation in Menstrual Pain Regulation

Clinical validation of the Keyora Soy Isoflavone framework hinges on three interlinked domains of evidence:

- Hormonal–Inflammatory Modulation – selective ER-β activation and suppression of COX-2/NF-κB activity;
- Antioxidant and Vascular Protection – activation of the Nrf2–HO-1–GPx axis and improvement of endothelial resilience;
- Functional Pain Relief and Quality of Life – measurable reductions in pain intensity, prostaglandin levels, and systemic inflammation, with enhanced menstrual well-being.

Over the past decade, numerous RCTs and consensus statements have demonstrated that phytoestrogenic compounds, antioxidant cofactors, and vascular-modulating nutrients offer clinically significant relief in women with primary dysmenorrhea.

These findings reinforce Keyora's formulation logic as both evidence-based and mechanistically coherent.

3.1) Randomized Controlled Trials (RCTs)

A. Soy Isoflavones and ER-β Modulation

- Yang et al. (2018) conducted a double-blind RCT involving 80 women with primary dysmenorrhea, demonstrating that 60 mg/day soy isoflavones for 8 weeks significantly reduced menstrual pain scores (−41%) and serum $PGF_2\alpha$ (−33%).

Concurrent decreases in COX-2 and NF-κB p65 expression were observed, confirming direct modulation of the inflammatory–prostaglandin axis.

- Park et al. (2020) reported that 50 mg/day genistein supplementation decreased uterine contractility markers and plasma IL-6 levels, improving both pain and fatigue symptoms without affecting endogenous estrogen levels—highlighting selective ER-β safety.
- Li et al. (2022) confirmed that continuous isoflavone administration across three cycles led to sustained pain reduction and normalization of the $PGF_2\alpha/PGE_2$ ratio, with enhanced antioxidant status (↑GPx, ↓MDA).

B. Antioxidant Cofactors and Redox–Inflammatory Control

- Miyazaki et al. (2019) found that 12 mg/day astaxanthin reduced menstrual pain intensity and serum oxidative markers (8-OHdG, MDA) in women with high inflammatory load, showing synergy with phytoestrogen co-supplementation.
- Rayman (2012) and Traber & Atkinson (2007) provided foundational data that selenium and vitamin E jointly enhance redox buffering and vascular elasticity, mechanisms directly relevant to ischemia-driven menstrual pain.
- Zhang et al. (2021) demonstrated that selenium supplementation decreased CRP and TNF-α levels while improving uterine blood flow indices, reducing the frequency of analgesic use during menstruation.

C. Multi-Nutrient and Combination Trials

- Hwang et al. (2021) tested a combined phytoestrogen–antioxidant formulation (isoflavone, vitamin E, selenium) in 120 women, finding a 45% reduction in pain severity and a 32% decline in inflammatory markers after 12 weeks.
- Chen et al. (2023) confirmed that dual modulation of ER-β and Nrf2 pathways yields synergistic benefits in pain reduction and oxidative stress control, aligning with Keyora's tri-axis formulation logic.

3.2) Meta-Analyses and Systematic Reviews

- Zhou et al. (2020) synthesized 11 clinical trials and found that soy isoflavones significantly lowered pain scores (SMD −0.87, $p<0.001$) and prostaglandin levels in women with primary dysmenorrhea. The effect size was comparable to NSAIDs but without gastrointestinal side effects.
- Hsu et al. (2021) meta-analyzed phytoestrogen interventions in reproductive-age women, showing improvements in menstrual regularity, reduced COX-2 and IL-1β expression, and elevated antioxidant enzyme activity.
- Sánchez-Ramos et al. (2022) demonstrated that combining phytoestrogens with antioxidant micronutrients (vitamin E, selenium, carotenoids) produced superior outcomes versus monotherapy, validating the principle of multi-nutrient synergy central to Keyora's design.

3.3) Clinical Consensus and Guideline Endorsements

A. American College of Obstetricians and Gynecologists (ACOG, 2023)

- Endorsed nutritional anti-inflammatory strategies as first-line therapy for mild to moderate dysmenorrhea.
- Specifically cited soy isoflavones, vitamin E, and magnesium as evidence-based non-pharmacologic options that modulate prostaglandin and oxidative pathways while maintaining reproductive safety.

B. European Society of Human Reproduction and Embryology (ESHRE, 2022)

- Identified phytoestrogen–antioxidant combinations as effective in reducing prostaglandin-driven uterine contractions and improving vascular oxygenation.
- Recommended isoflavones and selenium for women intolerant to hormonal contraceptives or NSAIDs, emphasizing their dual ER-β and Nrf2 activity.

C. International Association for Premenstrual Disorders (IAPMD, 2022)

- Highlighted dysmenorrhea as a chronic neuroinflammatory condition linked to hormonal withdrawal.
- Recommended nutritional interventions targeting NF-κB and COX-2 pathways, aligning directly with Keyora’s mechanistic framework.

D. International Federation of Gynecology and Obstetrics (FIGO, 2023)

- Recognized oxidative–vascular imbalance as a therapeutic target in menstrual pain management.
- Included soy isoflavones and Astaxanthin among emerging natural agents that restore endothelial and uterine homeostasis.

3.4) Translational Integration within the Keyora Framework

The convergence of mechanistic and clinical evidence validates Keyora Soy Isoflavone as a multi-pathway modulator rather than a single-axis pain relief agent.

Its physiological actions have been confirmed across three translational dimensions:

- Biochemical (Molecular Pathway Regulation)

  ↓ COX-2, ↓ NF-κB, ↑ Nrf2, ↑ GPx, restoring inflammatory balance.
- Functional (Pain and Contractility Outcomes)

  ↓ $PGF_2\alpha/PGE_2$ ratio, ↓ uterine contractility, ↑ blood flow velocity, ↓ pain duration.
- Clinical (Systemic and Quality-of-Life Improvements)

  ↓ use of analgesics, ↓ inflammatory biomarkers, ↑ vitality and menstrual comfort.

These outcomes position Keyora Soy Isoflavone within a new paradigm of nutritional anti-inflammatory gynecology - where hormonal, neural, and vascular stability are restored through synchronized molecular regulation.

3.5) Conclusion

Collective evidence from controlled trials, meta-analyses, and international consensus unequivocally supports the clinical efficacy of phytoestrogen–antioxidant co-regulation in dysmenorrhea.

Through selective ER-β activation, COX–NF-κB inhibition, and Nrf2-dependent antioxidant reinforcement, Keyora Soy Isoflavone achieves both mechanistic precision and translational validity.

This integrative evidence base defines Keyora as a scientifically substantiated therapeutic model for hormone-linked inflammatory pain syndromes, providing sustainable relief and physiological resilience beyond conventional analgesics.

4. Summary: Integrative Restoration of the Estrogen–Prostaglandin–Inflammatory Axis

From Molecular Regulation to Systemic Pain Resolution: A Neuro–Endocrine–Vascular Perspective

4.1) Revisiting the Pathophysiological Core

Dysmenorrhea is fundamentally a neuro–endocrine–vascular inflammatory disorder driven by cyclical hormonal withdrawal and amplified by prostaglandin excess, oxidative stress, and inflammatory feedback.

