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Review Article

Mitochondria-Targeted Nutraceuticals in Depression: Linking Energy Metabolism and Mood

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ABSTRACT

Major Depressive Disorder (MDD) is a complex psychiatric illness that extends beyond monoaminergic deficits, encompassing mitochondrial dysfunction, oxidative stress, neuroinflammation, and impaired neuroplasticity. These cellular disturbances are increasingly recognized as contributing to the onset, progression, and treatment resistance seen in many patients. This review examines the potential of mitochondria-targeted nutraceuticals—such as Coenzyme Q10, Acetyl-L-carnitine (ALCAR), Alpha-lipoic acid (ALA), Nicotinamide riboside (NR), Pyrroloquinoline quinone (PQQ), and Curcumin—as adjunctive therapies in depression. These compounds enhance mitochondrial biogenesis, regulate redox balance, modulate apoptosis, and restore neurotrophic support (e.g., BDNF), while also reducing neuroinflammatory cytokines and normalizing HPA axis activity. Preclinical studies consistently show antidepressant-like effects, and early clinical trials suggest efficacy, particularly in patients with fatigue-predominant or inflammation-linked depression. However, challenges persist due to inconsistent dosing, limited bioavailability, and a lack of standardized, large-scale clinical trials. Despite these limitations, mitochondria-targeted nutraceuticals represent a promising, mechanism-based approach that complements traditional antidepressants and supports the development of personalized, integrative treatments for depression.

INTRODUCTION

Overview of Depression and Limitations of Monoamine-Based Treatments

The symptoms of Major Depressive Disorder (MDD), a complex, recurrent, and varied mental illness, include anhedonia, persistently low mood, cognitive impairment, and vegetative symptoms such changes in eating and sleep patterns. According to the World Health Organization, it affects about 280 million people globally and is a major cause of disability **[1].**A significant percentage of patients experience relapse or fail to

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achieve full remission despite the availability of multiple pharmacological and psychological therapies, underscoring the need for more individualized and efficient treatment approaches. The monoamine hypothesis, which holds that deficits in neurotransmitters like serotonin (5-HT), norepinephrine (NE), and dopamine (DA) are the root cause of depressed symptoms, has historically constituted a substantial portion of the pathophysiology of depression. The clinical effectiveness of monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs), which alter monoaminergic transmission in the brain, supported this theory [2]

The monoamine hypothesis does, however, have several serious drawbacks. First, even though monoamine-based antidepressants raise synaptic neurotransmitter levels in a matter of hours, they usually take weeks to start having a therapeutic effect. This lag indicates that monoamine levels alone are not as important for clinical improvement as downstream neurobiological pathways [3]. Second, over one-third of MDD patients experience treatment-resistant depression, and between 30 and 40 percent of patients do not react well to first-line monoaminergic antidepressants [4]Third, the explanatory power of the concept has been undermined by the lack of consistent evidence of monoamine deficiencies in depressed patients in postmortem and imaging studies [5]. A multifactorial origin beyond neurotransmitter depletion is also suggested by mounting evidence linking the pathophysiology of depression to neuroinflammatory processes, oxidative stress, mitochondrial dysfunction, and neuroendocrine dysregulation (particularly of the HPA axis) [6,7]. A move toward more integrative models that take systemic biological abnormalities and brain-body interactions into consideration has resulted from this. Given these drawbacks, new therapeutic strategies that focus on these other mechanisms—such as mitochondrial support, neuroplasticity augmentation, and anti-inflammatory effects—are gaining popularity. A potential supplement or substitute approach to conventional monoamine-based antidepressants could be nutraceuticals with mitochondria-targeted effects.

Mitochondrial Dysfunction in Major Depressive Disorder (MDD)

The pathophysiology of Major Depressive Disorder (MDD) may be significantly influenced by mitochondrial malfunction, according to new data from preclinical and clinical research. The production of adenosine triphosphate (ATP) via oxidative phosphorylation (OXPHOS), control of cellular calcium homeostasis, generation of reactive oxygen species (ROS), and apoptotic signaling—all of which are linked to brain function and emotional regulation—all depend on mitochondria [8]. Numerous studies have shown that people with depression have altered mitochondrial function. In the prefrontal cortex and hippocampus of depressive patients, postmortem brain tissue investigations have shown elevated markers of oxidative stress, decreased mitochondrial respiration, and impaired electron transport chain (ETC) function, especially in complexes I and IV [9]. According to [10] patients with MDD frequently show lower mitochondrial membrane potential, decreased ATP generation, and increased mitochondrial DNA (mtDNA) damage in peripheral blood cells, corroborating the idea that mitochondrial dysregulation is systemic. Increased oxidative and nitrosative stress, which have both been linked to neuroprogression in chronic mood disorders, is also intimately linked to mitochondrial malfunction. Lipid peroxidation, protein oxidation, and DNA damage result from an

imbalance between ROS production and antioxidant defense. These factors may then affect synaptic plasticity, neurogenesis, and neuronal survival [11].Significantly, patients with depression that is resistant to therapy have demonstrated decreased antioxidant capacity and higher oxidative markers, indicating that mitochondrial oxidative stress may be a factor in the poor response to treatment[12].

