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Review Article

Network-Based Supplementation in Lipedema Management: Synergistic Interactions Among Lipecoffee® Bioactives

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Abstract

Background: Lipedema is a chronic, progressive loose-connective-tissue disorder characterized by adipose-tissue inflammation, microangiopathy, Extracellular-Matrix (ECM) remodeling, mitochondrial dysfunction and persistent pain. Increasing evidence indicates that its pathophysiology is driven by sustained activation of NF-κB, COX-2, pro-inflammatory cytokines (IL-6, TNF-α), oxidative stress, and metabolic inflexibility. Because affected women often develop caloric–protein insufficiency due to repeated restrictive dieting (and given the metabolic resistance of lipedema adipose depots) nutritional strategies targeting isolated nutrients appear insufficient. Instead, a systems-biology perspective suggests that coordinated, multi-nutrient interactions may exert synergistic metabolic and anti-inflammatory effects.

Objective: This integrative review examines the mechanistic and clinical relevance of "network-based supplementation," using the nutrient matrix of LipeCoffee® as a case model. The formulation combines bioactives that interact across shared biochemical axes: antioxidant (Nrf2), inflammatory (NF-κB/COX-2), mitochondrial–energetic (SIRT1–AMPK), microvascular and neuromodulation.

Methods: A narrative review was conducted using PubMed/MEDLINE, Cochrane Library, JAMA Network and related sources (1990–2025), selecting randomized controlled trials, mechanistic studies and meta-analyses evaluating compounds identical or mechanistically analogous to those in the formulation. Extracted pathways included redox modulation, mitochondrial biogenesis, adipose-tissue inflammation, microvascular function, ECM stability, and neuromodulatory mechanisms.

Results: The combined effects of polyphenols (curcumin, quercetin, trans-resveratrol, citrus bioflavonoids, Pinus pinaster, Moro orange), metabolic cofactors (L- carnitine, creatine, CoQ10, B-complex, magnesium), structural nutrients (type II collagen peptides, silicon, hyaluronic acid), amino acids (taurine, L-theanine) and coffee-derived compounds produce convergent actions on oxidative stress, inflammatory signaling, mitochondrial respiration, endothelial function and ECM organization. Evidence from multi-ingredient trials demonstrates that nutrient combinations often outperform isolated nutrients in modulating metabolic, cognitive and stress-response parameters, supporting the theoretical basis for network supplementation.

Conclusion: The nutrient matrix examined exemplifies how coordinated nutrient interactions may generate emergent physiological benefits aligned with lipedema pathophysiology. Network-based supplementation provides a mechanistic rationale for targeting lipedema's multisystemic dysfunctions, chronic inflammation, microangiopathy, mitochondrial fatigue, ECM fragility and neurocognitive burden. Well-designed randomized clinical trials are needed to confirm translational efficacy in lipedema populations.

Keywords: Network-based supplementation, Lipedema, Chronic inflammation, Bioactives, Antioxidant, Redox modulation, Mitochondrial biogenesis, Adipose-tissue inflammation, Neuromodulation

Introduction

Lipedema is a chronic inflammatory-metabolic disease, characterized by progressive disorder of loose connective tissue, particularly the subcutaneous adipose compartment, that predominantly affects women worldwide. Individuals with lipedema commonly experience intense pain, disproportionate and unexplained fat accumulation, a persistent sensation of heaviness and tension in the lower limbs, muscle weakness, sleep-disordered breathing, and marked impairment in quality of life [1, 2]. Because its clinical presentation overlaps with several other conditions, including: obesity, lymphedema, and chronic venous disease; lipedema is frequently underrecognized or misdiagnosed in routine clinical practice [1,3]. Current evidence characterizes lipedema as a meta-inflammatory disorder involving tightly interconnected immune and metabolic dysfunctions. These alterations appear to be driven by sustained NF-κB activation, COX-2 upregulation, increased release of pro-inflammatory cytokines (IL-6, TNF-α), chronic oxidative stress, and extensive extracellular matrix remodeling [4, 5, 6]. *Rabiee* [4] demonstrated a significant increase in IL-6, TNF-α, and COX-2 expression within lipedema-affected adipose tissue. *Sun et al.* [5] and *Kruppa et al.* [6] further documented adipocyte hyperplasia, interstitial fibrosis, and persistent oxidative stress as hallmark features of the disease. These pathological changes culminate in microangiopathy, localized hypoxemia, and neurogenic inflammation, mechanisms that clinically manifest as pain, a sensation of heaviness, and heightened cutaneous sensitivity. Importantly, low-grade chronic inflammation functions as a central pathogenic axis, linking endothelial dysfunction, lymphatic impairment, and mitochondrial fatigue. Consequently, therapeutic strategies must extend beyond isolated anti-inflammatory interventions and instead aim to re-orchestrate global metabolic networks, a goal that network-based supplementation seeks to address.

Although lipedema is frequently mischaracterized as a disorder of caloric excess, emerging clinical reports indicate that many affected women (particularly those who repeatedly engage in restrictive dieting in an effort to reduce lower-body volume) may develop varying degrees of caloric–protein malnutrition. Wright and Herbst [1] describe a representative case in which prolonged dietary restriction led to hypoalbuminemia, lymphopenia, hypolipidemia and global nutrient deficiency, while the pathognomonic adipose tissue of lipedema remained largely unchanged. This paradox reflects the metabolic resistance of lipedema-affected adipose depots to weight-loss interventions and highlights the clinical risk of catabolic nutritional states. Caloric-protein inadequacy may further impair lymphatic and mitochondrial function, exacerbate low-grade inflammation and increase fatigue, factors that compromise tissue repair and metabolic resilience. Within this context, targeted nutritional strategies, including network-based supplementation, become particularly relevant: by supplying bioactive compounds, micronutrients and metabolic cofactors that are difficult to obtain in adequate amounts through highly restrictive diets, supplementation may help correct subclinical deficiencies, modulate inflammatory pathways, support mitochondrial bioenergetics and restore metabolic homeostasis in lipedema.

Network-based supplementation is grounded in the hypothesis that the concomitant action of multiple nutrients may elicit more robust physiological effects than those observed when the same nutrients are administered individually, due to mechanisms of cooperation, complementarity, and metabolic interaction [7]. Although much of the nutrition literature has traditionally focused on evaluating micronutrients and bioactive compounds in isolation, it is widely recognized that these elements participate in interconnected metabolic networks, in which interdependent relationships may generate additive, synergistic, or modulatory responses [7]. Importantly, the study of how a single nutrient influences human physiology is not without merit, as adequate intake of individual nutrients remains fundamental for preventing specific nutritional deficiencies and for supporting essential biochemical pathways. However, the Dietary Reference Intakes (DRIs), while crucial for establishing thresholds that prevent inadequacy or excess, were not designed to capture or quantify the emergent properties or synergistic effects that may arise from the simultaneous consumption of multiple nutrients.

A meta-analysis of 35 randomized controlled trials demonstrated significantly greater gains in lean mass and strength among healthy adults who consumed multi- ingredient supplements, formulations designed to influence multiple physiological pathways, compared with those who consumed protein alone [8]. In another randomized, double-blind, placebo-controlled clinical trial, Coenzyme Q10 (CoQ10) was combined with a multivitamin complex, and the findings indicated that this combination modulated parameters associated with cerebral blood flow, which the authors hypothesized could confer beneficial effects on neurovascular function [9]. With respect to anxiety and stress, *Boyle et al.* [10] examined the synergistic effects of nutrient combinations in 100 moderately stressed adults. Participants received oral supplementation with one of the following: (1) rhodiola + green tea extract + magnesium (Mg) + B-complex vitamins; (2) rhodiola + Mg + B-complex vitamins; (3) green tea extract + Mg + B-complex vitamins; or (4) placebo, in a parallel, double-blind design. All participants subsequently underwent the Trier Social Stress Test, consisting of a public speech and a mental arithmetic task performed before a non-responsive human panel. A synergistic effect was observed: although most interventions produced some degree of benefit, the most pronounced increase in resting theta-band Electroencephalographic (EEG) activity, typically associated with a relaxed yet attentive state, occurred in the group receiving the full nutrient combination (rhodiola + green tea extract + Mg + B-complex vitamins). This comprehensive combination attenuated subjective stress, anxiety, and mood disturbances to a greater extent than any individual subset of nutrients. In a subsequent study conducted by the same research group, the identical multi-nutrient formula (rhodiola + green tea extract + Mg + B-complex vitamins) was shown to enhance spectral theta activity during two attention-demanding cognitive tasks, suggesting an improved attentional capacity under stress when compared with smaller, isolated nutrient groupings [11]. In light

of these considerations, this review aims to critically examine the potential physiological, metabolic, and clinical benefits associated with the combined intake of the various nutrients contained in the Lipecoffee® supplement, relating them to scientific evidence of antioxidant, anti-inflammatory, and metabolic modulation within the context of lipedema and low-grade chronic inflammation.

Materials and Methods

This study was conducted as an integrative narrative review, covering the period from January 1990 to January 2025, with the aim of analyzing the concept of network supplementation through mechanistic, clinical, and translational evidence of the bioactive compounds contained in the LipeCoffee® formulation. A systematic search was performed in the main indexed databases, including PubMed/MEDLINE, Cochrane Library, JAMA Network, Frontiers in Nutrition, Clinical Nutrition ESPEN, in addition to complementary manual searches in the reference lists of important publications. The search strategy incorporated a combination of MeSH and free-text terms, including: lipedema, loose connective tissue disorders, low-grade chronic inflammation, nutrient synergy, network nutrition, systems biology, mitochondrial function, oxidative stress, Nrf2, NF-κB, SIRT1, AMPK, microcirculation, and endothelial dysfunction. Additional molecular descriptors related to the mechanisms of action of the bioactives in LipeCoffee® were also included, such as: curcumin, resveratrol, quercetin, caffeine, chlorogenic acids, L-carnitine, creatine, citrus bioflavonoids, vitamin C, B-complex vitamins, magnesium, zinc, silicon, hyaluronic acid and collagen.

Eligibility Criteria Included

1) Randomized controlled trials, clinical trials, meta- analyses, systematic reviews, mechanistic studies, and high-quality preclinical evidence directly evaluating nutrients or compounds identical (or mechanistically analogous) to those present in LipeCoffee®; 2) Studies examining effects on inflammatory and metabolic pathways relevant to lipedema, specifically the molecular axis Nrf2↑ → NF-κB↓

→ COX-2↓ → SIRT1↑ → AMPK↑; 3) Publications assessing outcomes related to oxidative stress reduction, mitochondrial bioenergetics, microvascular function, endothelial integrity, adipose-tissue inflammation, neurogenic pain, and metabolic modulation.

Excluded Were

Non-peer-reviewed sources, opinion pieces without biochemical evidence, animal studies lacking translational relevance, and studies evaluating compounds at doses not comparable to physiologically meaningful human intake.

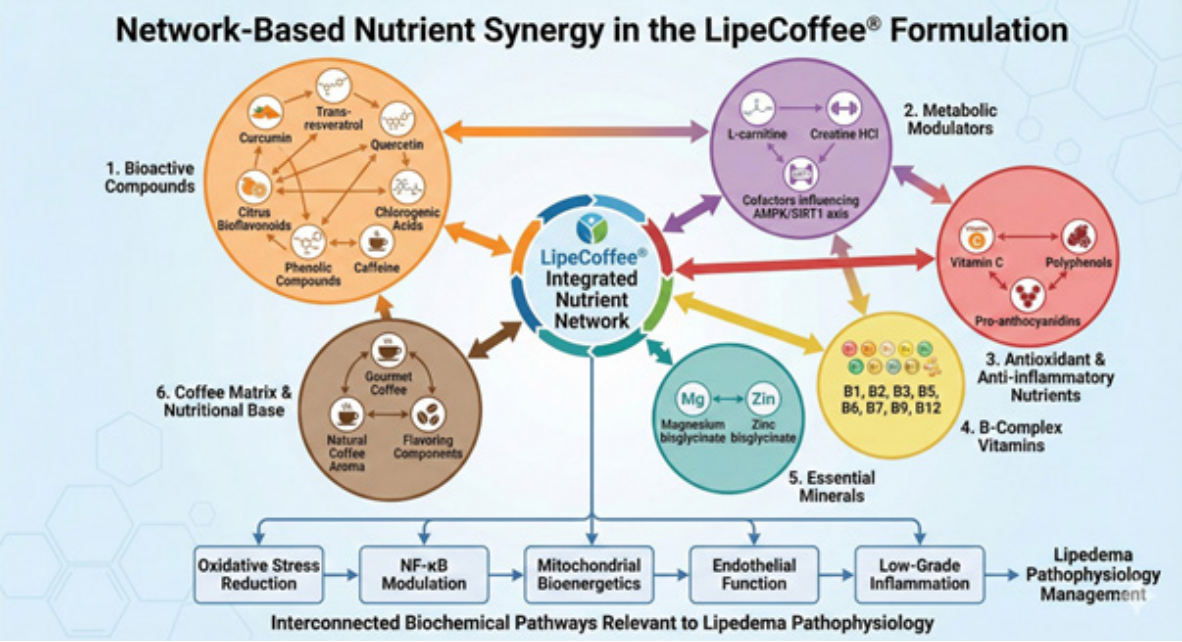

Figure 1: Network-Based Nutrient Synergy in the LipeCoffee® Formulation. This figure illustrates the integrated nutrient network present in the LipeCoffee® formulation, emphasizing the coordinated interactions among bioactive compounds, metabolic modulators, antioxidant micronutrients, B-complex vitamins, essential minerals, and the coffee matrix. The circular diagram depicts six functional domains: (1) Bioactive Compounds (curcumin, trans-resveratrol, quercetin, moro orange extract, chlorogenic acids, caffeine, phenolic compounds); (2) Metabolic Modulators (L-carnitine, creatine HCl, taurine, L-theanine);(3) Antioxidant and Anti-inflammatory Nutrients (vitamin D3, vitamin C, polyphenols, pro-anthocyanidins); (4) B-Complex Vitamins (B1, B2, B3, B5, B6, B7, B9, B12); (5) Essential Minerals (magnesium bisglycinate, zinc bisglycinate, copper, selenium); and (6) Coffee Matrix & Nutritional Base (gourmet coffee, natural coffee aroma, whey protein isolate). Together, these nutrients support interconnected biochemical pathways linked to oxidative stress reduction, NF-κB modulation, mitochondrial bioenergetics, endothelial function, and low-grade inflammation relevant to lipedema pathophysiology.