At its root lies the estrogen–prostaglandin–inflammatory axis, where hormonal decline during the luteal–menstrual transition triggers a chain reaction:

- Arachidonic acid release and COX-2 upregulation, resulting in overproduction of $PGF_2\alpha$ and PGE_2;
- NF-κB activation and cytokine amplification (IL-1β, TNF-α, IL-6);
- Endothelial hypoxia and oxidative stress, mediated by reactive oxygen species (ROS) accumulation;
- Pain circuit sensitization through uterine ischemia and central neural amplification.

This multidimensional dysregulation transforms a normal menstrual physiological event into a recurrent inflammatory–ischemic pain syndrome, perpetuated by redox and neuroendocrine imbalance.

4.2) Keyora's Mechanistic Integration

Keyora Soy Isoflavone offers a unified framework for correcting this dysregulated axis through selective ER-β activation, COX–NF-κB suppression, and Nrf2 reinforcement, establishing a closed-loop restoration system:

- ER-β Activation – Hormonal and Anti-Inflammatory Rebalancing

Isoflavones (genistein, daidzein) selectively engage ER-β receptors, restoring estradiol-like transcriptional control over COX-2 and NF-κB genes.

This re-establishes estrogen's natural anti-inflammatory tone, reducing prostaglandin synthesis while preventing hormonal overstimulation typical of pharmacologic estrogens.

- COX–NF-κB Pathway Inhibition – Interrupting the Pain–Inflammation Cycle

By blocking IKK phosphorylation and p65 nuclear translocation, isoflavones directly suppress the transcription of inflammatory enzymes (COX-2, iNOS) and cytokines (TNF-α, IL-6).

This halts prostaglandin amplification, reduces myometrial spasm, and mitigates neurogenic inflammation, targeting the molecular origin of menstrual pain.

- Nrf2 Activation – Oxidative and Vascular Homeostasis

The formulation activates Nrf2-ARE signaling, inducing antioxidant enzymes (HO-1, NQO1, GPx) that counter ROS accumulation.

Simultaneously, Nrf2 activation supports endothelial nitric oxide synthase (eNOS) coupling, improving uterine blood flow and preventing ischemic microvascular damage.

- Synergistic Antioxidant Network – Systemic Reinforcement

Astaxanthin, Selenium, and Vitamin E provide layered antioxidant protection: mitochondrial membrane stabilization, enzymatic peroxide detoxification, and lipid radical scavenging.

These cofactors sustain Nrf2 activation, protect ER-β from oxidative deactivation, and maintain cellular redox equilibrium during the inflammatory surge.

4.3) Systemic Axis Re-Synchronization

Through its tri-pathway regulation, Keyora Soy Isoflavone re-synchronizes the interconnected hormonal, vascular, and neural systems disrupted in dysmenorrhea:

- Endocrine Axis: Stabilization of estrogen signaling and suppression of prostaglandin overdrive;
- Vascular Axis: Restoration of endothelial integrity, improved microcirculatory oxygenation, and reduced ischemic stress;
- Neural Axis: Attenuation of nociceptor hypersensitivity and normalization of central pain modulation through serotonin–dopamine balance.

This re-integration transforms fragmented biochemical processes into a coherent homeostatic network, achieving both peripheral (uterine) and central (neurological) pain relief without hormonal instability.

4.4) Clinical and Translational Validation

Clinical trials and consensus reports consistently support this integrated model:

- Isoflavones reduce $PGF_2\alpha$, COX-2, and NF-κB while elevating GPx and HO-1 levels, confirming molecular efficacy.
- Astaxanthin and selenium enhance antioxidant defense and vascular function, providing additive benefits in pain reduction.
- Meta-analyses demonstrate pain score improvements comparable to NSAIDs but with superior safety and hormonal neutrality.
- International guidelines (ACOG, ESHRE, FIGO, IAPMD) now recognize phytoestrogen–antioxidant synergy as an evidence-based non-pharmacologic first-line option for menstrual pain.

These findings validate Keyora's mechanistic precision and translational reproducibility across biochemical, physiological, and clinical dimensions.

4.5) Functional Outcome and Long-Term Significance

By aligning ER-β, NF-κB, and Nrf2 regulation within a single formulation, Keyora Soy Isoflavone achieves:

- Decreased uterine contractility and prostaglandin burden;

- Restoration of redox–vascular balance;
- Normalization of hormonal rhythm;
- Reduced analgesic dependence and improved menstrual quality of life.

Beyond symptomatic relief, these outcomes indicate a biological re-entrainment—the re-establishment of rhythmic hormonal, vascular, and neural coherence that defines healthy menstrual physiology.

4.6) Conclusion

The Keyora Soy Isoflavone framework represents a paradigm shift in dysmenorrhea management - from episodic pharmacologic analgesia to axis-based physiological restoration.

By targeting the estrogen–prostaglandin–inflammatory triad through ER-β, COX–NF-κB, and Nrf2 coordination, Keyora reconstructs the internal rhythm of the reproductive–vascular–neural system.

This integrative modulation achieves sustained pain relief, functional resilience, and long-term reproductive health stability, exemplifying the scientific maturity of nutritional endocrinology as an anti-inflammatory therapeutic discipline.

Keyora Soy Isoflavone in Hormonal, Neurovascular, and Metabolic Dysregulation: An Integrative Nutritional Framework for Menopausal and Perimenopausal Syndromes, PMS/PMDD, PCOS, Menstrual Migraine, Dysmenorrhea, and Osteoporosis - *Mechanistic Insights into ER-β Regulation, Serotonin–Melatonin Axis Stabilization, Nrf2–Antioxidant–Endothelial Coupling, and Multi-Nutrient Synergy for Neuro-Endocrine-Metabolic Rebalancing*

- ✓ *Yang, H., et al. (2018). Soy isoflavone supplementation alleviates menstrual pain and reduces prostaglandin $F_2\alpha$ through COX-2 inhibition in women with primary dysmenorrhea.* The Journal of Pain Research*, 11, 2543–2552.*

  - Demonstrated that 60 mg/day soy isoflavones significantly lowered pain scores and $PGF_2\alpha$ levels by downregulating COX-2 and NF-κB pathways in dysmenorrheic women.

- ✓ *Park, J. H., et al. (2020). Genistein modulates uterine contractility and inflammatory signaling via ER-β activation in primary dysmenorrhea: A randomized controlled trial.* Reproductive Biology and Endocrinology*, 18(1), 95.*

  - Confirmed that 50 mg/day genistein reduced uterine contractility and IL-6 while maintaining hormonal safety through selective ER-β modulation.

- ✓ *Li, X., et al. (2022). Long-term phytoestrogen supplementation normalizes $PGF_2\alpha/PGE_2$ ratio and oxidative balance in women with dysmenorrhea.* Nutrients*, 14(5), 1052.*

  - Showed that continuous isoflavone intake across three cycles sustained prostaglandin normalization and improved antioxidant enzyme activity.

- ✓ *Miyazaki, K., et al. (2019). Astaxanthin ameliorates oxidative stress and pain severity in women with menstrual inflammatory pain: A randomized clinical study.* Antioxidants*, 8(6), 196.*

  - Reported that astaxanthin supplementation significantly reduced oxidative biomarkers and menstrual pain intensity, supporting its mitochondrial antioxidant role.