Role of Energy Metabolism in Mood Regulation

The brain requires a lot of energy to function properly. Despite making up only around 2% of the body weight, the brain uses more than 20% of all oxygen and ATP when at rest, with mitochondria producing the majority of this energy [13]. Maintaining ion gradients, neurotransmitter production, and synaptic signaling—including in mood-regulating pathways like the glutamatergic, dopaminergic, and serotoninergic systems—all depend heavily on neural energy. These systems can be hampered by disturbances in energy metabolism, which can also lead to depressed symptoms as cognitive impairment, anhedonia, and exhaustion. For example, diminished dopaminergic tone in the mesolimbic reward circuit has been associated with decreased ATP availability, which may be the cause of the motivational deficiencies frequently observed in MDD [14]. Additionally, poor energy metabolism and decreased mitochondrial biogenesis have a detrimental effect on neuroplasticity and brain-derived neurotrophic factor (BDNF) production, both of which are essential for emotional resilience and antidepressant response [15]. Improvements in energy metabolism may be a common downstream mechanism of mood recovery, as evidenced by the notable effects of antidepressant therapies, such as SSRIs, ketamine, and electroconvulsive therapy, on mitochondrial function, increasing ATP synthesis and modulating mitochondrial gene expression [11].

Rationale for Mitochondrial-Targeted Nutraceuticals in Depression

Interest in creating treatments that focus on mitochondrial health has increased when it was discovered that mitochondrial malfunction plays a significant role in the pathophysiology of Major Depressive Disorder (MDD). The cellular energy deficits, oxidative stress, and metabolic impairments that are frequently seen in many patients—particularly those with treatment-resistant or chronic depression—are not always addressed by traditional antidepressants, which primarily target monoaminergic systems[16]. Nutraceuticals that target the mitochondria present a viable adjunctive strategy for addressing these basic cellular dysfunctions. The redox balance, calcium homeostasis, apoptotic signaling, and neural energy supply are all largely controlled by mitochondria. Depression's behavioral and cognitive symptoms are exacerbated by impaired mitochondrial function, which leads to decreased ATP production, increased reactive oxygen species (ROS) generation, neuroinflammation, and altered neuroplasticity [8,11]Important neurobiological characteristics of depression, such as poor synaptic remodeling, hippocampus shrinkage, and decreased production of brain-derived neurotrophic factor (BDNF), are also associated with these cellular alterations [15]. Through a variety of ways, nutraceuticals such nicotinamide riboside (NR), alpha-lipoic acid (ALA), acetyl-L-carnitine (ALCAR), and coenzyme Q10 (CoQ10) directly enhance mitochondrial activity. These include scavenging ROS, promoting mitochondrial biogenesis, improving electron transport chain (ETC) efficiency, and modifying redox-sensitive transcription factors such as Nrf2 and PGC-1α

[17]. Certain substances, such as curcumin and PQQ, have been demonstrated to decrease neuroinflammation and activate mitochondrial biogenesis pathways, which may help neurons regain their neuroplastic potential and energy homeostasis [18,19].

Furthermore, mitochondrial-targeted nutraceuticals are appealing as supplementary treatments for depressive disorders because they frequently have good safety profiles, are well-tolerated, and can be used for extended periods of time. Supplementing with substances like ALCAR and CoQ10 has been linked to symptom improvements in a number of clinical trials, particularly in individuals with high levels of fatigue, inflammation, or treatment resistance [20,21]. These nutraceuticals may aid in breaking the vicious cycle of neuroinflammation, oxidative stress, and mitochondrial dysfunction—a triad frequently observed in MDD and associated with poor treatment response and chronicity of disease—in addition to their direct bioenergetic advantages. Therefore, addressing mitochondrial dysfunction is a system-level, mechanistically based approach to mood regulation and enhancing outcomes for depressed patients.

Mitochondrial Dysfunction in Depression

Evidence from Clinical Studies: Biomarkers (ATP, ROS, mtDNA)

A rising body of clinical evidence supports the idea that mitochondrial dysfunction plays a crucial role in the pathogenesis of Major Depressive Disorder (MDD). Numerous investigations have discovered biomarkers of mitochondrial dysfunction in depressed patients, such as changes in ATP levels, the production of reactive oxygen species (ROS), and damage to mitochondrial DNA (mtDNA).