All eligible studies were independently screened for relevance to the bioactive matrix of LipeCoffee®, which includes: curcumin/phytosomal curcuminoids; trans- resveratrol; quercetin; citrus bioflavonoids; l-carnitine; creatine HCl; caffeine and chlorogenic acids (coffee extract); vitamin C; B-complex vitamins (B1, B2, B3, B5, B6, B7, B9, B12); magnesium bisglycinate; zinc bisglycinate (Figure 1). For each compound, mechanistic pathways were extracted and categorized according to their upstream or downstream role in antioxidant signaling (Nrf2/SOD/GPx), inflammatory suppression (NF-κB, COX-2, TNF-α, IL-6), metabolic regulation (SIRT1–AMPK axis), mitochondrial biogenesis (PGC-1α), and microcirculatory or endothelial modulation. The methodological approach prioritized conceptual coherence, assessing how the simultaneous activity of these bioactives may generate emergent, synergistic effects consistent with network-based supplementation models and the systems-biology framework applied to chronic inflammatory disorders such as lipedema (Figure 1).

Network-Based Supplementation in Lipedema Management

The results of this analysis indicate that the LipeCoffee® formulation comprises an interdependent matrix of nutrients, including soluble coffee (caffeine), proteins and bioactive peptides (isolated whey protein; type II collagen), functional amino acids (L- carnitine, taurine, L-theanine), essential mineral cofactors (magnesium, zinc, copper, selenium), vitamins (C, D3, and the complete B-complex), polyphenolic compounds (turmeric/curcumin, quercetin, resveratrol, Pinus pinaster extract, Moro orange extract), as well as coenzyme Q10 and hyaluronic acid. When considered collectively, these compounds form a coordinated network of metabolic, antioxidant, and anti-inflammatory modulators whose actions converge on three major molecular axes implicated in lipedema: (1) the Nrf2-driven cytoprotective response, (2) the NF-κB/COX-2 inflammatory cascade, and (3) the SIRT1–AMPK bioenergetic pathway. The synergistic physiological effects arising from this network-based supplementation approach are detailed below.

Bioenergetic–Mitochondrial Function

Caffeine: One of the key components of the mitochondrial-energetic axis of the LipeCoffee® formulation is soluble coffee, a natural source of caffeine. Caffeine is rapidly absorbed in the stomach and proximal small intestine and distributed throughout the body via systemic circulation, exerting well-characterized neuroactive and metabolic effects. Hepatic metabolism occurs primarily through cytochrome P450 1A2 (CYP1A2), generating three major dimethylxanthines (paraxanthine, theobromine and theophylline) which retain distinct biological activities [12] (Figure 2). Paraxanthine enhances lipolysis through increased mobilization of fatty acids; theobromine promotes vasodilation; and theophylline exerts bronchodilatory effects through relaxation of airway smooth muscle [13] (Figure 2).

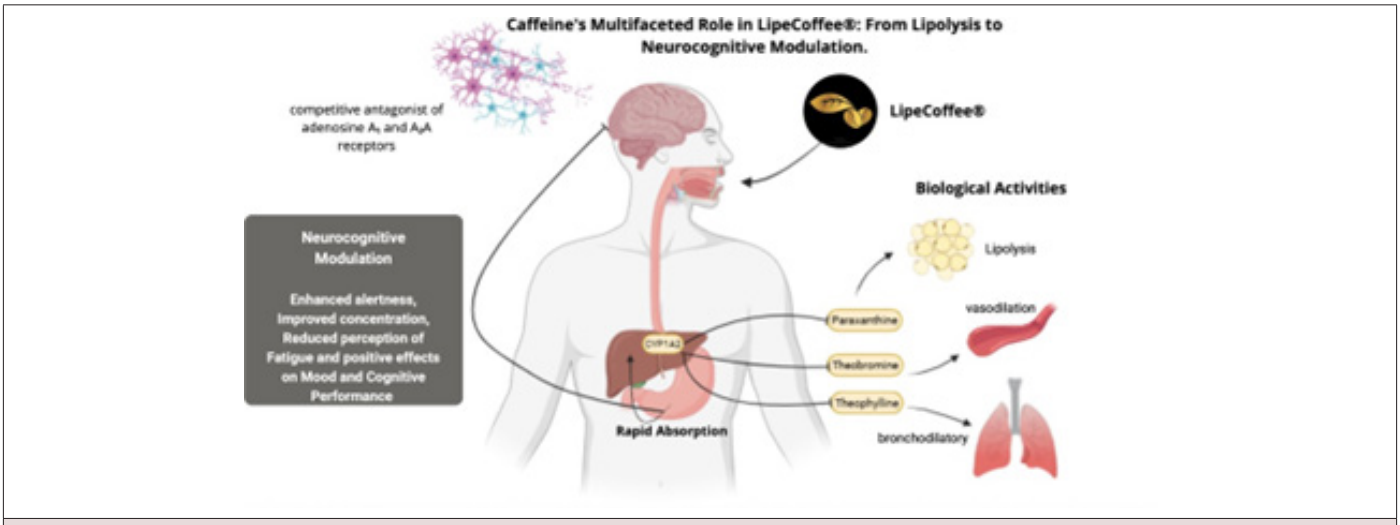

Figure 2: Integrated mechanisms of caffeine within the Bioenergetic–Mitochondrial Function domain of the LipeCoffee® formulation. Caffeine is rapidly absorbed in the stomach and proximal small intestine and distributed systemically, where it exerts metabolic and neuroactive effects through competitive antagonism of adenosine A_1 and A_2A receptors. After hepatic metabolism by cytochrome P450 1A2 (CYP1A2), caffeine generates three primary dimethylxanthines-paraxanthine, theobromine, and theophylline—each contributing distinct physiological actions. Paraxanthine enhances lipolysis by promoting fatty-acid mobilization; theobromine induces vasodilation; and theophylline exerts bronchodilatory effects through relaxation of airway smooth muscle. Together, these metabolites amplify caffeine's capacity to increase mitochondrial activity and support lipid mobilization.

Lipolysis, the hydrolytic breakdown of triacylglycerols stored within adipocytes is regulated by a highly coordinated endocrine and intracellular signaling network. Catecholamines (epinephrine and norepinephrine), glucagon and adrenocorticotropic hormone stimulate lipolysis, whereas insulin is its principal inhibitor [14,15]. Activation of β-adrenergic receptors induces conformational changes in G Protein–Coupled Receptors (GPCRs), stimulating adenylate cyclase and increasing intracellular Cyclic Adenosine

Monophosphate (cAMP). Elevated cAMP activates Protein Kinase A (PKA), which phosphorylates and activates Hormone-Sensitive Lipase (HSL) and Adipose Triglyceride Lipase (ATGL), accelerating the sequential hydrolysis of triglycerides into diacylglycerol, monoacylglycerol, free fatty acids and glycerol. Conversely, reduced cAMP concentrations suppress lipolytic flux [14, 15]. Phosphodiesterases (PDEs) degrade cAMP into AMP, and caffeine acts as a non-selective PDE inhibitor, thereby preventing cAMP breakdown and sustaining PKA-mediated lipolytic signaling [16]. In addition to PDE inhibition, caffeine enhances the release of catecholamines and augments β-adrenergic receptor activity, amplifying the upstream signaling cascade leading to HSL activation [16]. The combined effect is an increase in lipolytic rate, fatty-acid mobilization and metabolic substrate availability for mitochondrial β-oxidation [17,18,19]. Furthermore, caffeine has been shown to facilitate lymphatic drainage within adipose tissue, contributing to the clearance of lipolysis-derived metabolites, inflammatory byproducts and interstitial waste that can otherwise impair microcirculation, an especially relevant mechanism in disorders characterized by tissue congestion and microvascular dysfunction, such as lipedema [17,18,19]. Beyond its metabolic effects, caffeine exhibits notable antioxidant properties. Leon-Carmona and Galano [20] demonstrated that caffeine is an efficient scavenger of hydroxyl (•OH) and alkoxyl radicals, moderately effective against hydroperoxyl radicals (HOO•), though less potent against superoxide (O_2•$^-$) and alkylperoxyl species. Through these mechanisms, caffeine contributes to redox homeostasis and the mitigation of oxidative stress, a central driver of mitochondrial dysfunction and chronic low-grade inflammation [20].

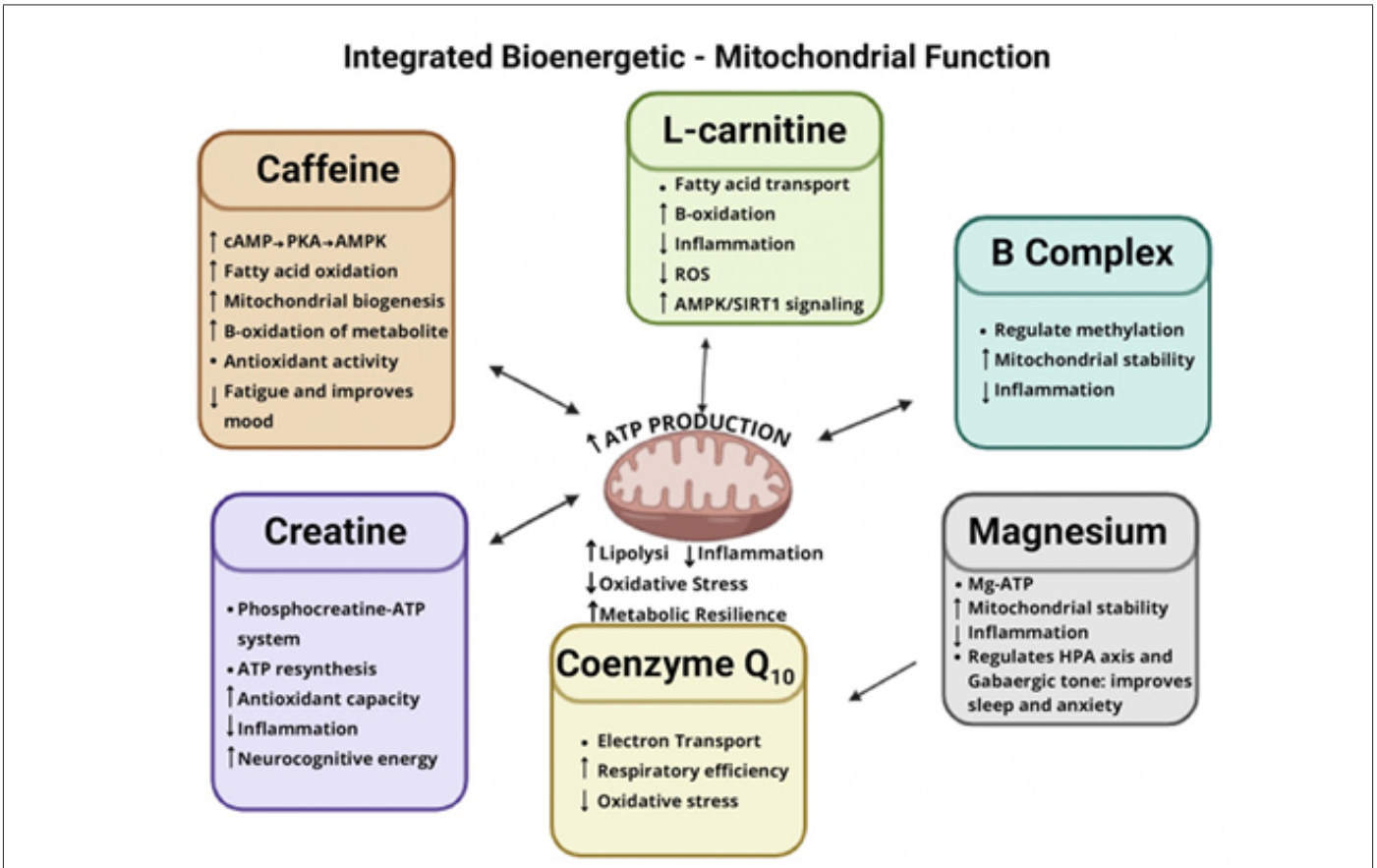

Figure 3: Integrated Bioenergetic – Mitochondrial Function. This figure illustrates the integrated LipeCoffee® bioactives involved in bioenergetic and mitochondrial function, highlighting their convergent effects on ATP synthesis, oxidative stress reduction, and the enhancement of metabolic resilienceCaffeine enhances lipolysis and mitochondrial biogenesis via cAMP–PKA–AMPK signaling, while creatine supports rapid ATP resynthesis and mitigates oxidative stress through the phosphocreatine system. L-carnitine facilitates fatty acid transport into mitochondria, increasing β-oxidation and reducing inflammation and ROS burden. The B-complex vitamins (B1, B2, B3, B5, B6, B9, B12) stabilize mitochondrial enzyme function and methylation-dependent metabolic regulation. Coenzyme Q10 acts within the electron transport chain to improve respiratory efficiency and antioxidant defense. Magnesium, essential for Mg-ATP complex formation, contributes to mitochondrial stability and modulates neuroendocrine stress responses. Collectively, these compounds converge on core bioenergetic pathways-enhancing ATP production, reducing inflammation and oxidative stress, and strengthening mitochondrial performance-mechanisms particularly relevant for conditions characterized by chronic low-grade inflammation such as lipedema.