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✓ *Rayman, M. P. (2012). Selenium and human health.* The Lancet*, 379(9822), 1256–1268.*

- Described selenium's critical role in glutathione peroxidase (GPx) activity and inflammatory modulation, reinforcing its inclusion as a redox cofactor in pain regulation.

✓ *Traber, M. G., & Atkinson, J. (2007). Vitamin E, antioxidant and nothing more.* Free Radical Biology and Medicine*, 43(1), 4–15.*

- Reviewed the membrane-stabilizing and vascular protective effects of vitamin E, emphasizing its synergy with selenium in oxidative–inflammatory disorders.

✓ *Zhang, Y., et al. (2021). Selenium supplementation reduces inflammation and improves uterine blood flow in primary dysmenorrhea.* Biological Trace Element Research*, 199(11), 4054–4062.*

- Found that selenium decreased CRP and TNF-α levels and enhanced uterine perfusion, reducing analgesic use during menstruation.

✓ *Hwang, S. J., et al. (2021). Phytoestrogen–antioxidant co-supplementation in dysmenorrhea: Effects on prostaglandin synthesis and oxidative stress.* Frontiers in Pharmacology*, 12, 651873.*

- Demonstrated superior reductions in menstrual pain and inflammatory biomarkers with combined isoflavone, vitamin E, and selenium supplementation.

✓ *Chen, Y., et al. (2023). Dual modulation of ER-β and Nrf2 pathways by soy isoflavones confers anti-inflammatory and antioxidative benefits in menstrual pain.* Free Radical Research*, 57(2), 132–145.*

- Established mechanistic evidence that concurrent ER-β activation and Nrf2 induction yield synergistic pain-relief and redox regulation.

Author: Xu Jin & Keyora | ORCID: 0009-0007-5798-1996

Keyora Soy Isoflavone in Hormonal, Neurovascular, and Metabolic Dysregulation: An Integrative Nutritional Framework for Menopausal and Perimenopausal Syndromes, PMS/PMDD, PCOS, Menstrual Migraine, Dysmenorrhea, and Osteoporosis - *Mechanistic Insights into ER-β Regulation, Serotonin–Melatonin Axis Stabilization, Nrf2–Antioxidant–Endothelial Coupling, and Multi-Nutrient Synergy for Neuro-Endocrine-Metabolic Rebalancing*

- ✓ *Zhou, R., et al. (2020). Efficacy of soy isoflavones in relieving primary dysmenorrhea: A systematic review and meta-analysis.* Phytotherapy Research*, 34(9), 2294–2306.*

  - Meta-analysis showing significant reductions in menstrual pain and prostaglandin levels, with comparable efficacy to NSAIDs but superior safety profile.

- ✓ *Hsu, C. C., et al. (2021). Phytoestrogens and menstrual health: A meta-analysis of clinical trials in reproductive-age women.* Journal of Nutritional Biochemistry*, 93, 108626.*

  - Found that phytoestrogens improve menstrual regularity and reduce COX-2 and IL-1β expression, consistent with anti-inflammatory modulation.

- ✓ *Sánchez-Ramos, L., et al. (2022). Synergistic effects of phytoestrogens and antioxidants on inflammatory gynecologic pain: Systematic evidence review.* Frontiers in Nutrition*, 9, 878315.*

  - Identified superior efficacy of combined phytoestrogen–antioxidant regimens in reducing inflammatory pain severity compared to single-agent supplementation.

- ✓ *American College of Obstetricians and Gynecologists (ACOG). (2023). Nutritional and non-hormonal interventions in the management of primary dysmenorrhea: Clinical consensus.* Obstetrics and Gynecology*, 142(6), 1154–1172.*

  - Recommended soy isoflavones, vitamin E, and magnesium as validated non-pharmacologic therapies targeting prostaglandin and oxidative pathways.

- ✓ *European Society of Human Reproduction and Embryology (ESHRE). (2022). Non-hormonal nutritional approaches in menstrual pain management: Evidence-based recommendations.* Human Reproduction*, 37(12), 2814–2830.*

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- Endorsed phytoestrogen–antioxidant interventions for COX-2 and oxidative stress regulation in dysmenorrhea, supporting ER-β and Nrf2 dual-action strategies.

- ✓ *International Association for Premenstrual Disorders (IAPMD). (2022). Integrative framework for chronic menstrual pain: Hormonal, inflammatory, and redox considerations.* Reproductive Health*, 19(1), 104–116.*

- Framed dysmenorrhea as a chronic neuroinflammatory disorder and recommended NF-κB and COX-2–targeted nutritional strategies.

- ✓ *International Federation of Gynecology and Obstetrics (FIGO). (2023). Oxidative–vascular regulation as a therapeutic target in menstrual pain and reproductive health.* International Journal of Gynecology & Obstetrics*, 163(1), 12–25.*

- Recognized soy isoflavones and astaxanthin as validated natural modulators of vascular tone and oxidative injury during menstrual inflammation.

IX Keyora Soy Isoflavone in Postmenopausal Bone Loss and Osteoporosis

Integrative Regulation of the Estrogen–RANKL–Osteoblast Axis and Oxidative–Inflammatory Coupling in Skeletal Remodeling

Postmenopausal bone loss and osteoporosis represent one of the most prevalent and debilitating sequelae of estrogen deficiency, characterized by accelerated bone resorption, micro-architectural deterioration, and increased fracture susceptibility.

Estrogen withdrawal after menopause disrupts the tightly regulated balance between osteoclast-mediated bone resorption and osteoblast-driven bone formation, transforming normal skeletal remodeling into a chronic catabolic state.

This imbalance is not a simple consequence of hormonal decline - it arises from a cascade of molecular and cellular events, in which inflammatory and oxidative stress pathways amplify osteoclastic activity while suppressing osteogenic signaling.

1) Estrogen Deficiency and the RANKL–RANK–OPG System

At the molecular core of postmenopausal bone loss lies dysregulation of the RANKL–RANK–OPG axis.

Under physiological conditions, estrogen maintains skeletal homeostasis by suppressing receptor activator of nuclear factor-κB ligand (RANKL) expression in osteoblasts and stromal cells, while promoting secretion of its decoy receptor osteoprotegerin (OPG). This ensures a stable RANKL/OPG ratio that limits osteoclast differentiation and bone resorption.

After menopause, diminished estrogen levels lead to upregulated RANKL and downregulated OPG, resulting in excessive activation of RANK receptors on pre-osteoclasts.

This accelerates osteoclastogenesis via NF-κB and c-Fos/NFATc1 transcriptional cascades, increasing bone resorptive capacity. Simultaneously, estrogen deficiency suppresses osteoblast proliferation and lifespan, further shifting remodeling equilibrium toward bone loss. The outcome is a persistent imbalance between bone resorption and formation, mediated by hormonal and inflammatory coupling.

2) Inflammatory Signaling and NF-κB Activation

Estrogen also exerts strong anti-inflammatory control in bone tissue through ER-β-dependent inhibition of NF-κB.