Caffeine metabolites also influence neurochemical signaling. After hepatic demethylation, paraxanthine, theobromine and theophylline are further converted to methylxanthine derivatives and uric acid; only approximately 10% of ingested caffeine is excreted unchanged in urine [12]. In the central nervous system, caffeine acts as a competitive antagonist of adenosine A_1 and A_2A receptors [21]. Owing to structural similarity with adenosine, caffeine occupies these receptors without activating them, thereby disinhibiting neuronal activity. This blockade modulates the release of acetylcholine, dopamine, norepinephrine, γ-Aminobutyric Acid (GABA) and serotonin, producing enhanced alertness, improved concentration, reduced perception of fatigue and positive effects on mood and cognitive performance [22]. Collectively, these actions highlight caffeine as a multifaceted bioactive compound with roles in lipolysis, mitochondrial substrate availability, antioxidant defense, microvascular function and neurocognitive modulation, mechanisms that synergize with other components of the LipeCoffee® formulation within a network-based supplementation framework (Figure 3).

L-Carnitine: is an essential determinant of mitochondrial fatty-acid transport and cellular bioenergetics. Its primary metabolic function involves shuttling long-chain fatty acids into the mitochondrial matrix via the carnitine shuttle system, coordinated by CPT1, CACT and CPT2, as extensively described by *Ramsay et al.* [23] and *Longo et al.* [24]. This mechanism enables β-oxidation and ATP production under conditions of elevated metabolic demand. Impairment of this transport pathway, whether secondary to metabolic inflexibility, chronic inflammation or mitochondrial dysfunction, reduces oxidative capacity and promotes lipid accumulation, a phenomenon relevant to adipose- tissue disorders with microvascular impairment and tissue hypoxia, such as lipedema [24]. Beyond substrate transport, L-carnitine modulates mitochondrial redox balance by buffering excess acyl-CoA and preventing buildup of toxic acyl intermediates that impair electron-transport efficiency, as noted by Malaguarnera [24,25]. Clinical and translational studies demonstrate that carnitine supplementation increases mitochondrial membrane potential, enhances fatty-acid oxidation rates, and supports NAD^+ regeneration through improved TCA-cycle flux. These adaptations attenuate mitochondrial fatigue, commonly reported in individuals with chronic low-grade inflammation, and preserve mitochondrial structure under oxidative stress [26].

L-carnitine also displays anti-inflammatory properties independent of its bioenergetic function. *Derosa et al.* [27] showed that supplementation reduces circulating IL-6, TNF-α and high-sensitivity CRP in individuals with metabolic syndrome. L-carnitine downregulates NF-κB activity and inhibits NLRP3 inflammasome signaling, mitigating chronic low-grade inflammation that contributes to adipocyte hypertrophy, fibrotic remodeling and nociceptive hypersensitivity [28], core elements of lipedema pathophysiology. Furthermore, L-carnitine interacts synergistically with other components of the LipeCoffee® formulation. Its combination with caffeine, creatine, B- complex vitamins and polyphenols augments AMPK/SIRT1 signaling, mitochondrial biogenesis and lipid mobilization. Studies by Volek et al. [29] demonstrate that L-carnitine improves exercise recovery, enhances tissue perfusion and reduces muscle soreness, effects particularly relevant for women with lipedema, who commonly report fatigue, impaired mitochondrial efficiency and reduced microvascular function. Together, these properties position L-carnitine as a mechanistically rational bioactive within a network- based supplementation model aimed at restoring metabolic flexibility, mitochondrial resilience and systemic bioenergetic homeostasis (Figure 3).

Creatine: Creatine plays a central role in cellular bioenergetics through the Phosphocreatine (PCr) system, which buffers ATP availability in tissues with high and fluctuating energy demands. The Creatine Kinase (CK) shuttle facilitates rapid phosphorylation of ADP to ATP, stabilizing the cellular energy charge and supporting mitochondrial efficiency. Wyss & Kaddurah-Daouk [30] describe the creatine– phosphocreatine system as a fundamental "energy thermostat" that sustains ATP turnover during metabolic stress. Beyond immediate ATP resynthesis, creatine exerts profound effects on mitochondrial physiology. Roschel & Gualano [31] demonstrated that creatine supplementation improves mitochondrial respiration, enhances oxidative capacity and increases the expression of genes involved in mitochondrial biogenesis. In parallel, *Kreider et al.* [32] report that creatine reduces mitochondrial oxidative stress by stabilizing mitochondrial permeability transition pores and attenuating Reactive Oxygen Species (ROS) production. This antioxidant-like effect complements the actions of polyphenols such as curcumin, quercetin and resveratrol present in LipeCoffee®, all of which modulate Nrf2 activity and reduce mitochondrial ROS generation. The combined impact is a more efficient, resilient mitochondrial network capable of supporting higher rates of lipid oxidation. This buffering capacity is particularly relevant in conditions characterized by impaired mitochondrial function, reduced oxidative phosphorylation and chronic fatigue, features frequently reported in women with lipedema. Creatine also exhibits clinically relevant anti-inflammatory properties. *Sestili et al.* [33] demonstrated that creatine decreases pro-inflammatory cytokine release and protects cellular structures from oxidative damage by functioning as a direct scavenger of reactive species and by enhancing phosphocreatine-dependent membrane stability. More recently, Rawson & Venezia [34] highlighted the role of creatine in reducing markers of systemic inflammation, improving endothelial function and modulating immune-cell energetics. These mechanisms integrate seamlessly with other anti-inflammatory compounds in LipeCoffee® (e.g., curcumin, citrus bioflavonoids, resveratrol), which act synergistically in suppressing NF-κB, COX-2 and cytokine-driven inflammatory cascades, core mechanisms underlying edema, pain and tissue hypersensitivity in lipedema. The synergy between creatine, caffeine and L-carnitine is particularly relevant within a network-based supplementation model. Caffeine enhances sympathetic activation and increases fatty- acid mobilization, providing substrates for mitochondrial β-oxidation. L-carnitine facilitates the transport of long-chain

fatty acids into mitochondria, while creatine sustains the ATP regeneration required to sustain β-oxidation and AMPK activation. *Guest et al.* [35] emphasize that creatine and caffeine may have complementary effects on muscular energetics, fatigue reduction and cognitive performance when combined appropriately. Additionally, the presence of B-complex vitamins and magnesium in LipeCoffee® further supports ATP synthesis, mitochondrial enzyme function and creatine phosphorylation, amplifying global bioenergetic efficiency.

Creatine also plays an important neuroenergetic role that extends beyond muscle metabolism and is particularly relevant for women with lipedema, who frequently report chronic fatigue, cognitive slowing, and emotional distress. By increasing brain phosphocreatine stores and stabilizing ATP turnover, creatine enhances neuronal energy availability under metabolic stress, as demonstrated by Roschel & Gualano [31] and *Candow, et al.* [36]. This improved energetic buffering supports attention, working memory and sustained cognitive performance, functions often impaired in inflammatory or fatigue-related conditions. In addition Creatine has also emerged as a promising adjunctive therapy for mood regulation. In women with major depressive disorder, the addition of creatine (5 g/day) accelerated symptom reduction and increased remission rates, according to *Lyo, et al.* [37]. More recently, *Sherpa, et al.* [38] demonstrated that creatine combined with cognitive-behavioral therapy produced significantly greater reductions in PHQ-9 scores than placebo. These clinical results are coherent with population-level data from *Bakian, et al.* [39], who found that higher dietary creatine intake was associated with a lower risk of depression, particularly among women.

Collectively, creatine functions as a potent metabolic enhancer that supports mitochondrial resilience, ATP turnover, redox stability and anti-inflammatory balance. When integrated into a multi-target system such as the LipeCoffee® formulation, creatine does not act in isolation; rather, it participates in an interdependent biochemical network that strengthens mitochondrial output, improves metabolic flexibility and mitigates inflammatory stress, mechanisms highly pertinent to chronic low-grade inflammation and bioenergetic dysfunction in lipedema (Figure 3). In this context, creatine operates synergistically with other neuroactive and metabolic compounds present in the formulation, including caffeine (enhanced alertness and catecholaminergic signaling), L- theanine and taurine (anxiolytic and neuromodulatory effects), B-complex vitamins (neurotransmitter synthesis and mitochondrial cofactor support), and polyphenols such as resveratrol and curcumin (neuroinflammatory modulation). Through these coordinated pathways, the combined nutrient matrix may help reduce mental fatigue, promote emotional resilience and attenuate cognitive impairment frequently reported by women with lipedema.

Coenzyme Q10: Coenzyme Q10 (CoQ10), an essential lipid-soluble quinone located in the inner mitochondrial membrane, plays a central role in electron transport between complexes I/II and complex III of the respiratory chain. Through this function, CoQ10 is indispensable for maintaining the proton gradient required for ATP synthesis and sustaining mitochondrial bioenergetic efficiency [40]. Reduced CoQ10 (ubiquinol) also acts as a potent antioxidant, protecting membrane phospholipids, mitochondrial proteins, and DNA from oxidative damage. In states of chronic inflammation or metabolic dysfunction (conditions consistently reported in lipedema) mitochondrial CoQ10 depletion exacerbates ROS accumulation and impairs ATP generation [41]. Beyond its canonical role in oxidative phosphorylation, CoQ10 exerts important anti-inflammatory and redox-modulating effects. Human clinical trials demonstrate that CoQ10 supplementation reduces circulating inflammatory markers such as TNF-α and IL-6, and lowers oxidative stress biomarkers including Malondialdehyde (MDA), contributing to improved inflammatory profiles [42]. These actions are particularly relevant to lipedema, in which systemic oxidative stress, mitochondrial dysfunction, and chronic low-grade inflammation contribute to pain, fatigue, and impaired tissue repair.

CoQ10 also influences endothelial and vascular mitochondrial function. Studies show improvements in endothelial nitric oxide bioavailability, reductions in vascular oxidative stress, and enhancements in microcirculatory efficiency following supplementation [43]. Such findings align with the broader concept that mitochondrial reinforcement and improved redox balance support not only metabolic homeostasis but also vascular health, an important pathophysiological component in lipedema. Within the network-based supplementation CoQ10 functions synergistically with creatine (ATP buffering), B-complex vitamins (electron carrier cofactors), magnesium (ATP-Mg formation), and L-carnitine (fatty acid oxidation). This coordinated biochemical matrix strengthens mitochondrial output, enhances redox stability, and sustains cellular energy availability, offering a mechanistic basis for mitigating fatigue, exercise intolerance, and impaired metabolic recovery commonly reported in lipedema patients.

B-Complex Vitamins: B-complex vitamins constitute a group of essential water- soluble micronutrients that serve as indispensable cofactors in mitochondrial oxidative metabolism [44]. Thiamine (B1), riboflavin (B2), niacin (B3) and pantothenic acid (B5) support the function of multiple dehydrogenases and electron carriers within the Tricarboxylic Acid (TCA) cycle and electron transport chain. Thiamine pyrophosphate is required for pyruvate dehydrogenase and α-ketoglutarate dehydrogenase; riboflavin provides FAD/$FADH_2$ for complexes I and II; niacin supplies NAD^+/NADH essential for oxidative phosphorylation; and pantothenate forms coenzyme A, enabling acetyl-CoA entry into the TCA cycle [45]. Collectively, these vitamins maintain ATP production and mitochondrial redox control, core mechanisms disrupted in conditions of metabolic inflexibility and chronic inflammation such as lipedema. Pyridoxine (B6), folate (B9) and cobalamin (B12) are central to one-carbon metabolism, regulating methylation reactions, homocysteine clearance and synthesis of neurotransmitters including serotonin, dopamine and GABA. Elevated homocysteine promotes endothelial oxidative stress and impairs mitochondrial function, whereas adequate levels of B6, B9 and B12 restore redox homeostasis and mitochondrial enzyme

activity [44]. Clinical studies demonstrate that supplementation with these vitamins reduces homocysteine concentrations and improves endothelial function and microcirculatory health [46], processes that directly relate to pain, edema and impaired tissue perfusion in lipedema. Niacin (B3) is particularly relevant to mitochondrial bioenergetics because it regulates cellular NAD^+ pools, which are necessary for sirtuin activity and AMPK–SIRT1–PGC-1α signaling cascades. Restoration of NAD^+ availability improves mitochondrial biogenesis, fatty acid oxidation and metabolic resilience [47]. These pathways are increasingly implicated in the pathophysiology of adipose tissue dysfunction, hypoxic stress and low-grade inflammation, hallmarks of lipedema. In this context, B3 contributes to improved metabolic flexibility and enhanced mitochondrial turnover. B-complex vitamins also exert immunomodulatory and anti-inflammatory effects. Riboflavin supplementation has been shown to suppress NF-κB activation and enhance glutathione reductase activity, reducing oxidative stress burden [48]. Similarly, vitamin B6 deficiency is associated with increased IL-6, TNF-α and heightened inflammatory responses, whereas adequate intake normalizes cytokine profiles and supports lymphocyte function [49]. These effects help counteract the chronic inflammatory milieu observed in lipedema and support tissue repair and anti-fibrotic processes. In a network-based supplementation context (Figure 3), B-complex vitamins provide essential metabolic cofactors that act synergistically with creatine (ATP buffer), CoQ10 (electron transport), L-carnitine (fatty acid oxidation), and magnesium (stabilization of the ATP-Mg complex). This integrated biochemical support increases mitochondrial efficiency, reduces metabolic stress, and contributes to improved energy levels, cognitive performance, and metabolic homeostasis in women with lipedema.

Magnesium: Magnesium (Mg^{2+}) is an essential divalent cation that participates in more than 300 enzymatic reactions, many of which are fundamental for mitochondrial respiration, ATP generation and maintenance of cellular bioenergetic stability. Approximately 90% of intracellular magnesium is bound to ATP, nucleotides and proteins, making Mg^{2+} a structural requirement for ATP synthesis, ATPase activity and phosphorylation reactions [50]. Because ATP exists biologically as Mg-ATP, inadequate Mg^{2+} availability compromises oxidative phosphorylation, impairs mitochondrial enzyme function and reduces metabolic efficiency, mechanisms closely linked to chronic fatigue, impaired muscle recovery and metabolic inflexibility.

Magnesium also plays a central role in mitochondrial membrane integrity. Deficiency of Mg^{2+} increases mitochondrial susceptibility to opening of the permeability transition pore, leading to depolarization, impaired electron transport, excess ROS generation and apoptosis [51]. By stabilizing mitochondrial membranes and reducing calcium overload, magnesium preserves the proton gradient necessary for ATP production and mitigates oxidative damage. These mechanisms are particularly relevant in lipedema, a condition marked by microvascular hypoxia, chronic low-grade inflammation and mitochondrial dysfunction. From an immunometabolic perspective, magnesium modulates inflammatory signaling pathways, especially NF-κB and NLRP3 inflammasome activation. Human studies demonstrate that magnesium supplementation reduces circulating CRP, IL-6 and TNF-α, indicating a broad anti-inflammatory effect [52,53]. Magnesium deficiency, conversely, is associated with heightened oxidative stress, endothelial dysfunction and amplified inflammatory responses, all of which are documented contributors to pain, edema and fibrotic progression in lipedema. In the nervous system, magnesium functions as a physiological NMDA receptor antagonist, reducing excitatory glutamatergic signaling and protecting neurons from excitotoxic injury. Clinical trials show that Mg supplementation reduces anxiety symptoms, improves stress resilience and enhances sleep quality, likely through modulation of the Hypothalamic–Pituitary–Adrenal (HPA) axis and GABAergic tone [54]. These mechanisms directly support the mental and emotional burden commonly reported by women with lipedema, including fatigue, cognitive overload and chronic stress. With supplementation based on metabolic networks (Figure 3), magnesium can act synergistically with B-complex vitamins (cofactors in mitochondrial metabolism), creatine (ATP buffering), CoQ10 (electron transport), and L-carnitine (fatty acid import), forming a metabolic matrix that enhances oxidative phosphorylation, stabilizes bioenergetic output and reduces mitochondrial oxidative stress. This integrative effect contributes to improved physical energy, reduced inflammatory stress and greater metabolic adaptability, core therapeutic targets in lipedema (Figure 3).

Antioxidant–Redox Modulation

Several actives described in the preceding section (Bioenergetic–Mitochondrial Function) also display meaningful antioxidant properties that indirectly contribute to redox equilibrium (Figure 4). Coenzyme Q10, a lipid-soluble electron carrier, acts as a potent scavenger of reactive oxygen species, reducing lipid peroxidation and enhancing endothelial redox balance [43]. L-carnitine attenuates mitochondrial oxidative stress by lowering intracellular acyl-CoA accumulation and suppressing pro-inflammatory cytokines such as IL-6 and TNF-α, thereby improving mitochondrial redox efficiency [28]. Creatine exhibits intrinsic antioxidant activity, functioning both as a direct ROS scavenger and as a stabilizer of mitochondrial membrane potential, which collectively diminish oxidative damage during metabolic stress [33]. Magnesium, although not a classical antioxidant, mitigates oxidative stress indirectly by preventing calcium-dependent mitochondrial injury and downregulating NF-κB–mediated inflammatory pathways [53]. Together, these bioenergetic compounds form an auxiliary antioxidant defense matrix that strengthens mitochondrial resilience and supports redox homeostasis in metabolic conditions characterized by chronic low-grade inflammation, such as lipedema. Building upon this auxiliary antioxidant contribution, the following section focuses on the dedicated redox-modulating actives within the LipeCoffee® formulation, detailing their biochemical mechanisms and relevance to lipedema pathophysiology.

Vitamin C: Vitamin C (ascorbic acid) is a powerful water-soluble antioxidant that plays a central role in maintaining redox homeostasis in human tissues. As a primary electron donor, vitamin C directly neutralizes several Reactive Oxygen Species (ROS), including superoxide, hydroxyl radicals, singlet oxygen, and peroxyl radicals, thereby preventing oxidative damage to lipids, proteins, and mitochondrial membranes [55]. Within the mitochondrial compartment, ascorbate contributes to the recycling of α- tocopherol (vitamin E) and supports glutathione regeneration through the glutathione– ascorbate cycle, enhancing the endogenous buffering capacity against oxidative stress. These mechanisms are particularly relevant in lipedema, where chronic microvascular hypoxia and adipose tissue inflammation promote sustained ROS production and oxidative injury. Beyond its classical antioxidative role, vitamin C functions as an essential cofactor for a family of Fe^{2+}/2-oxoglutarate–dependent dioxygenases involved in collagen biosynthesis and extracellular matrix remodeling. It is required for the hydroxylation of proline and lysine residues within procollagen, enabling proper triple-helix formation and stabilization of connective tissue [56]. Given that lipedema is characterized by extracellular matrix alterations, increased fibrosis, and microvascular fragility, adequate ascorbate availability is crucial for maintaining vascular integrity and tissue remodeling capacity. Furthermore, vitamin C supports endothelial nitric oxide bioavailability by reducing superoxide-mediated NO degradation, thereby improving microcirculatory perfusion.

Vitamin C also modulates key inflammatory signaling pathways. Supplementation has been shown to attenuate NF-κB activation, reduce circulating CRP and IL-6, and diminish monocyte adhesion to the endothelium [57]. These effects link vitamin C not only to redox balance but also to immunometabolic regulation, both of which are disturbed in lipedema. By reducing oxidative stress and pro-inflammatory cytokine release, ascorbate may help mitigate pain, edema, and neuroinflammatory sensitization, features frequently reported in affected women. Additionally, emerging evidence highlights vitamin C's role in mitochondrial function and bioenergetic efficiency. Ascorbate supports the activity of L-carnitine biosynthetic enzymes (e.g., trimethyllysine dioxygenase), which influences fatty acid transport into the mitochondria [58]. It also maintains iron in its reduced state (Fe^{2+}), essential for the function of mitochondrial respiratory complexes. Together, these bioenergetic and antioxidant mechanisms cause vitamin C to contribute to greater mitochondrial resilience, reduced oxidative stress, and improved microvascular function in the context of lipedema (Figure 4).

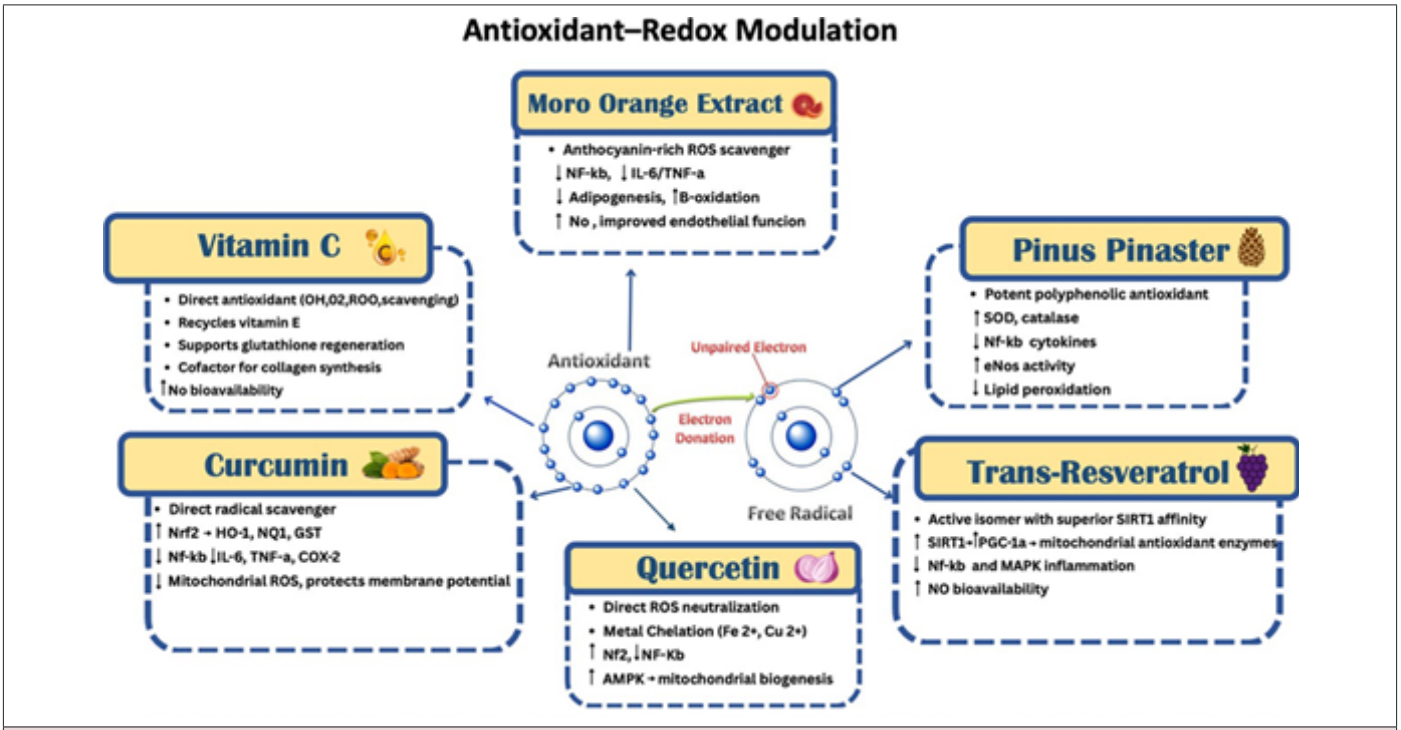

Figure 4: Integrated Antioxidant–Redox Modulation by LipeCoffee® Bioactives. This schematic summarizes the coordinated antioxidant mechanisms contributed by both auxiliary bioenergetic compounds (Coenzyme Q10, L-carnitine, creatine, magnesium) and the dedicated redox-modulating actives within the LipeCoffee® formulation (vitamin C, curcumin, quercetin, trans-resveratrol, Pinus pinaster extract, and Moro orange anthocyanins). Together, these compounds directly scavenge reactive oxygen species (ROS), activate endogenous cytoprotective pathways (Nrf2–ARE), inhibit inflammatory transcriptional programs (NF-κB, MAPK), stabilize mitochondrial membrane function, and improve endothelial nitric oxide bioavailability. By converging on mitochondrial and microvascular redox control, these bioactives collectively enhance cellular resilience in conditions characterized by chronic low-grade inflammation and oxidative stress, such as lipedema.

Curcumin: Curcumin, the principal bioactive polyphenol derived from Curcuma longa, exerts profound antioxidant and anti-inflammatory actions mediated through both direct radical-scavenging activity and modulation of intracellular signaling pathways [59]. Structurally, curcumin contains conjugated dienone and phenolic groups capable of directly neutralizing Reactive Oxygen Species (ROS), including superoxide, hydroxyl radicals and peroxyl radicals [59]. However, its most biologically relevant antioxidant actions arise from its ability to upregulate endogenous cytoprotective pathways, notably the Nrf2–ARE system. Curcumin promotes Nrf2 nuclear translocation, enhancing transcription of enzymes such as Heme Oxygenase-1 (HO-1), glutathione S-transferases, and NAD(P)H:quinone oxidoreductase-1 (NQO1), thereby strengthening cellular redox buffering capacity [60]. In parallel, curcumin potently inhibits pro-inflammatory signaling, particularly the NF-κB pathway. By preventing phosphorylation and degradation of IκBα, curcumin suppresses NF-κB nuclear translocation and downstream transcription of IL-6, TNF-α, COX-2, MCP-1 and other cytokines central to adipose tissue inflammation [61]. This dual modulation, activation of Nrf2 and inhibition of NF-κB, positions curcumin as one of the most potent nutraceutical regulators of the inflammation–oxidative stress axis. Such mechanisms are especially relevant for lipedema, a condition marked by chronic low-grade inflammation, extracellular matrix remodeling, oxidative stress and microvascular dysfunction.

Curcumin also influences mitochondrial function. Experimental studies show that curcumin stabilizes mitochondrial membrane potential, limits opening of the permeability transition pore, reduces mitochondrial ROS output and preserves ATP levels under inflammatory or oxidative stress conditions [61]. It additionally modulates mitochondrial biogenesis pathways via activation of PGC-1α and SIRT1. These mechanisms may alleviate symptoms frequently reported in lipedema: fatigue, reduced metabolic efficiency, neuroinflammatory pain and microvascular congestion. Emerging clinical evidence supports curcumin's systemic benefits (Figure 4). Randomized controlled trials demonstrate that curcumin supplementation reduces circulating CRP, IL- 6 and malondialdehyde, while increasing total antioxidant capacity and glutathione levels [62,63]. In metabolic disorders, curcumin improves endothelial function, reduces adipose inflammation and modulates adipokine secretion, including leptin and adiponectin imbalance, features shared with lipedema pathophysiology. These findings underscore curcumin's therapeutic potential as a multi-target modulator of oxidative stress, inflammation and metabolic dysregulation.

Quercetin: Quercetin is a flavonol abundantly found in fruits and vegetables and is recognized as one of the most potent natural modulators of oxidative stress and inflammation. Its antioxidant activity is mediated through both direct and indirect mechanisms [64]. Structurally, quercetin contains multiple hydroxyl groups capable of directly scavenging Reactive Oxygen Species (ROS), including superoxide, hydroxyl radicals, and peroxynitrite [65]. Additionally, quercetin chelates transition metals such as Fe^{2+} and Cu^{2+}, thereby preventing Fenton chemistry and reducing the generation of highly reactive hydroxyl radicals. These direct effects protect lipid membranes, mitochondrial structures, and endothelial cells from oxidative injury. Beyond radical scavenging, quercetin exerts strong regulatory effects on endogenous antioxidant pathways, particularly via activation of the Nrf2–ARE system. By promoting Nrf2 nuclear translocation, quercetin enhances the expression of detoxifying and antioxidant enzymes including HO-1, NQO1, SOD, and catalase [64]. In parallel, quercetin inhibits pro- inflammatory signaling by suppressing NF-κB activation, thereby reducing transcription of IL-6, TNF-α, COX-2, and adhesion molecules such as ICAM-1 and VCAM-1 [66]. This dual modulation (activation of Nrf2 and inhibition of NF-κB) positions quercetin as a key nutraceutical for managing chronic low-grade inflammation and oxidative imbalance (Figure 4). Quercetin also plays an important role in mitochondrial bioenergetics. Experimental studies indicate that quercetin enhances AMPK activation, increases mitochondrial biogenesis via PGC-1α, and improves fatty acid oxidation [67]. By reducing mitochondrial ROS production and protecting mitochondrial DNA from oxidative damage, quercetin attenuates cellular stress responses that are commonly amplified in inflammatory adipose tissue, a hallmark of lipedema.