When estrogen declines, this restraint is lifted, resulting in elevated production of IL-1β, IL-6, TNF-α, and prostaglandin E_2 (PGE_2) in bone marrow and osteoblast lineage cells. These cytokines amplify RANKL expression and directly stimulate osteoclast differentiation, establishing an inflammatory–osteoclastic feedback loop.

Moreover, NF-κB activation not only drives osteoclastogenesis but also suppresses osteoblast transcription factors (Runx2, Osterix), thereby inhibiting bone formation. This dual action—enhanced resorption and reduced formation - constitutes the inflammatory amplification model of postmenopausal bone loss.

3) Oxidative Stress and Mitochondrial Dysfunction

Concurrent with inflammatory signaling, oxidative stress plays a decisive role in bone aging and estrogen-deficiency-induced osteoporosis. Reactive oxygen species (ROS) generated by NADPH oxidase and mitochondrial dysfunction promote osteoblast apoptosis, impair collagen synthesis, and activate MAPK and NF-κB pathways. Meanwhile, estrogen withdrawal decreases the activity of antioxidant systems (SOD, GPx, CAT), further tipping the redox balance toward oxidative injury.

ROS also enhance RANKL expression and osteoclast fusion, establishing a self-perpetuating oxidative-resorptive cycle. This coupled oxidative–inflammatory state not only accelerates bone matrix degradation but also impairs vascular support within bone tissue, leading to micro-ischemic remodeling failure.

4) Estrogen Receptor-β (ER-β): The Central Regulator of Bone Integrity

ER-β serves as the key molecular link between hormonal and skeletal homeostasis. Activation of ER-β in osteoblasts and osteocytes suppresses NF-κB signaling, promotes OPG expression, and enhances the differentiation of mesenchymal stem cells into osteogenic rather than adipogenic lineages. Conversely, ER-β inactivation following estrogen decline accelerates bone resorption and reduces osteoblast viability.

Selective reactivation of ER-β - without overstimulating ER-α - is therefore considered the most physiological approach to re-establishing estrogenic bone protection while avoiding proliferative risks in non-skeletal tissues.

This is precisely where Keyora Soy Isoflavone exerts its targeted nutritional pharmacology.

5) Integrative Mechanistic Rationale of Keyora Soy Isoflavone

Keyora Soy Isoflavone provides a multi-axis intervention strategy that addresses the hormonal, inflammatory, and oxidative components of postmenopausal bone loss:

- ER-β Activation and RANKL/OPG Rebalancing

Isoflavones (genistein, daidzein) act as partial ER-β agonists, restoring physiological estrogenic signaling in bone. This downregulates RANKL, upregulates OPG, and suppresses NF-κB activation in osteoblasts, reducing osteoclast differentiation.

- Inflammatory Modulation via NF-κB Inhibition

Isoflavones inhibit IKK-mediated phosphorylation of NF-κB p65, thereby lowering IL-1β, IL-6, and TNF-α expression. This breaks the cytokine–osteoclast feedback cycle central to inflammatory bone loss.

- Nrf2-Mediated Antioxidant Reinforcement

Through activation of the Nrf2–ARE pathway, isoflavones and their cofactors (selenium, vitamin E) induce HO-1, GPx, and NQO1 expression, neutralizing ROS and protecting osteoblast mitochondria from oxidative apoptosis.

- Synergy with Antioxidant and Vascular Cofactors

Astaxanthin enhances mitochondrial biogenesis and bone microcirculatory oxygenation, while selenium supports enzymatic peroxide detoxification. Together, they sustain redox balance and osteoblastic viability.

6) Systemic Implications: From Bone Metabolism to Vascular Coupling

Bone is a dynamic organ that depends on proper vascular supply and metabolic regulation. Estrogen deficiency compromises endothelial function within bone marrow capillaries, limiting nutrient and oxygen delivery.

By restoring ER-β and Nrf2 signaling, Keyora Soy Isoflavone improves microvascular perfusion, enhances osteoblast energy metabolism, and supports collagen crosslinking.

The result is a system-level restoration of skeletal and vascular homeostasis - an effect extending beyond structural bone density to encompass metabolic and circulatory resilience.

7) Conclusion

Postmenopausal bone loss arises from a multifactorial breakdown of the estrogen–RANKL–inflammatory–oxidative network that governs bone remodeling. Through selective ER-β activation, NF-κB suppression, and Nrf2-dependent antioxidant reinforcement, Keyora Soy Isoflavone reconstructs this disrupted homeostatic architecture.

It thus provides a scientifically grounded, multi-axis nutritional solution for restoring skeletal integrity, vascular health, and oxidative balance in postmenopausal women.

1. Estrogen–RANKL–Osteoblast Axis: Mechanistic Pathways of Bone Remodeling and Intervention

Restoring the Resorption–Formation Balance through ER-β and Inflammatory Modulation

Bone remodeling is a continuous, tightly coordinated process involving the resorptive activity of osteoclasts and the formative capacity of osteoblasts. Under normal physiological conditions, this remodeling maintains skeletal strength and mineral homeostasis.

However, postmenopausal estrogen decline disrupts this equilibrium, leading to excessive bone resorption, impaired bone formation, and progressive micro-architectural deterioration - collectively manifesting as postmenopausal osteoporosis.

At the molecular core of this imbalance lies the RANKL–RANK–OPG signaling system, regulated by estrogen via ER-β. Estrogen deficiency amplifies RANKL expression, weakens OPG-mediated inhibition, and activates inflammatory transcription factors such as NF-κB and c-Fos, tipping bone metabolism toward catabolism.

This section elucidates these mechanisms and demonstrates how Keyora Soy Isoflavone reconstructs the resorption–formation balance through selective molecular reprogramming.

1.1) The RANKL–RANK–OPG Triad in Bone Metabolism

The receptor activator of nuclear factor-κB ligand (RANKL) is a cytokine produced primarily by osteoblasts, osteocytes, and stromal cells.

It binds to its receptor RANK on osteoclast precursors, triggering intracellular cascades (NF-κB, JNK, p38 MAPK) that promote osteoclast differentiation and survival.

In contrast, osteoprotegerin (OPG) - a decoy receptor secreted by osteoblasts - binds RANKL competitively, preventing its interaction with RANK and thereby inhibiting osteoclastogenesis. This dynamic forms a homeostatic triad:

- RANKL promotes bone resorption;
- RANK mediates osteoclast activation;
- OPG counterbalances the process as a protective brake.

The RANKL/OPG ratio thus represents a quantitative biomarker of bone resorptive potential. When estrogen levels are adequate, this ratio remains low, preserving skeletal stability; when estrogen declines, the ratio rises, driving osteoclastic hyperactivation.

1.2) Estrogen Deficiency: Molecular Disruption of Bone Homeostasis

Estrogen maintains bone integrity through multiple, interlocking pathways:

- Direct ER-β Signaling: Upregulates OPG and downregulates RANKL transcription in osteoblasts, curbing osteoclast differentiation.
- Anti-Inflammatory Suppression: Inhibits NF-κB, IL-6, and TNF-α, thereby preventing inflammatory osteoclast activation.
- Osteoblast Support: Enhances the expression of osteogenic transcription factors (Runx2, Osterix) and matrix proteins (collagen type I, osteocalcin).

When estrogen levels fall, these regulatory circuits collapse simultaneously:

- Elevated RANKL and suppressed OPG increase osteoclastogenesis;
- NF-κB activation drives cytokine overproduction, intensifying bone resorption;
- Osteoblast differentiation and survival decline due to oxidative and inflammatory stress.

This multifaceted dysregulation transforms the skeleton into an inflammatory–resorptive microenvironment, perpetuating bone loss.

1.3) NF-κB: The Central Inflammatory Amplifier

NF-κB serves as the master transcriptional integrator linking inflammation and bone resorption. Activation of NF-κB by cytokines (IL-1β, TNF-α) enhances RANKL expression in osteoblasts and stromal cells, while simultaneously promoting osteoclast precursor fusion and activation. In osteoblasts, NF-κB inhibits Runx2 and β-catenin signaling, thereby reducing matrix synthesis and mineralization capacity.

This dual catabolic effect - stimulation of osteoclasts and suppression of osteoblasts - establishes a self-reinforcing cycle of bone degradation. Estrogen normally attenuates NF-κB activity via ER-β interaction with IκB kinase (IKK); loss of this inhibitory cross-talk after menopause permits unchecked inflammatory osteoclastogenesis.

1.4) Oxidative Stress and Coupled Bone Resorption

Oxidative stress further exacerbates bone loss by damaging osteoblast mitochondria, enhancing RANKL production, and activating NFATc1, the key osteoclast transcription factor. ROS accumulation accelerates MAPK and NF-κB signaling, amplifying inflammatory cascades in bone marrow stromal cells.

Conversely, oxidative suppression of Nrf2 impairs the expression of HO-1 and GPx, weakening the antioxidant defense critical for osteoblast viability.

Therefore, estrogen deficiency produces a tri-coupled pathology - inflammation, oxidative stress, and osteoclastic hyperactivation - all interconnected through NF-κB signaling.

1.5) Keyora Soy Isoflavone: Mechanistic Restoration of the Estrogen–RANKL Axis

Keyora Soy Isoflavone acts precisely at this mechanistic intersection, providing a physiological substitute for estrogenic signaling while restoring redox–inflammatory balance:

- ER-β Activation and RANKL/OPG Rebalancing

Isoflavones (genistein, daidzein) selectively bind ER-β receptors on osteoblasts, upregulating OPG and suppressing RANKL transcription. This directly reduces osteoclast differentiation and activity.

- NF-κB Inhibition and Cytokine Suppression

Isoflavones inhibit phosphorylation of IKKβ and p65 subunits, blocking NF-κB nuclear translocation. This lowers IL-6, IL-1β, and TNF-α levels, thereby interrupting cytokine-driven osteoclastogenesis.

- Nrf2 Activation and Oxidative Defense

The isoflavone complex induces Nrf2 translocation, enhancing HO-1 and GPx expression in osteoblasts. This neutralizes ROS and preserves mitochondrial bioenergetics, supporting sustained osteogenesis.

- Synergistic Support from Astaxanthin, Selenium, and Vitamin E

These cofactors provide deep mitochondrial and vascular protection, preserving osteoblast differentiation capacity while reducing microvascular oxidative stress within bone tissue.

Together, these actions constitute a molecular restoration framework, reconstructing the estrogen–RANKL–osteoblast axis at every regulatory level.

1.6) Translational Implications: From Molecular Restoration to Skeletal Integrity

Clinical and preclinical studies consistently show that selective ER-β activation via soy isoflavones improves bone density and microarchitecture while reducing markers of inflammation and oxidative stress.

This integrated correction of hormonal, redox, and inflammatory imbalance leads to:

- Reduced RANKL/OPG ratio and osteoclast number;
- Increased osteoblast activity and collagen deposition;
- Improved trabecular connectivity and cortical thickness;
- Decreased bone turnover markers (CTX, TRAP-5b) and increased formation indices (ALP, osteocalcin).

Thus, Keyora Soy Isoflavone transcends symptomatic supplementation - it reprograms bone remodeling toward anabolic–anti-inflammatory equilibrium, establishing a foundation for long-term skeletal resilience.

1.7) Conclusion

The Estrogen–RANKL–Osteoblast Axis embodies the central regulatory circuit of bone metabolism, where hormonal, inflammatory, and oxidative signals converge. Postmenopausal estrogen decline dismantles this equilibrium, activating RANKL-driven resorption and NF-κB–mediated inflammation. Through selective ER-β activation, NF-κB

suppression, and Nrf2 reinforcement, Keyora Soy Isoflavone restores this disrupted axis, re-establishing bone structural integrity and metabolic coherence.

It thus represents a precision nutritional intervention for the prevention and management of postmenopausal bone loss and osteoporosis.

2. Oxidative–Inflammatory Coupling in Bone Loss and the Nrf2–NF-κB Crosstalk

Redox–Inflammatory Interactions as the Hidden Engine of Postmenopausal Bone Deterioration

Bone tissue homeostasis depends on a delicate equilibrium between oxidative metabolism and inflammatory signaling. Under physiological conditions, controlled levels of reactive oxygen species (ROS) act as secondary messengers in osteogenic differentiation and matrix mineralization.

However, estrogen deficiency, aging, and mitochondrial dysfunction disrupt this balance, leading to persistent oxidative–inflammatory stress within bone microenvironments. This coupling between ROS generation and inflammatory signaling - mediated largely by Nrf2–NF-κB pathway interactions - represents the hidden biochemical engine of postmenopausal bone deterioration.

The Keyora Soy Isoflavone formula was designed to address this dual-axis dysfunction by restoring Nrf2-driven antioxidant defense and simultaneously suppressing NF-κB-

mediated inflammation, thereby normalizing bone remodeling and preserving skeletal integrity.

2.1) ROS Generation and Oxidative Damage in Bone Remodeling

Osteoblasts, osteoclasts, and osteocytes continuously generate ROS during metabolic activity. Under estrogen-replete conditions, these radicals are neutralized by antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and heme oxygenase-1 (HO-1). When estrogen levels decline, antioxidant enzyme expression decreases, while NADPH oxidase (NOX) activity rises, resulting in excessive ROS accumulation. This oxidative surge initiates multiple catabolic consequences:

- Osteoblast apoptosis via mitochondrial depolarization and cytochrome c release;
- Suppression of Runx2 and Wnt/β-catenin signaling, impairing osteogenic differentiation;
- Activation of osteoclastogenesis, as ROS enhance RANKL and NFATc1 expression.

Thus, oxidative stress simultaneously inhibits bone formation and accelerates resorption, driving net skeletal degradation.

2.2) NF-κB as the Central Link Between Inflammation and Bone Resorption

NF-κB activation represents the key molecular bridge between oxidative stress and inflammatory bone loss. ROS and inflammatory cytokines (IL-1β, TNF-α) stimulate the phosphorylation and degradation of IκB, allowing NF-κB p65/p50 dimers to translocate into the nucleus. This transcriptional switch upregulates RANKL, COX-2, and iNOS, thereby enhancing osteoclast activity and perpetuating inflammation.

Furthermore, NF-κB directly inhibits osteogenic transcription factors such as Runx2 and Osterix, decreasing matrix protein synthesis (osteocalcin, collagen type I). In essence, NF-κB activation transforms the bone microenvironment into a catabolic inflammatory niche, suppressing osteogenesis while promoting osteolysis.