Clinically, quercetin has been shown to reduce CRP, IL-6 and markers of lipid peroxidation in randomized trials, while improving endothelial function and microcirculatory perfusion [68]. Improved endothelial reactivity is particularly relevant in lipedema, where microvascular fragility, increased permeability, tissue edema and impaired nitric oxide signaling contribute to pain, heaviness and tissue hypoxia. Quercetin's vascular benefits derive not only from its antioxidant actions but also from its ability to enhance eNOS activity and reduce endothelin-1 expression. In the context of network supplementation, quercetin can play a complementary role to curcumin, resveratrol, vitamin C, and Pinus pinaster, forming a synergistic antioxidant network that acts on multiple points of the redox-inflammatory axis. This synergy is particularly valuable in lipedema, where oxidative stress, microvascular dysfunction, and immune activation coexist and reinforce each other.

Trans-Resveratrol: Resveratrol is a polyphenolic stilbene that exists in two stereoisomeric forms, cis-resveratrol and trans-resveratrol, with the trans configuration being the biologically active and clinically relevant isomer [69]. The transform possesses superior structural stability, higher affinity for molecular targets such as SIRT1, and greater potency in modulating antioxidant and anti-inflammatory pathways compared with the cis form, which rapidly degrades under light or heat exposure [70]. Trans-resveratrol is also significantly more bioavailable in vivo due to its improved interaction with membrane transporters and metabolic enzymes. As a direct antioxidant, trans- resveratrol can neutralize Reactive Oxygen Species (ROS), including hydroxyl radicals, superoxide anions and peroxynitrite, thereby protecting mitochondrial and endothelial membranes from oxidative injury. However, its most potent actions occur through indirect activation of the SIRT1–PGC-1α axis, a master regulator of mitochondrial biogenesis and oxidative metabolism. Activation of SIRT1 enhances PGC-1α deacetylation, increases transcription of mitochondrial

antioxidant enzymes (e.g., SOD2, catalase), and improves oxidative phosphorylation efficiency [70]. These mechanisms support mitochondrial resilience and energy homeostasis, processes frequently impaired in chronic inflammatory states such as lipedema. Trans-resveratrol also exerts robust anti- inflammatory effects. Through SIRT1-mediated deacetylation, the compound suppresses NF-κB p65 activity and downregulates expression of IL-6, TNF-α, COX-2 and adhesion molecules including VCAM-1 and ICAM-1 [71]. In addition, trans-resveratrol inhibits MAPK signaling pathways, further attenuating cytokine production and oxidative stress [71]. This dual anti-inflammatory and antioxidant action is particularly relevant to lipedema, where persistent low-grade inflammation, adipose tissue dysfunction, and extracellular matrix remodeling coexist with microvascular impairment (Figure 4).

Significant endothelial benefits have also been documented. Trans-resveratrol enhances Nitric Oxide (NO) bioavailability by stimulating Akt-mediated eNOS phosphorylation, reducing oxidative inactivation of NO, and preventing eNOS uncoupling [72]. These vascular effects improve microcirculatory perfusion, reduce capillary fragility and support tissue oxygenation, core components of symptom relief in lipedema, particularly regarding pain, heaviness and edema. Clinical trials reinforce these mechanistic findings. Supplementation with trans-resveratrol reduces CRP, IL-6, TNF-α and markers of oxidative DNA and lipid damage in individuals with metabolic syndrome, obesity, and high cardiovascular risk [73]. Improvements in insulin sensitivity, mitochondrial efficiency and endothelial function further underscore its relevance to lipedema pathophysiology.

Pinus Pinaster: Pinus pinaster bark extract, commercially known as Pycnogenol®, is a standardized mixture of polyphenols composed primarily of procyanidins, catechins, taxifolin, and phenolic acids. These compounds exhibit potent antioxidant activity through both direct scavenging of Reactive Oxygen Species (ROS) and upregulation of endogenous antioxidant defenses. Pinus pinaster neutralizes hydroxyl radicals, superoxide anions and peroxyl radicals, while simultaneously enhancing the activity of key antioxidant enzymes, including Superoxide Dismutase (SOD) and catalase [74] (Figure 4). Through modulation of the Nrf2–ARE pathway, Pycnogenol increases expression of cytoprotective genes such as HO-1 and NQO1, reinforcing cellular redox buffering capacity and protecting mitochondrial and endothelial membranes from oxidative injury. Beyond its antioxidant effects, Pycnogenol exerts clinically relevant anti- inflammatory actions. It inhibits NF-κB activation and downregulates expression of IL-6, TNF-α and COX-2, thereby reducing inflammatory cytokine production and leukocyte adhesion [75]. These mechanisms are particularly meaningful in lipedema, where chronic low-grade inflammation and adipose tissue immunoactivation play central roles in symptom progression. In addition, Pycnogenol modulates Endothelial Nitric Oxide Synthase (eNOS) activity, increasing nitric oxide bioavailability and reducing oxidative degradation of NO, a pathway essential for maintaining microvascular perfusion and limiting tissue hypoxia.

One of the most clinically validated benefits of Pycnogenol relates to microcirculatory improvement, which aligns directly with known microvascular dysfunction in lipedema. In a randomized controlled trial, *Belcaro et al.* [76] showed that Pycnogenol significantly improved microcirculatory parameters, reduced ankle edema, and enhanced capillary filtration in women with chronic venous disease, conditions whose pathophysiology overlaps with the impaired lymphatic flow and venous hypertension frequently documented in lipedema. *Fan et al.* [75] demonstrate that Pycnogenol enhances capillary permeability, reduces lower-limb edema, improves venous tone, and decreases biomarkers of endothelial activation [75]. On a mechanistic level, Pycnogenol enhances Endothelial Nitric Oxide Synthase (eNOS) activity, increases nitric oxide bioavailability, and reduces biomarkers of endothelial dysfunction, including VCAM-1 and E-selectin [77]. These effects are complemented by a robust antioxidant profile: Pycnogenol decreases lipid peroxidation, scavenges reactive oxygen species, and preserves mitochondrial membrane integrity under oxidative stress conditions [75]. Such redox-modulating activity is critical in lipedema, a disorder characterized by chronic low- grade inflammation and microvascular oxidative injury.

Moro Orange Extract: Moro orange extract, derived from the anthocyanin-rich Citrus sinensis, has gained scientific interest due to its unique polyphenolic composition and metabolic effects. Unlike conventional sweet oranges, Moro oranges contain high concentrations of Cyanidin-3-Glucoside (C3G), along with flavanones such as hesperidin and naringenin, which display potent antioxidant, anti-inflammatory, and mitochondrial- modulating activities [78]. Anthocyanins from Moro orange demonstrate strong Reactive Oxygen Species (ROS) scavenging ability and effectively reduce oxidative injury in adipocytes and endothelial cells, thereby targeting mechanisms central to lipedema pathophysiology, such as microangiopathy, adipocyte hypertrophy, and chronic low-grade inflammation [78]. A seminal placebo-controlled study by *Titta et al.* [78] showed that daily supplementation with Moro orange extract significantly reduced body weight, body mass index, waist circumference, and subcutaneous fat accumulation in overweight subjects. Mechanistic evaluation revealed that C3G and associated polyphenols downregulated genes involved in adipogenesis (PPARγ) while upregulating genes associated with fatty acid oxidation (CPT-1), indicating a shift toward mitochondrial β- oxidation and improved metabolic efficiency. Importantly, Moro extract also decreased circulating triglycerides and improved insulin sensitivity, suggesting systemic metabolic modulation with clinical applicability in conditions characterized by adipocyte dysfunction and metabolic rigidity, such as lipedema. Anthocyanins from Moro oranges also modulate inflammatory pathways relevant to the chronic inflammatory environment of lipedema. Experimental studies demonstrate that C3G inhibits NF-κB activation, reduces TNF-α and IL-6 secretion, and attenuates macrophage infiltration into adipose tissue [79] (Figure 4). Given that lipedema adipose tissue exhibits increased inflammatory cell infiltration, elevated cytokine levels, and impaired extracellular matrix remodeling, these anti-inflammatory actions may help counteract pain, edema,

and fibrotic progression observed clinically. In addition to metabolic and anti-inflammatory benefits, Moro orange extract improves endothelial function and microcirculatory parameters through enhanced Nitric Oxide (NO) signaling and reduction of oxidative stress–induced endothelial injury. The flavanone hesperidin (present in high amounts in Moro oranges) has specifically been shown to enhance Endothelial NO Synthase (eNOS) activity and reduce oxidative burden in vascular tissue [80]. These effects are relevant for lipedema, where endothelial dysfunction, increased capillary fragility, and microangiopathy contribute to edema, bruising, and tissue hypoxia (Figure 4).

Immunometabolic & Inflammatory Regulation

Vitamin D3: Vitamin D3 (cholecalciferol) plays a central immunometabolic role through its active form, 1,25-dihydroxyvitamin D (calcitriol), which binds to the vitamin D Receptor (VDR) expressed in immune cells, adipocytes, endothelial tissue, and skeletal muscle [81]. Activation of the VDR modulates transcriptional programs involved in inflammation, oxidative stress, adipogenesis, and insulin sensitivity, processes highly relevant to the chronic low-grade inflammatory state observed in lipedema. Importantly, women with adipose-tissue disorders, obesity, or chronic inflammation frequently present with lower circulating 25(OH)D levels due to volumetric dilution, impaired adipocyte release, and sequestration within dysfunctional adipose tissue [81]. This deficiency may worsen inflammatory activation and fatigue, commonly reported by lipedema patients.

From an immunological perspective, vitamin D3 is a potent modulator of both innate and adaptive immune pathways. Calcitriol suppresses NF-κB signaling by inhibiting nuclear translocation of p65 and increasing expression of IκBα, thereby down- regulating pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α [82] (Figure 5). Vitamin D also shifts macrophage polarization toward the anti-inflammatory M2 phenotype and reduces dendritic cell maturation, mechanisms that collectively attenuate chronic inflammation and local tissue sensitivity [83]. Given that lipedema adipose tissue exhibits macrophage infiltration and upregulated inflammatory signaling, these immunomodulatory effects are pathophysiologically relevant. Vitamin D3 additionally influences metabolic regulation through improvement of insulin sensitivity and mitochondrial function. Calcitriol increases insulin receptor expression and enhances GLUT4 translocation in muscle and adipose tissue, thereby optimizing glucose uptake and reducing metabolic inflexibility [84]. It also modulates mitochondrial oxidative phosphorylation by regulating genes controlling calcium handling, ATP synthesis, and reactive oxygen species balance, leading to improved fatigue resistance and enhanced muscle performance, issues frequently compromised in lipedema patients [85]. Moreover, vitamin D deficiency is associated with increased oxidative stress and impaired redox homeostasis, further amplifying chronic inflammation [86].

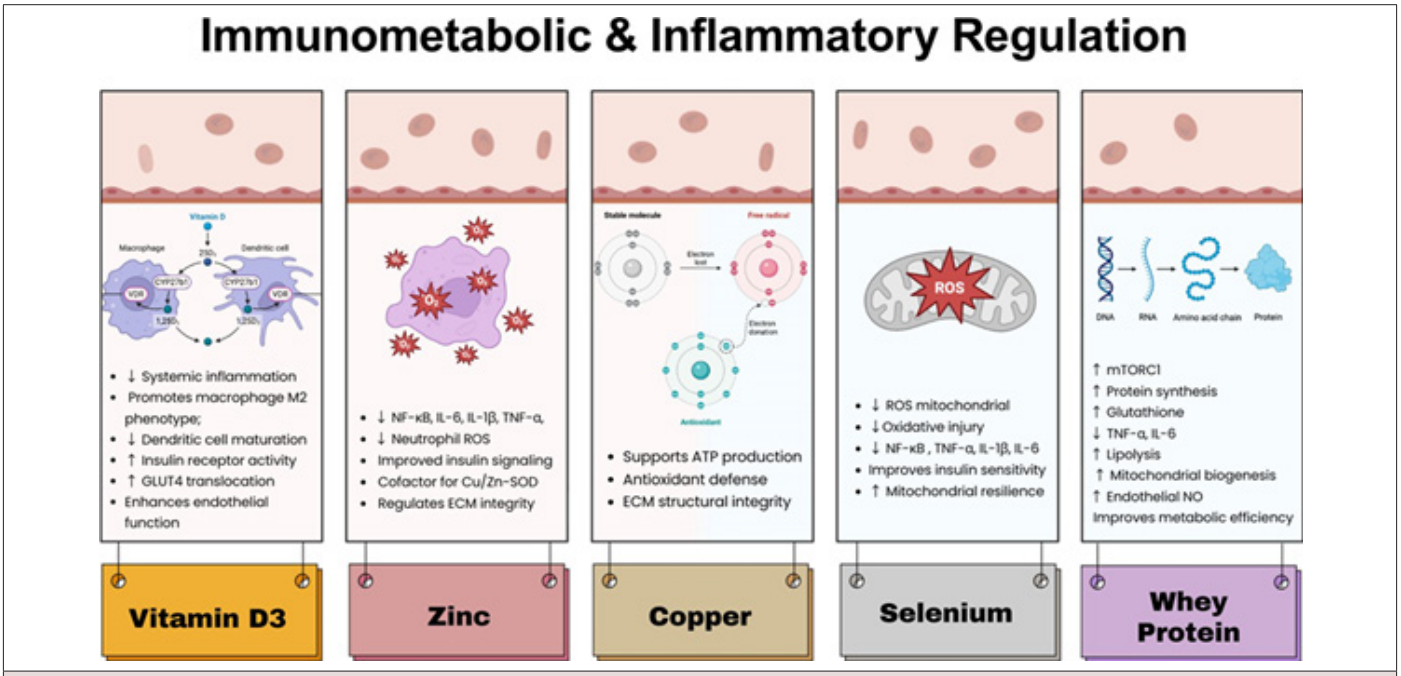

Figure 5: Overview of the immunometabolic and inflammatory regulatory mechanisms modulated by LipeCoffee® bioactives. Vitamin D3 modulates both innate and adaptive immunity by enhancing antimicrobial peptide expression, suppressing Th17 responses, increasing Treg activity, and improving endothelial nitric oxide availability. Zinc, copper, and selenium function as essential cofactors for antioxidant and redox-regulating enzymes (e.g., Cu/Zn-SOD, GPx, TrxR), mitigating NF-κB activation, reducing IL-6 and TNF-α production, and supporting mitochondrial redox homeostasis. Whey protein peptides improve metabolic signaling by enhancing PI3K/Akt pathways, reducing adipocyte inflammation, and supporting microvascular stability. Collectively, these interactions contribute to the reduction of chronic low-grade inflammation and restoration of immunometabolic balance in lipedema.