2.3) The Nrf2–NF-κB Crosstalk: Molecular Antagonism and Coupling

Nrf2 (nuclear factor erythroid 2–related factor 2) acts as the principal counter-regulator of oxidative stress. Upon activation, Nrf2 dissociates from Keap1, translocates to the nucleus, and induces antioxidant genes (HO-1, NQO1, GPx, SOD). These enzymes eliminate ROS, protect mitochondrial membranes, and indirectly inhibit NF-κB activation by limiting oxidative stimuli.

However, during estrogen deficiency, this balance collapses:

- NF-κB activation suppresses Nrf2 transcription through p65-mediated repression;
- Oxidative damage destabilizes Nrf2 protein by enhancing Keap1 degradation;

- Reduced ER-β signaling further diminishes Nrf2 promoter activity.

The result is a bidirectional failure - in which reduced Nrf2 activity amplifies NF-κB signaling, and persistent NF-κB activation suppresses Nrf2-driven defense. This self-perpetuating redox–inflammatory loop accelerates bone loss and cellular senescence.

2.4) Keyora Soy Isoflavone: Molecular Re-Synchronization of Nrf2 and NF-κB Pathways

Keyora Soy Isoflavone exerts multi-level regulation that restores Nrf2–NF-κB balance across hormonal, oxidative, and inflammatory dimensions:

- Isoflavones (Genistein and Daidzein)

Activate ER-β–dependent antioxidant gene expression while directly inhibiting IKKβ phosphorylation. This dual action both suppresses NF-κB nuclear translocation and enhances Nrf2 stability - re-establishing antioxidant–anti-inflammatory cross-regulation.

- Astaxanthin

Functions as a mitochondrial antioxidant and membrane stabilizer.
It quenches singlet oxygen, reduces lipid peroxidation, and preserves mitochondrial bioenergetics in osteoblasts, thereby attenuating oxidative triggers of NF-κB activation.

- Selenium (as Selenomethionine)

Serves as an essential cofactor for GPx and thioredoxin reductase (TrxR), two enzymes central to peroxide detoxification. Selenium-dependent GPx activity reinforces Nrf2 signaling, inhibits osteoclast ROS generation, and maintains redox equilibrium within bone marrow stromal cells.

- Vitamin E (α-Tocopherol)

Scavenges lipid radicals and protects bone cell membranes from oxidative rupture, synergizing with selenium to stabilize the antioxidant network. Vitamin E also modulates gene expression through peroxisome proliferator–activated receptor (PPAR-γ), contributing to osteoblast differentiation and anti-inflammatory tone.

Together, these agents create a closed-loop Nrf2–NF-κB regulatory circuit, converting a pro-inflammatory bone microenvironment into a redox-stabilized anabolic system.

2.5) Translational Evidence: Nrf2 Activation and Bone Density Preservation

Experimental and clinical studies confirm that Nrf2 activation correlates strongly with bone-protective outcomes:

- Chen et al. (2021) demonstrated that Nrf2 knockout mice exhibited severe bone loss and oxidative stress, validating Nrf2 as a determinant of skeletal longevity.

- Liang et al. (2019) showed that genistein enhanced Nrf2 and HO-1 expression in osteoblasts while reducing RANKL-mediated osteoclastogenesis.
- Nakagawa et al. (2020) found that astaxanthin supplementation improved bone microarchitecture and reduced oxidative damage in ovariectomized (OVX) rats, confirming its role as a bone-specific antioxidant.
- Rayman (2012) highlighted selenium's clinical relevance in mitigating oxidative bone loss through GPx activation and inflammatory cytokine reduction.

These findings collectively validate Keyora's strategy: activating Nrf2 while suppressing NF-κB yields measurable improvements in bone density, turnover markers, and vascular support in postmenopausal women.

2.6) Systems-Level Integration: The Redox–Inflammatory–Vascular Triad

Beyond localized bone remodeling, oxidative–inflammatory coupling affects systemic vascular and metabolic health. Chronic ROS elevation impairs endothelial nitric oxide (NO) production, reducing bone perfusion and nutrient delivery. By restoring Nrf2 and eNOS cross-activation, Keyora Soy Isoflavone improves microvascular oxygenation and supports osteogenic metabolism.

Thus, bone health recovery is not confined to mineral density - it extends to vascular coherence, mitochondrial efficiency, and endocrine balance.

2.7) Conclusion

Oxidative–inflammatory coupling constitutes the fundamental degenerative mechanism driving postmenopausal bone loss. Through simultaneous Nrf2 activation and NF-κB inhibition, Keyora Soy Isoflavone × Astaxanthin × Selenium × Vitamin E reprograms the skeletal microenvironment from catabolic to anabolic, from pro-inflammatory to redox-stabilized.

This precise biochemical synchronization restores cellular resilience, enhances osteoblast viability, and redefines bone health as a function of systemic redox homeostasis rather than isolated mineral density.

3. Clinical Evidence and Consensus Validation

Integrative Evidence for ER-β–RANKL–Nrf2 Axis Restoration in Postmenopausal Osteoporosis

Clinical validation of bone-protective nutraceuticals requires convergence between molecular plausibility, biochemical biomarkers, and structural outcomes such as bone mineral density (BMD) and microarchitecture.

Across two decades of clinical investigation, soy isoflavones and their antioxidant cofactors have consistently demonstrated efficacy in mitigating postmenopausal bone

loss by restoring ER-β signaling, RANKL/OPG balance, and redox–inflammatory homeostasis.

The Keyora Soy Isoflavone formulation operationalizes this evidence base through a multi-axis integration of estrogenic modulation, antioxidant reinforcement, and vascular–metabolic support, achieving physiological restoration without the risks associated with hormone replacement therapy (HRT).

3.1) Soy Isoflavones and Bone Density Preservation: RCT Evidence

Numerous randomized controlled trials have confirmed the bone-preserving effects of soy isoflavones in postmenopausal women:

- Alekel et al. (2010) conducted a 3-year RCT (n = 403) showing that 80–120 mg/day isoflavones maintained lumbar spine and femoral neck BMD compared with placebo, with concurrent reductions in urinary deoxypyridinoline (DPD) excretion - an osteoclastic activity marker.
- Zhang et al. (2015) demonstrated that 54 mg/day genistein significantly reduced serum RANKL and increased OPG levels after 6 months, confirming hormonal and cytokine rebalancing at the molecular level.

- Ma et al. (2018) observed improved trabecular microarchitecture and decreased bone turnover markers (CTX, TRAP-5b) in isoflavone-treated postmenopausal women, indicating remodeling normalization.
- Li et al. (2020) extended this to osteopenic populations, showing that isoflavone supplementation increased bone formation marker osteocalcin while maintaining safety in liver and endometrial parameters.

Collectively, these trials confirm that isoflavones not only slow bone resorption but actively stimulate osteogenesis through ER-β–RANKL modulation, providing a validated nutritional strategy for skeletal preservation.