Vitamin D status has been directly linked to endothelial dysfunction and increased arterial stiffness. In a landmark study, *Al Mheid et al.* [87] demonstrated that individuals with lower serum 25(OH)D levels exhibit impaired flow-mediated dilation, increased arterial stiffness, and elevated markers of vascular oxidative stress. These vascular abnormalities overlap mechanistically with the microangiopathic features described in lipedema, where endothelial dysfunction and capillary fragility contribute to edema, pain, and tissue hypoxia. Collectively, these mechanisms make vitamin D3 a biologically plausible adjunct for modulating inflammatory tone, energy metabolism, muscle function, and microvascular health, domains central to the multisystemic dysfunctions characteristic of lipedema.

Zinc: Zinc is an essential trace element with pivotal regulatory roles in immune function, redox control, adipose-tissue biology, and metabolic homeostasis [88], domains that substantially overlap with the immunometabolic disturbances observed in lipedema. As a catalytic and structural cofactor for more than 300 enzymes and approximately 1,000 transcription factors, zinc modulates DNA synthesis, mitochondrial enzymatic function, cellular repair pathways, and inflammatory signaling cascades [89]. Zinc deficiency, commonly documented in individuals with chronic inflammation or metabolic dysfunction, impairs antioxidant defenses, increases cytokine production, and disrupts adipocyte metabolic regulation [89, 88]. At the immunological level, zinc acts as a potent modulator of both innate and adaptive immunity. It suppresses NF-κB activation by inducing the zinc-finger protein A20 and related inhibitory regulators, thereby reducing the expression of IL-6, IL-1β, TNF-α, and MCP-1 [90, 88] Zinc also stabilizes cellular membranes, decreases neutrophil-derived Reactive Oxygen Species (ROS), and promotes macrophage polarization toward the anti-inflammatory M2 phenotype, mechanisms directly relevant to the chronic low-grade inflammatory signature of lipedema. Additionally, zinc facilitates regulatory T-cell development while inhibiting Th17-driven inflammation, contributing to restoration of immunometabolic equilibrium [89,91].

Zinc also exerts significant metabolic effects. Experimental and clinical studies demonstrate that zinc enhances insulin signaling by facilitating PI3K/Akt activation, promoting GLUT4 translocation, and reducing oxidative stress–induced insulin resistance [92]. Supplementation has been shown to reduce adipocyte hypertrophy, improve lipid mobilization, and lower systemic inflammatory markers such as CRP and IL-6 in metabolic syndrome and obesity [88]. Moreover, zinc is indispensable for the activity of the antioxidant enzyme Cu/Zn-Superoxide Dismutase (SOD), a central defense against mitochondrial and cytosolic oxidative stress [91] (Figure 5). Beyond metabolic and immune modulation, zinc contributes to Extracellular Matrix (ECM) organization and microvascular stability. It regulates the activity of Matrix Metalloproteinases (MMPs), which govern collagen turnover, vascular permeability, and tissue remodeling, physiological processes disrupted in lipedema, contributing to connective-tissue fragility, easy bruising, and fibrotic progression. Zinc also improves endothelial function by enhancing nitric oxide bioavailability, reducing oxidative stress, and downregulating endothelial adhesion molecules, thereby counteracting microangiopathy and edema formation [88,91]. Collectively, zinc occupies a central regulatory position at the intersection of inflammation, oxidative stress, adipocyte metabolism, and vascular integrity. Its broad biological actions support its inclusion in strategies targeting chronic low-grade inflammation and connective-tissue dysfunction, hallmarks of lipedema's complex pathophysiology.

Copper: Copper is a redox-active trace mineral essential for mitochondrial bioenergetics, antioxidant defense, immune competence and Extracellular Matrix (ECM) integrity, domains directly implicated in lipedema pathophysiology [93]. As a catalytic cofactor for cytochrome c oxidase (Complex IV), copper is indispensable for oxidative phosphorylation and ATP synthesis. Copper deficiency impairs mitochondrial electron transport, increases electron leakage and promotes Reactive Oxygen Species (ROS) formation, contributing to fatigue, reduced exercise tolerance, and metabolic inflexibility [93] Conversely, copper excess can also generate oxidative stress due to its ability to cycle between Cu^{+} and Cu^{2+}, emphasizing the importance of maintaining homeostatic balance [94]. Copper is also central to the enzymatic activity of Cu/Zn-Superoxide Dismutase (SOD1), a primary intracellular antioxidant enzyme responsible for catalyzing the dismutation of superoxide radicals into molecular oxygen and hydrogen peroxide. Through SOD1, copper indirectly protects mitochondrial membranes, endothelial cells and adipocytes from oxidative injury, mechanisms relevant to lipedema, where microangiopathy, oxidative stress and adipose inflammation are consistently reported [94, 91]. Additionally, copper contributes to the function of Lysyl Oxidase (LOX), a key ECM enzyme that catalyzes collagen and elastin cross-linking. Dysregulation of LOX is associated with connective-tissue fragility, impaired vascular stability and altered interstitial matrix remodeling, clinical features commonly observed in lipedema [95].

From an immunological perspective, copper participates in both innate and adaptive responses. Adequate copper levels support neutrophil maturation, T-cell proliferation and interleukin signaling, while copper deficiency results in neutropenia, impaired phagocytic activity and heightened susceptibility to infection [96]. Copper also modulates inflammatory tone via effects on NF-κB, macrophage function and cytokine regulation (Figure 5). Experimental studies show that copper supplementation can downregulate TNF-α and IL-1β expression and enhance antioxidant defenses, whereas deficiency promotes systemic inflammation [95]. These findings intersect with lipedema's chronic inflammatory phenotype and dysfunctional adipose immune microenvironment. Copper further influences adipocyte metabolism. Research demonstrates that copper regulates lipid mobilization by modulating phosphodiesterase activity and cyclic AMP levels, thereby impacting lipolysis and adipocyte size [97]. Copper imbalance has also been linked to altered insulin signaling, dysregulated glucose metabolism and increased oxidative stress, metabolic abnormalities that parallel features of lipedema, including fatigue, adipocyte hypertrophy and inflammation. By contributing

to antioxidant defense, mitochondrial energy production, ECM integrity and immunoregulation, copper plays a multifaceted role in maintaining tissue homeostasis and counteracting physiological disturbances relevant to lipedema.

Selenium: Selenium is an essential trace element incorporated into at least 25 human selenoproteins, many of which play critical roles in antioxidant defense, immune homeostasis, endocrine regulation and mitochondrial function [98]. Its biological activity arises primarily through selenocysteine-containing enzymes such as Glutathione Peroxidases (GPxs), Thioredoxin Reductases (TrxRs) and iodothyronine deiodinases, systems that collectively maintain redox balance, regulate inflammatory signaling and support mitochondrial integrity [99,98]. Selenium deficiency significantly increases susceptibility to oxidative damage, heightens inflammatory responses and impairs mitochondrial resilience [99,98]. These mechanisms are clinically relevant to lipedema, a condition marked by oxidative stress, microangiopathy and chronic low-grade inflammation. A central immunometabolic role of selenium is its regulation of inflammatory pathways. Selenoproteins inhibit NF-κB activation and suppress the production of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 [100]. Selenium supplementation has been shown to modulate macrophage phenotype, promote anti- inflammatory M2 polarization and reduce oxidative burst activity in neutrophils, restoring immune balance in chronic inflammatory states (Figure 5). Since lipedema adipose tissue exhibits macrophage infiltration, increased cytokine expression and persistent microinflammation, selenium's regulatory effects on redox-immune crosstalk may help mitigate pain, tissue sensitivity and inflammatory edema.

Furthermore, selenium is fundamental to mitochondrial bioenergetics. GPx and TrxR systems protect mitochondrial membranes from peroxidation, maintain thiol redox balance and preserve Electron Transport Chain (ETC) function under metabolic stress. Selenium deficiency impairs ATP production, increases ROS generation and contributes to mitochondrial dysfunction, mechanisms often implicated in fatigue, reduced exercise tolerance and metabolic inflexibility [101]. These features parallel clinical complaints frequently reported in lipedema. Moreover, selenium influences adipocyte metabolism and endocrine signaling. Adequate selenium status improves insulin sensitivity by enhancing antioxidant defense in adipocytes, attenuating ER stress and decreasing pro- inflammatory adipokine secretion [101]. Clinical studies demonstrate that selenium supplementation can reduce CRP, improve lipid profiles and lower oxidative biomarkers in metabolic syndrome and obesity, metabolic disturbances that may exacerbate lipedema progression [99]. Additionally, selenium contributes to Extracellular Matrix (ECM) integrity through modulation of redox-sensitive MMP activity, which may help counteract connective-tissue fragility and microvascular dysfunction characteristic of lipedema.

Taken together, the antioxidant, immunomodulatory, and metabolic actions of selenium contribute meaningfully to restoring redox equilibrium, supporting mitochondrial resilience, and maintaining adipose-tissue and vascular integrity. These biological effects directly counteract the chronic low-grade inflammation, microvascular dysfunction, and metabolic impairments that characterize lipedema, underscoring selenium's relevance as a key micronutrient within an immunometabolic therapeutic framework.

Whey Protein Isolate: Whey protein is a rapidly absorbed, leucine-rich protein source with profound effects on muscle metabolism, immune regulation, redox homeostasis and adipose-tissue biology, mechanistic domains highly relevant to lipedema, where metabolic inflexibility, chronic inflammation and connective-tissue alterations frequently coexist. Due to its high content of Branched-Chain Amino Acids (BCAAs), particularly leucine, whey protein potently activates mTORC1 signaling, thereby stimulating muscle protein synthesis, improving mitochondrial function and enhancing metabolic efficiency [102]. These effects may counteract muscle weakness, fatigue and reduced physical capacity commonly reported in women with lipedema. Beyond its anabolic properties, whey protein exerts immunomodulatory and anti-inflammatory effects. Clinical and experimental studies demonstrate that whey-derived peptides can reduce circulating levels of TNF-α, IL-6 and CRP, while enhancing Glutathione (GSH) synthesis, a major intracellular antioxidant [103]. The high cysteine content of whey protein promotes glutathione replenishment, strengthening antioxidant defenses and decreasing oxidative stress–mediated adipocyte dysfunction. Since lipedema is characterized by heightened oxidative stress, microinflammation and impaired lymphatic microcirculation, the ability of whey to restore redox balance and suppress inflammatory cytokines has direct clinical relevance.

Moreover, whey protein modulates adipose-tissue metabolism. Supplementation has been shown to reduce fat mass, improve insulin sensitivity and attenuate adipocyte hypertrophy, effects mediated through increased lipolysis, enhanced mitochondrial biogenesis and improved adipokine profiles [104]. Additionally, whey protein can decrease postprandial glucose excursions and improve incretin response (GLP-1), contributing to improved metabolic control. Given that lipedema patients frequently exhibit disproportionate lower-body adiposity, metabolic rigidity and impaired adipocyte turnover, the metabolic effects of whey protein are physiologically meaningful. Furthermore, whey protein may influence connective-tissue remodeling and endothelial function. Bioactive peptides derived from whey digestion have been shown to improve endothelial nitric oxide availability, reduce blood pressure and decrease arterial stiffness [105]. Improved endothelial function has implications for lipedema, in which microvascular fragility, reduced capillary perfusion and lymphatic dysfunction contribute to pain, edema and tissue hypoxia. Collectively, the anabolic, antioxidant, immunomodulatory and metabolic actions of whey protein complement the multisystemic therapeutic aims relevant to lipedema (Figure 5), supporting muscle function, mitigating inflammation, enhancing mitochondrial metabolism and improving microvascular physiology (Figure 5).