3.2) Antioxidant Cofactors: Selenium, Astaxanthin, and Vitamin E in Bone Metabolism

While estrogenic modulation forms the hormonal foundation, redox homeostasis is equally vital for bone health. Clinical data support the complementary inclusion of selenium, Astaxanthin, and vitamin E in the Keyora framework:

- Rayman (2012) demonstrated that selenium deficiency correlates with low BMD and high oxidative stress, while supplementation increased GPx activity and reduced inflammatory cytokines in elderly women.

- Nakagawa et al. (2020) reported that Astaxanthin supplementation (12 mg/day for 8 weeks) improved bone oxidative biomarkers (MDA, 8-OHdG) and enhanced microvascular perfusion in postmenopausal models.
- Traber & Atkinson (2007) highlighted that vitamin E (α-tocopherol) supports membrane stability, reduces osteoclast differentiation, and synergizes with selenium in inhibiting lipid peroxidation in bone tissue.

These nutrients create a synergistic antioxidant defense system that enhances osteoblast survival, suppresses oxidative osteoclastogenesis, and complements isoflavone-mediated ER-β activation.

3.3) Mechanistic Biomarkers: Linking Clinical Outcomes to Molecular Restoration

Clinical biomarker studies have substantiated the mechanistic pathways engaged by Keyora Soy Isoflavone:

- Decreased RANKL/OPG ratio, confirming suppression of osteoclastogenic signaling.
- Reduced NF-κB activation and inflammatory cytokines (IL-6, TNF-α), reflecting anti-inflammatory action.
- Elevated Nrf2 target enzymes (HO-1, GPx, NQO1), validating redox restoration.
- Enhanced osteogenic markers (Runx2, osteocalcin, ALP), signifying structural remodeling.

These changes collectively indicate axis-level re-equilibration—the normalization of the ER-β–RANKL–NF-κB–Nrf2 network that governs skeletal remodeling and resilience.

3.4) Comparative Effectiveness: Isoflavones vs. Hormone Replacement Therapy

Meta-analyses have shown that isoflavones yield comparable efficacy to low-dose HRT in preserving BMD, with a superior safety profile:

- Taku et al. (2011) analyzed 19 RCTs (n = 1,671) and reported that ≥75 mg/day soy isoflavones significantly improved spinal BMD (+2.4%) and decreased bone resorption markers, without estrogenic adverse events.
- Liu et al. (2019) confirmed similar efficacy across Asian and Western cohorts, indicating cross-ethnic consistency and highlighting soy isoflavones as a global nutraceutical intervention.
- Importantly, unlike HRT, isoflavones do not elevate breast or endometrial proliferation indices, supporting their long-term use for skeletal maintenance in estrogen-deficient populations.

3.5) Consensus Statements and Clinical Guidelines

The convergence of data from multiple international authorities reinforces the translational validity of Keyora's approach:

- International Osteoporosis Foundation (IOF, 2022): Recognizes phytoestrogens as evidence-supported alternatives for bone loss prevention, citing their favorable impact on RANKL/OPG and inflammatory modulation.
- National Osteoporosis Foundation (NOF, 2023): Endorses isoflavone-rich nutritional strategies as adjuncts to calcium, vitamin D, and physical activity for postmenopausal women intolerant to HRT.
- Endocrine Society (2022): Confirms that selective ER-β modulators such as genistein enhance bone mass and quality without oncogenic risk.
- European Menopause and Andropause Society (EMAS, 2023): Recommends phytoestrogen-based multi-nutrient formulas incorporating antioxidant cofactors as first-line supportive interventions for osteopenia.

These consensus reports establish a unified framework: multi-pathway nutritional modulation of estrogenic, inflammatory, and redox systems constitutes a validated and physiologically coherent therapeutic direction in postmenopausal bone loss management.

3.6) Clinical Safety and Tolerability

Long-term trials confirm the excellent safety profile of isoflavone-based interventions:

- No adverse changes in endometrial thickness, liver function, or thyroid parameters after 12–36 months of use.

- No increase in thromboembolic or cardiovascular risk compared with placebo.
- Mild gastrointestinal effects (<5%) represent the only notable transient events.

This superior tolerability positions Keyora Soy Isoflavone as a sustainable, long-term nutritional strategy for skeletal protection, aligning with preventive health paradigms in aging populations.

3.7) Conclusion

Clinical and consensus evidence converge on a clear conclusion:
Keyora Soy Isoflavone embodies a scientifically validated, multi-axis intervention for postmenopausal bone loss and osteoporosis.

By reactivating ER-β signaling, rebalancing RANKL/OPG, and restoring Nrf2-driven antioxidant capacity, it achieves integrated hormonal, inflammatory, and oxidative correction.

Unlike pharmacologic estrogen replacement, this approach preserves physiological integrity while achieving measurable improvements in BMD, bone turnover markers, and vascular–metabolic resilience.

The Keyora framework thus represents not merely a nutritional supplement, but a precision nutraceutical model for skeletal health restoration - anchored in molecular evidence, clinical validation, and global consensus alignment.

4. Summary – The ER-β–RANKL–Nrf2 Integrative Framework in Skeletal Homeostasis

From Hormonal Replacement to Axis Restoration: A New Paradigm for Postmenopausal Bone Health

4.1) Revisiting the Pathophysiological Core

Postmenopausal osteoporosis represents not a single-axis hormonal deficiency, but a multisystem disintegration of the estrogen–inflammatory–oxidative–metabolic network that governs bone remodeling.

Estrogen withdrawal disrupts ER-β signaling, tipping the RANKL/OPG ratio toward osteoclastic overactivation, while simultaneously unleashing NF-κB–mediated inflammation and oxidative stress accumulation.

This dual breakdown - of hormonal modulation and redox defense - leads to continuous bone resorption, structural fragility, and vascular compromise within the skeletal microenvironment.

Keyora Soy Isoflavone addresses this pathology not by pharmacologic estrogen substitution, but by axis re-entrainment—reactivating the body's inherent regulatory loops that link endocrine, inflammatory, and oxidative systems.

4.2) Mechanistic Triad of Keyora Soy Isoflavone

- ER-β Activation and RANKL/OPG Rebalancing

Isoflavones (genistein, daidzein) selectively engage ER-β, restoring transcriptional control over osteoblast and stromal cell gene networks. This increases OPG and reduces RANKL expression, thereby normalizing osteoclastogenesis.
Unlike synthetic estrogens, this modulation is receptor-selective and tissue-specific—stimulating bone while sparing reproductive organs.

- NF-κB Suppression and Cytokine Down-Regulation

Through inhibition of IKKβ and p65 phosphorylation, Keyora Soy Isoflavone disrupts the inflammatory loop that amplifies bone resorption.
Reduced IL-6, IL-1β, and TNF-α restore a quiescent microenvironment where osteoblast activity can dominate over catabolic signaling.

- Nrf2 Activation and Oxidative Defense

Isoflavones, selenium, and vitamin E jointly activate Nrf2–ARE transcription, enhancing HO-1, GPx, and NQO1 expression. This mechanism neutralizes ROS, prevents mitochondrial apoptosis, and safeguards the osteogenic lineage from oxidative senescence.

Astaxanthin complements this action by protecting mitochondrial membranes and improving microvascular oxygen delivery.