Microvascular & Extracellular Matrix Integrity

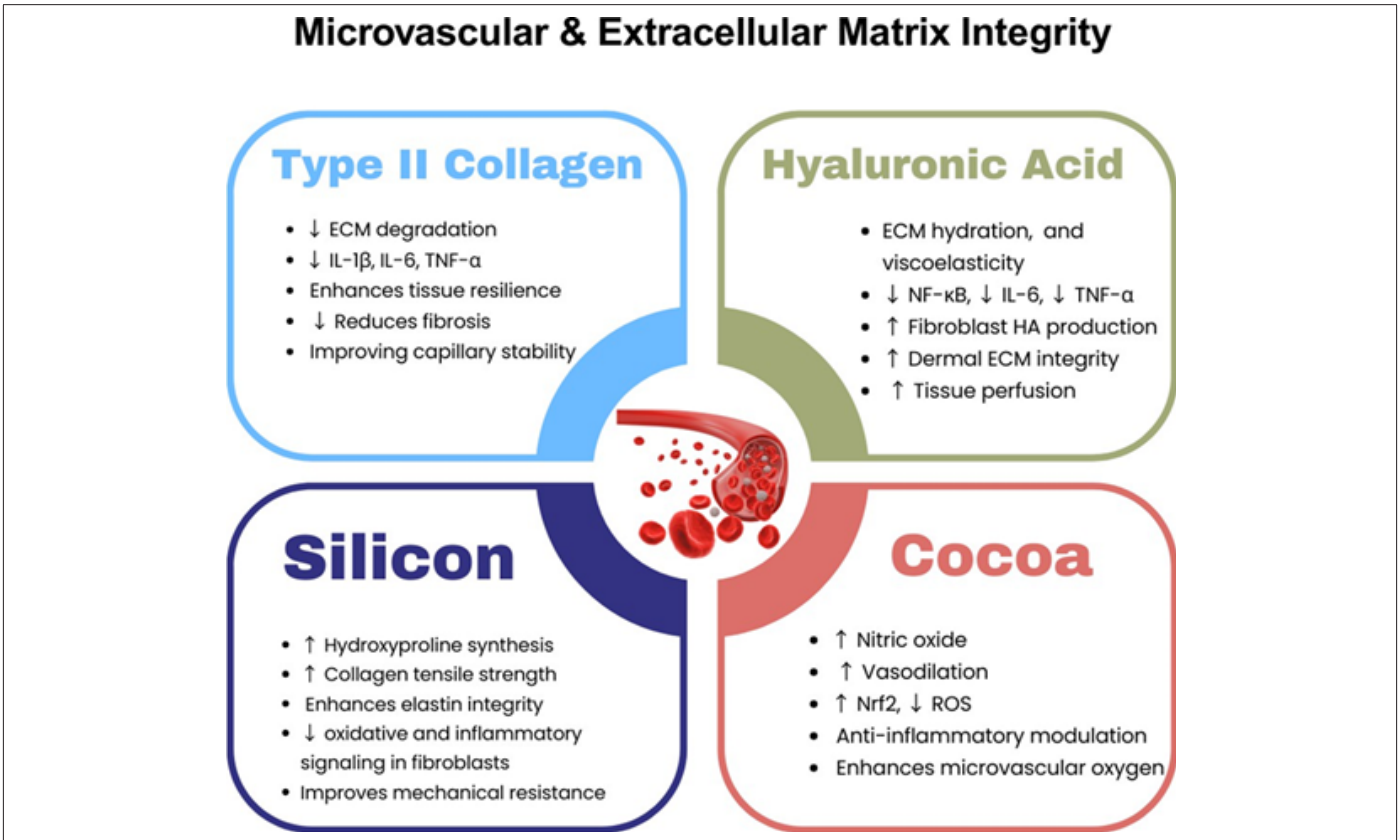

Figure 6: Microvascular and Extracellular Matrix Integrity Supported by Key Bioactive Compounds in LipeCoffee® This figure illustrates the coordinated actions of four extracellular-matrix–targeting bioactives: Type II collagen peptides, silicon (orthosilicic acid), hyaluronic acid, and cocoa polyphenols, highlighting their structural, biochemical, and microvascular contributions relevant to lipedema pathology. Type II collagen peptides enhance fibroblast activity, promote the synthesis of collagen types I and III, and modulate MMP signaling to reduce ECM degradation. These mechanisms strengthen the perivascular matrix and improve capillary stability. Silicon supports ECM maturation through collagen cross-linking, increased hydroxyproline formation, and elastin reinforcement, thereby reducing microvascular fragility and connective-tissue susceptibility to bruising. Hyaluronic acid regulates ECM hydration and viscoelasticity, while high–molecular-weight HA exerts anti-inflammatory effects by suppressing NF-κB and cytokine signaling. Oral HA supplementation promotes dermal ECM integrity, reduces DAMP-associated inflammatory signaling, and enhances microvascular perfusion through improved nitric oxide bioavailability. Cocoa polyphenols, particularly epicatechin, potentiate endothelial nitric oxide synthase activity, stimulate vasodilation, activate antioxidant defense pathways (Nrf2), and attenuate oxidative and inflammatory endothelial injury. Together, these compounds reinforce extracellular matrix architecture, stabilize microvascular networks, enhance tissue perfusion, and counteract fibrosis, edema, and connective-tissue fragility characteristic of lipedema.

Type II Collagen: Type II collagen is a fibrillar collagen subclass classically associated with cartilaginous tissues, but its bioactive peptides, obtained through hydrolysis or undenatured preparations, exert systemic effects on Extracellular Matrix (ECM) remodeling, inflammation, and connective-tissue homeostasis [106]. These mechanisms are relevant to lipedema, a condition characterized by ECM disorganization, microangiopathy, increased capillary fragility, and perivascular fibrosis. Bioactive type II collagen peptides modulate chondrocyte and fibroblast activity, enhance the synthesis of structural ECM proteins, including types I and III collagen, and regulate Matrix Metalloproteinases (MMPs) and Tissue Inhibitors of Metalloproteinases (TIMPs) [106] (Figure 6). Since lipedema tissue exhibits altered collagen architecture, increased MMP activity, and impaired connective-tissue stability, type II collagen may contribute to restoring matrix integrity and biomechanical resilience. Undenatured Type II Collagen (UC-II) has demonstrated additional immunomodulatory properties through an oral tolerance mechanism. Research shows that low-dose UC-II interacts with Peyer's patch– associated lymphoid tissue, promoting regulatory T-cell (Treg) differentiation and reducing Th17-driven inflammatory pathways, leading to decreased expression of IL-1β, IL-6, TNF-α, and MMP-13 [107]. Although much of this work has been investigated in joint and autoimmune contexts, the underlying biology, immune modulation, reduced cytokine signaling, and suppression of ECM degradation, directly parallels pathological features observed in lipedema, which includes T-cell infiltration

and chronic low-grade inflammation contributing to tissue tenderness and fibrosis. Type II collagen peptides also contribute to microvascular integrity through their effects on extracellular matrix remodeling rather than direct endothelial nitric oxide modulation. Experimental and clinical studies demonstrate that collagen-derived peptides stimulate fibroblast activity, enhance the synthesis of structural collagens (types I and III), and modulate Matrix Metalloproteinases (MMPs), thereby improving the mechanical stability of the perivascular extracellular matrix [106]. Additional data show that oral collagen peptides increase dermal collagen density and extracellular matrix hydration, reinforcing the structural scaffold that supports microvascular networks [108]. These ECM-mediated mechanisms indirectly strengthen capillary resistance and may help mitigate the microangiopathy and tissue fragility frequently reported in lipedema. Given that lipedema is accompanied by alterations in the dermal–subdermal transition zone, including fibrosis, glycosaminoglycan accumulation, and ECM stiffening, improving ECM turnover and organization may help mitigate pain, reduce tissue congestion, and enhance overall mechanical tissue properties. Summarizing, type II collagen contributes to ECM restoration, endothelial stabilization, and immune modulation, physiological domains highly relevant to lipedema, where microvascular fragility, inflammation, and matrix disorganization converge to drive symptoms and disease progression.

Silicon: Silicon is an essential trace element involved in the structural organization and biomechanical resilience of connective tissues. It plays a fundamental role in collagen synthesis, cross-linking and stabilization of the Extracellular Matrix (ECM), largely through modulation of prolyl hydroxylase activity and enhancement of collagen fibril assembly [109]. In its bioavailable form (orthosilicic acid) silicon improves the architecture of collagen-rich tissues, increases hydroxyproline content and promotes the formation of stronger and more uniform collagen fibers [110]. These mechanisms are particularly relevant to lipedema, a condition marked by connective-tissue fragility, ECM disorganization, fibrosis and microvascular instability. Silicon also impacts microvascular health indirectly by strengthening the perivascular ECM scaffolding that supports capillary networks [110] (Figure 6). Experimental and human studies indicate that orthosilicic acid increases elastin and collagen type I synthesis in fibroblasts, improving dermal ECM elasticity and resistance to mechanical stress [111]. Because lipedema is characterized by increased capillary fragility, easy bruising and impaired microcirculatory support, silicon's structural benefits may help enhance vascular resilience and reduce susceptibility to microvascular leakage. Beyond structural effects, silicon exhibits anti-inflammatory and antioxidant properties that further contribute to tissue stability [112]. Supplementation with orthosilicic acid has been shown to reduce markers of oxidative stress and downregulate inflammatory signaling in fibroblasts and endothelial cells [112]. These findings align with the chronic low-grade inflammation and redox imbalance described in lipedema tissue, suggesting a potential role for silicon in restoring ECM homeostasis and dampening inflammatory-driven matrix degradation.

Clinically, bioavailable silicon has demonstrated benefits for skin thickness, elasticity, hair tensile strength and nail integrity, tissues that share molecular and biomechanical characteristics with the dermal-subdermal ECM altered in lipedema [113]. Improvements in ECM hydration and collagen density observed in silicon-supplemented individuals may reflect enhanced fibroblast metabolism and improved glycosaminoglycan interactions, mechanisms that may help mitigate tissue congestion, tenderness and dermal stiffening commonly reported by lipedema patients. Taken together, silicon exerts integrative effects on extracellular matrix architecture by enhancing collagen biosynthesis, improving fibrillar organization, and reinforcing dermal structural integrity. In parallel, its supportive influence on perivascular connective tissue contributes to greater microvascular stability and reduced susceptibility to capillary fragility. Through these convergent molecular and biomechanical actions, bioavailable silicon emerges as a biologically relevant adjunct for strategies aiming to enhance connective-tissue robustness and microvascular resilience in individuals with lipedema.

Hyaluronic Acid: Hyaluronic Acid (HA) is a high–molecular weight glycosaminoglycan composed of repeating disaccharide units of N-acetyl-glucosamine and glucuronic acid, widely distributed within the Extracellular Matrix (ECM) of connective, epithelial, and neural tissues. Its physicochemical properties, particularly its strong hydrophilicity and viscoelastic behavior, allow HA to regulate tissue hydration, osmotic balance, lubrication, and mechanical resilience [114]. In adipose and connective tissues, HA contributes to ECM organization, collagen fibrillogenesis, and fibroblast mechanotransduction [114]. Changes in HA molecular weight and turnover are strongly associated with tissue inflammation, fibrosis, and impaired microvascular function, features that overlap with those described in lipedema. From an immunometabolic perspective, HA exhibits molecular weight–dependent biological activity. High–Molecular Weight HA (HMW-HA) exerts anti-inflammatory effects by inhibiting Toll-Like Receptor (TLR2/4) signaling, suppressing NF-κB activation, and reducing pro-inflammatory cytokines such as IL-6 and TNF-α [115]. Conversely, fragmented Low–Molecular Weight HA (LMW-HA) acts as a Danger-Associated Molecular Pattern (DAMP), promoting macrophage activation, angiogenesis, and extracellular matrix remodeling. Supplemental HA (particularly orally bioavailable forms) has been shown to increase circulating HMW- HA, improving inflammatory tone and supporting ECM stabilization.

Human studies demonstrate that oral hyaluronic acid improves dermal hydration, elasticity, and barrier function, effects mediated by increased fibroblast hyaluronan synthesis and improved ECM integrity [116]. HA also enhances microvascular perfusion and endothelial function by modulating nitric oxide bioavailability and reducing oxidative stress. In the context of lipedema, where microangiopathy, connective-tissue fragility, and interstitial edema are hallmarks, HA may support dermal and subdermal ECM cohesion, reduce stiffness, and improve tissue compliance. Finally, HA interacts synergistically with other ECM-targeting nutrients found in LipeCoffee®, including silicon (required for collagen cross-

linking), type II collagen peptides (stimulating fibroblast activity), and antioxidant polyphenols such as quercetin and resveratrol (which reduce HA fragmentation by limiting ROS). Together, these nutrients may enhance HA bioactivity, promote ECM repair, and counteract the progressive tissue remodeling and fluid imbalance characteristic of lipedema.

Cocoa: Cocoa is one of the richest natural sources of flavanols, particularly epicatechin, catechin and procyanidins, compounds with well-documented vascular, metabolic and anti-inflammatory effects [117]. Epicatechin, the primary bioactive compound, enhances endothelial function by upregulating endothelial Nitric Oxide Synthase (eNOS), increasing Nitric Oxide (NO) bioavailability, and reducing oxidative inactivation of NO [117] (Figure 6). These mechanisms collectively improve microvascular blood flow, capillary recruitment and tissue oxygenation, domains that are frequently impaired in lipedema due to microangiopathy, capillary fragility and reduced perfusion. Cocoa polyphenols exert potent antioxidant activity by scavenging Reactive Oxygen Species (ROS) and upregulating phase II antioxidant enzymes through Nrf2 pathway activation [118]. Human trials indicate that regular cocoa flavanol intake significantly reduces biomarkers of oxidative stress, including F2-isoprostanes, and increases plasma antioxidant capacity [118]. Because lipedema involves chronic low- grade inflammation and heightened oxidative stress within adipose and microvascular tissues, the antioxidant capacity of cocoa may support redox balance and mitigate oxidative injury linked to adipocyte dysfunction and connective tissue remodeling. In addition to improving redox status, cocoa flavanols modulate inflammatory pathways. Clinical and experimental studies show reduced circulating levels of CRP, IL-1β, TNF-α, and adhesion molecules (VCAM-1, ICAM-1) following cocoa supplementation [119]. This anti-inflammatory profile aligns with the immunometabolic disturbances observed in lipedema, where chronic inflammation contributes to pain, edema, adipose tissue hypertrophy and impaired lymphatic flow. Cocoa also influences glucose metabolism, mitochondrial bioenergetics and muscle perfusion, with studies demonstrating improved insulin sensitivity, enhanced mitochondrial respiration and greater skeletal-muscle oxygen delivery during exercise [120]. These mechanisms may be particularly relevant for women with lipedema, who frequently report fatigue, reduced exercise tolerance and metabolic inflexibility (Figure 6).

Neuromodulatory Mechanisms and Mental Health

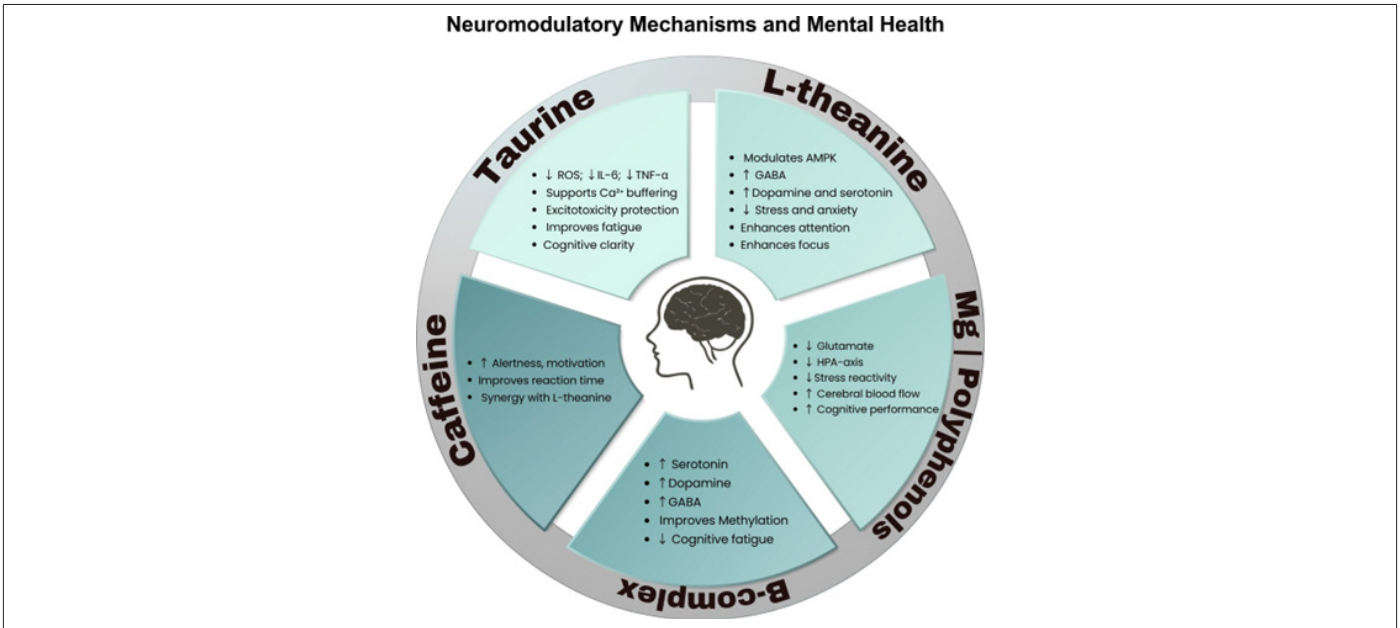

Figure 7: Neuromodulatory mechanisms of LipeCoffee® bioactives and their contribution to mental health. This schematic illustrates how key neuroactive nutrients present in the LipeCoffee® formulation interact with central neurotransmission, stress physiology and mitochondrial neuroprotection. Taurine stabilizes mitochondrial membranes, buffers Ca^{2+} influx, reduces ROS and cytokine generation, and protects neuronal and glial cells from excitotoxicity, supporting cognitive clarity and fatigue reduction. L-theanine modulates glutamatergic signaling, increases α-wave EEG activity, and enhances GABAergic, dopaminergic and serotonergic tone, resulting in reduced anxiety and improved attentional focus. Caffeine, previously described for its bioenergetic effects, exerts central adenosine receptor antagonism to enhance alertness, vigilance and mood, with synergistic balancing effects when combined with L-theanine. B-complex vitamins support neurotransmitter synthesis, one-carbon metabolism and methylation pathways essential for neurochemical homeostasis and cognitive resilience. Magnesium and cocoa flavanols contribute additional neuromodulatory effects by reducing HPA-axis hyperreactivity, stabilizing NMDA-mediated excitatory signaling, and improving cerebral blood flow. Together, these compounds form an integrated neuromodulatory network that may alleviate mental fatigue, stress sensitivity, cognitive slowing and emotional dysregulation frequently reported by women with lipedema.

Taurine: Taurine (2-aminoethanesulfonic acid) is a sulfur-containing amino acid present in high concentrations in excitable tissues, including skeletal muscle, myocardium, brain and retina. It is not incorporated into proteins, but functions as a conditionally essential osmolyte, modulator of calcium homeostasis, membrane stabilizer and cytoprotective agent under metabolic and oxidative stress [121,122,123] (Figure 7). Experimental and translational data indicate that taurine deficiency accelerates mitochondrial dysfunction, inflammaging and cardiometabolic deterioration, whereas supplementation restores mitochondrial resilience and redox balance in multiple models of chronic disease [121,122,123]. At the mitochondrial level, taurine conjugates with uridine residues in mitochondrial tRNA, supporting accurate translation of electron-transport chain subunits and preserving oxidative phosphorylation efficiency [121]. It also modulates calcium buffering within mitochondria, limiting calcium overload– induced permeability transition pore opening and apoptotic signaling [124]. In neuronal and glial cells, taurine exerts neuroprotective effects by improving mitochondrial membrane potential, reducing Reactive Oxygen Species (ROS) generation and attenuating glutamate-induced excitotoxicity, thereby preserving synaptic function and cognitive performance in experimental models of neurodegeneration [124,125,126]. These mechanistic actions are directly relevant to lipedema, a condition in which patients frequently report fatigue, "brain fog" and reduced stress tolerance, consistent with low- grade mitochondrial and neuroinflammatory stress.

Taurine also exhibits robust antioxidant and anti-inflammatory properties. In preclinical models, taurine upregulates Nrf2 and downstream antioxidant enzymes while attenuating activation of NF-κB, MAPK and NLRP3 inflammasome pathways, resulting in reduced cytokine output (IL-6, TNF-α, CRP) and lipid peroxidation [127]. In humans with type 2 diabetes, randomized controlled trials demonstrated that taurine supplementation (~3 g/day) significantly increased superoxide dismutase and catalase activities while lowering malondialdehyde, hs-CRP and TNF-α, indicating an improvement in systemic oxidative stress and inflammatory tone [128]. Similar benefits on oxidative and inflammatory biomarkers have been observed in women with obesity and in older women, where taurine supplementation reduced markers of oxidative damage and was proposed as a potential anti-aging strategy [129,130]. A recent meta-analysis of 34 randomized clinical trials confirmed that taurine doses between 1.5–3 g/day reduced fasting glucose, HbA1c, triglycerides, LDL-cholesterol, blood pressure, CRP, TNF-α and malondialdehyde, reinforcing its role as a pleiotropic modulator of cardiometabolic and inflammatory risk [131].

From a vascular perspective, taurine improves endothelial function and microcirculatory dynamics by enhancing nitric oxide bioavailability, reducing endothelin- 1, attenuating vascular smooth muscle hyperreactivity and limiting structural remodeling of resistance arteries [132,133]. Clinical trials in hypertensive and diabetic patients have shown reductions in systolic and diastolic blood pressure and improvements in arterial stiffness and flow-mediated dilation after taurine supplementation [134,135]. Given that lipedema is characterized by microangiopathy, tissue hypoxia, capillary fragility and impaired lymphatic–venous crosstalk, taurine's endothelial-protective and microcirculatory actions are mechanistically aligned with the pathophysiology of pain, heaviness and edema in these patients. Within the LipeCoffee® formulation, taurine integrates into a broader bioenergetic–mitochondrial network alongside caffeine, creatine, L-carnitine, CoQ10, B-complex vitamins, magnesium and polyphenols such as resveratrol and curcumin. While taurine stabilizes mitochondrial membranes, buffers calcium and dampens ROS and cytokine production, caffeine and L-carnitine enhance fatty-acid oxidation and AMP-Activated Protein Kinase (AMPK) signaling; creatine sustains ATP turnover and phosphocreatine buffering; CoQ10 supports electron transport; and polyphenols further activate Nrf2 and inhibit NF-κB. In aggregate, this network-based supplementation strategy may translate into reduced fatigue, better exercise tolerance, attenuation of low-grade inflammation and potential relief of pain and heaviness in women with lipedema, outcomes that are biologically plausible given the convergent effects of taurine and these co-nutrients on mitochondrial function, redox homeostasis, endothelial integrity and cardiometabolic risk profiles [130,131].

L-Theanine: L-theanine (γ-glutamylethylamide) is a unique non-proteinogenic amino acid found almost exclusively in Camellia sinensis, known for its modulatory effects on central neurotransmission and stress physiology [136]. After oral ingestion, L- theanine readily crosses the blood–brain barrier via leucine-preferring transporters and accumulates in brain regions involved in emotional regulation, including the hippocampus, amygdala and prefrontal cortex [137]. At the molecular level, L-theanine modulates glutamatergic signaling by acting as a low-affinity antagonist of AMPA and kainate receptors, thereby dampening hyperexcitatory neurotransmission, an important mechanism underlying its anxiolytic and stress-reducing properties [136]. A core neuromodulatory effect of L-theanine is its ability to increase α-wave activity on Electroencephalography (EEG), a biomarker associated with relaxed wakefulness, improved attentional control and reduced autonomic arousal. Multiple human trials demonstrate that a single 200 mg dose significantly enhances resting-state α-oscillations within 30–40 minutes, without inducing sedation [138]. This dual profile (elaxation without cognitive impairment) distinguishes L-theanine from traditional anxiolytics, making it clinically relevant for individuals with lipedema who frequently experience anxiety, heightened stress reactivity and difficulties with concentration.

In addition, L-theanine influences key neurotransmitter systems involved in mood and mental resilience. Experimental and clinical evidence shows elevations in brain GABA, dopamine, and serotonin following supplementation, which collectively contribute to anxiolytic tone, improved mood stability and enhanced cognitive flexibility [139] (Figure 7). Through its interaction with glutamate receptors, L-theanine reduces excitotoxicity and modulates cortico-limbic neural circuits implicated in emotional dysregulation, mechanisms particularly relevant in chronic pain conditions such as lipedema. A growing body of randomized controlled trials has demonstrated that L- theanine reduces psychological stress,

cortisol secretion, subjective anxiety, and sleep disturbances. A 2019 double-blind placebo-controlled trial in individuals with high stress levels showed that 200 mg/day for four weeks led to significant improvements in anxiety, sleep quality, cognitive performance and executive functioning [140]. These outcomes reflect L-theanine's stabilizing effect on autonomic balance, HPA-axis activity and prefrontal inhibitory control, domains commonly impaired in chronic inflammatory states. Finally, L-theanine has emerging relevance as a cognitive-support compound. Studies in healthy adults and older individuals demonstrate improvements in working memory, attention-switching accuracy, reaction time and resistance to cognitive fatigue [141]. Given that many women with lipedema report mental fatigue, cognitive clouding ("brain fog") and emotional exhaustion, symptoms partly driven by chronic inflammation and metabolic stress, L-theanine's neuroprotective and neuromodulatory effects may support overall mental resilience. Within the LipeCoffee® formulation, L-theanine synergizes with caffeine to enhance alertness while buffering caffeine-induced overstimulation, producing a smoother cognitive and emotional profile.

Some bioactives described in previous sessions, also exert meaningful neuromodulatory and psychophysiological effects. Caffeine, for example, already discussed as a mitochondrial stimulant, functions centrally as an adenosine A1/A2A receptor antagonist, thereby enhancing dopaminergic and cholinergic neurotransmission, improving vigilance, reaction time, and mood state. Its capacity to increase cortical excitability and reduce perceived fatigue is well documented and becomes particularly relevant in women with lipedema, who frequently describe reductions in cognitive energy and motivational drive [64, 142]. Importantly, in the presence of L-theanine, caffeine produces a more balanced neurocognitive profile, with enhanced attentional control and reduced overstimulation, reflecting a synergistic interaction within the formulation.

B-complex vitamins, previously addressed for their metabolic roles, are indispensable for neurotransmitter synthesis and neurochemical homeostasis. Vitamin B6 (pyridoxine) serves as a cofactor for decarboxylases involved in the formation of serotonin, dopamine, GABA, and norepinephrine, directly influencing mood regulation and emotional stability [45]. Folate (B9) and vitamin B12 participate in one-carbon metabolism and methylation pathways essential for monoamine production and myelin integrity. Their deficiency states, commonly associated with fatigue, cognitive slowing, and depressive symptoms are mechanistically aligned with the neuropsychological complaints frequently reported in chronic inflammatory phenotypes, including lipedema [49]. Thus, the presence of a full B-complex in LipeCoffee® contributes not only to metabolic optimization but also to neuromodulatory support (Figure 7). Magnesium and cacao polyphenols (Figure 7), previously described in metabolic and antioxidant sections, further reinforce neuromodulatory pathways. Magnesium modulates NMDA receptor activity, stabilizes glutamatergic signaling, and reduces HPA- axis hyperreactivity, mechanisms associated with decreased anxiety and improved stress resilience [53, 54]. Cacao flavanols, through enhancement of endothelial nitric oxide availability and cerebral blood flow, support cognitive performance and emotional well- being, particularly under conditions of stress and fatigue [143]. Together, these compounds complement the anxiolytic and cognitive-enhancing properties of L-theanine and taurine forming a coordinated neuromodulatory network within the formulation (Figure 7).

Conclusion

In conclusion, an expanding body of evidence indicates that specific nutrients, when consumed in combination, may exert greater physiological efficacy than when administered individually, producing meaningful reductions in inflammation and contributing to improved health outcomes. Understanding the complex mechanisms underlying nutrient synergy holds important implications for the development of targeted dietary strategies capable of enhancing lipedema management. The LipeCoffee® formulation integrates an interdependent matrix of nutrients, including soluble coffee (caffeine), proteins and bioactive peptides (isolated whey protein; type II collagen), functional amino acids (L-carnitine, taurine, L-theanine), essential mineral cofactors (magnesium, zinc, copper, selenium), vitamins (C, D3, and the B-complex), polyphenolic compounds (turmeric/curcumin, quercetin, resveratrol, Pinus pinaster extract, Moro orange extract), as well as Coenzyme Q10 and hyaluronic acid. These bioactives exert synergistic modulation across key molecular pathways— upregulating Nrf2-mediated antioxidant responses, attenuating NF-κB/COX-2 inflammatory signaling, and activating the SIRT1/AMPK bioenergetic axis—thereby supporting redox homeostasis, cytokine regulation, mitochondrial function, and microvascular integrity. Thus, LipeCoffee® exemplifies a network-based supplementation model in which coordinated interactions among bioactive compounds yield emergent, system-level effects consistent with the principles of synergistic potentiation of combined nutrients. This integrative approach may represent a promising nutritional strategy for addressing lipedema and chronic low-grade inflammation. Nevertheless, rigorously designed pragmatic randomized controlled trials remain necessary to validate clinical outcomes, characterize biomarker trajectories, and strengthen the translational evidence base in lipedema populations.

Acknowledgments

None.

Conflict of Interest

None.

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