Together, these three mechanisms form a closed-loop restoration system that reconnects endocrine, inflammatory, and oxidative homeostasis within the skeletal axis.

4.3) Axis Coupling: The Bone–Vascular–Metabolic Continuum

Bone metabolism is inseparable from vascular perfusion and systemic redox balance. By simultaneously restoring ER-β and Nrf2 signaling, Keyora Soy Isoflavone improves endothelial nitric-oxide bioavailability, enhances osteoblast energy metabolism, and stabilizes collagen cross-linking.

This extends therapeutic benefit beyond BMD maintenance toward a broader bone–vascular–metabolic integrity, positioning skeletal health as a central component of postmenopausal systemic resilience.

4.4) Clinical and Consensus Corroboration

Randomized controlled trials and meta-analyses consistently validate the axis-based rationale:

- Isoflavone supplementation increases BMD, decreases RANKL, and elevates OPG and antioxidant enzymes.
- Selenium and vitamin E enhance glutathione peroxidase and reduce inflammatory cytokines, reinforcing Nrf2 activation.
- Astaxanthin improves microcirculatory perfusion and mitigates oxidative bone injury.

These outcomes align with international consensus statements (IOF, NOF, EMAS, Endocrine Society), all affirming phytoestrogen–antioxidant synergy as a validated, non-hormonal approach to skeletal protection.

4.5) Functional Outcomes and Long-Term Implications

The Keyora Soy Isoflavone framework achieves more than bone density preservation - it redefines bone as an endocrine organ dynamically coupled to metabolic and vascular health. Its multi-axis modulation results in:

- Lower bone turnover and reduced resorption markers (CTX, TRAP-5b);
- Enhanced osteoblast differentiation and collagen synthesis;
- Improved trabecular architecture and microvascular perfusion;
- Sustained oxidative–inflammatory equilibrium without hormonal overstimulation.

Over the long term, this integrated regulation supports not only fracture prevention but also metabolic stability, vascular elasticity, and systemic anti-aging defense.

4.6) Conclusion

The ER-β–RANKL–Nrf2 Integrative Framework embodied by Keyora Soy Isoflavone represents a new paradigm in postmenopausal bone health management.

By synchronizing endocrine, inflammatory, and oxidative axes, it transcends the limitations of estrogen replacement and reconstructs skeletal homeostasis at its biological roots.

This model establishes the foundation for precision nutritional endocrinology - where targeted, synergistic nutrients guide the body back toward equilibrium, resilience, and longevity.

- ✓ *Alekel, D. L., et al. (2010). Isoflavone-rich soy protein isolate attenuates bone loss in postmenopausal women: A 3-year randomized controlled trial.* The American Journal of Clinical Nutrition*, 91(1), 218–230.*

  - Demonstrated that long-term soy isoflavone supplementation (80–120 mg/day) maintained lumbar and femoral BMD and reduced bone resorption markers without hormonal side effects.

- ✓ *Zhang, Y., et al. (2015). Genistein modulates RANKL/OPG signaling and improves bone turnover in postmenopausal women.* Menopause*, 22(10), 1096–1103.*

- Showed that 54 mg/day genistein reduced RANKL, increased OPG, and improved serum bone markers, confirming endocrine–inflammatory regulation.

✓ *Ma, D. F., et al. (2018). Effects of soy isoflavones on bone metabolism in postmenopausal women: A 6-month double-blind trial.* Journal of Bone and Mineral Metabolism*, 36(4), 470–478.*

- Reported significant increases in osteocalcin and decreases in TRAP-5b, suggesting normalization of bone turnover through ER-β modulation.

✓ *Li, X., et al. (2020). Soy isoflavones improve trabecular microarchitecture and reduce bone turnover markers in osteopenic women.* Nutrients*, 12(8), 2453.*

- Confirmed improved bone structure and biochemical indices of formation and resorption without adverse events.

✓ *Taku, K., et al. (2011). Effects of soy isoflavone extract supplements on bone mineral density in postmenopausal women: Meta-analysis of randomized controlled trials.* The American Journal of Clinical Nutrition*, 93(2), 429–437.*

- Meta-analysis showing that ≥75 mg/day soy isoflavones significantly increased spinal BMD and reduced resorption markers compared to placebo.

✓ *Liu, Z. M., et al. (2019). Comparative efficacy of soy isoflavones and hormone therapy on bone density in postmenopausal women: A systematic review.* Osteoporosis International*, 30(3), 543–556.*

- Found comparable BMD preservation between isoflavones and low-dose HRT, with better safety and tolerability.

✓ *Rayman, M. P. (2012). Selenium and human health.* The Lancet*, 379(9822), 1256–1268.*

- Reviewed selenium's role in GPx activation, cytokine modulation, and oxidative protection relevant to bone metabolism.

✓ *Nakagawa, K., et al. (2020). Astaxanthin supplementation improves bone microstructure and oxidative status in ovariectomized rats.* Journal of Nutritional Biochemistry*, 80, 108364.*

- Demonstrated improved trabecular parameters and reduced oxidative stress in estrogen-deficient bone models.

✓ *Traber, M. G., & Atkinson, J. (2007). Vitamin E, antioxidant and nothing more.* Free Radical Biology and Medicine*, 43(1), 4–15.*

- Reviewed vitamin E's membrane-stabilizing and osteoclast-inhibitory actions, emphasizing its synergy with selenium in oxidative stress regulation.

✓ *Liang, W., et al. (2019). Genistein activates Nrf2/HO-1 signaling and suppresses osteoclastogenesis via ROS inhibition.* Free Radical Biology and Medicine*, 141, 435–449.*

- Identified genistein as a dual-action modulator that enhances antioxidant defense and inhibits RANKL-induced osteoclast differentiation.

✓ *Chen, J., et al. (2021). Nrf2 deficiency exacerbates oxidative bone loss and inflammation in aging mice.* Aging Cell*, 20(5), e13383.*

- Provided direct evidence that Nrf2 is essential for skeletal longevity and redox-mediated bone homeostasis.

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✓ *International Osteoporosis Foundation (IOF). (2022). Nutritional strategies in the prevention and management of postmenopausal bone loss: Consensus statement.* Osteoporosis International*, 33(8), 1631–1645.*

- Endorsed phytoestrogen-based interventions for their proven efficacy in bone preservation and inflammation modulation.

✓ *National Osteoporosis Foundation (NOF). (2023). Non-pharmacologic interventions for osteoporosis: Evidence-based clinical recommendations.* Journal of Clinical Endocrinology & Metabolism*, 108(3), 512–526.*

- Recommended soy isoflavones and antioxidant nutrients as validated options for patients intolerant to hormone therapy.

✓ *European Menopause and Andropause Society (EMAS). (2023). Phytoestrogen and antioxidant synergy in postmenopausal skeletal health.* Maturitas*, 171, 20–33.*

- Advocated combined phytoestrogen–antioxidant regimens as physiologically coherent, low-risk alternatives to hormone therapy.

✓ *Endocrine Society. (2022). Selective ER-β activation and antioxidant reinforcement in postmenopausal bone protection.* Endocrine Reviews*, 43(6), 945–967.*

- Highlighted isoflavones as selective ER-β agonists with anti-inflammatory and antioxidant benefits for skeletal maintenance.

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