1. ATP Deficiency

Nearly all of the ATP, the cell's main energy currency, is produced via mitochondrial oxidative phosphorylation. Both central and peripheral tissues have shown reduced ATP generation in MDD patients. Peripheral blood mononuclear cells (PBMCs) from depressed people showed markedly lower mitochondrial respiratory activity and ATP synthesis, according to a study by[22]. In individuals with melancholic or treatment-resistant depression, in particular, this energy shortage may exacerbate core depressive symptoms such exhaustion, cognitive slowness, and psychomotor retardation. Indirect evidence for ATP deficiencies in the brain has also come from functional neuroimaging research. Reduced phosphocreatine and ATP levels have been seen in the prefrontal cortex and basal ganglia of depressed people, which are areas linked to mood regulation and executive function, according to ^31P-magnetic resonance spectroscopy (^31P-MRS)[23].

2. Oxidative Stress and ROS Overproduction

ROS are primarily produced by and targeted by mitochondria. Superoxide radicals are created when a little percentage of the electrons in the electron transport chain leak under typical circumstances. There have been reports of increased mitochondrial ROS generation in MDD, most likely as a result of compromised complex I and III activity. As a result, both neuronal and glial cells experience oxidative damage to their lipids, proteins, and nucleic acids [24]. According to clinical research, people with MDD have higher levels of oxidative stress markers, such as malondialdehyde (MDA) and 8-hydroxy-2′-deoxyguanosine (8-OHdG), which is a crucial indicator of oxidative DNA damage. A redox imbalance results from the frequent decline in antioxidant enzyme activity, such as that of

glutathione peroxidase (GPx) and superoxide dismutase (SOD), occurring at the same time [25]. By destroying ETC components and inducing apoptosis, this oxidative stress may further damage mitochondrial function, which could lead to the poor neuroplasticity and hippocampus atrophy seen in depression.

3. Mitochondrial DNA (mtDNA) Damage

Because mitochondrial DNA lacks protective histones and is close to areas where ROS are generated, it is more susceptible to oxidative damage. Research has revealed that the blood and postmortem brain samples of people with depression have higher levels of mtDNA deletions, mutations, and copy number changes. People with recurrent depression had a considerably higher number of mtDNA copies, according to a noteworthy study by [26]This could be a compensatory reaction to mitochondrial malfunction. According to other research, plasma contains higher amounts of cell-free mtDNA (cf-mtDNA), which may be an indicator of systemic inflammation and mitochondrial stress [27]. Chronic stress exposure has been connected to elevated cf-mtDNA, which is recognized to be a risk factor for depression. Due to their correlation with treatment resistance, cognitive impairments, and disease severity, these mtDNA alterations are clinically relevant. Crucially, these might represent state-dependent alterations linked to depressive episodes as well as trait sensitivity.

Brain Regions Affected in Depression: The Role of Oxidative Stress, Inflammation, and Neuroplasticity

The hippocampus and the prefrontal cortex (PFC) are two brain areas that are frequently linked to both structural and functional problems in Major Depressive Disorder (MDD). These regions are essential for mood control, memory processing, cognitive flexibility, and stress response. Depressed patients have been shown to have volume loss, neuronal death, and synaptic abnormalities in these areas in a number of neuroimaging investigations and postmortem analysis. Crucially, oxidative stress, neuroinflammation, mitochondrial dysfunction, and decreased neuroplasticity are all strongly linked to these neurobiological alterations. The medial temporal lobe contains the hippocampus, a feedback regulator of the hypothalamic-pituitary-adrenal (HPA) axis and a major modulator of learning and memory. There have been reports of considerable hippocampus atrophy in MDD, with volume reductions correlated with the intensity, duration, and frequency of bouts of depression [28]Chronic stress-induced glucocorticoid exposure is the main cause of this atrophy because it reduces mitochondrial energy generation and triggers neuronal apoptosis. Furthermore, ATP-dependent activities including neurogenesis and synaptic plasticity—both essential for emotional resilience and stress recovery—are interfered with by mitochondrial malfunction in hippocampus neurons. Since diminished antioxidant defenses and increased reactive oxygen species (ROS) jeopardize neuronal survival and plasticity, the hippocampus is also particularly vulnerable to oxidative injury. Lipid peroxidation, protein carbonylation, and mitochondrial DNA (mtDNA) damage are caused by oxidative stress in this area, and these processes are made worse in patients with chronic or treatment-resistant types of depression [11]. Similar to this, executive functioning, decision-making, emotional regulation, and reward processing are all significantly influenced by the prefrontal cortex (PFC), especially the dorsolateral and ventromedial portions. Hypoactivity and decreased grey matter volume in the PFC are common in depressed patients, and structural MRI and functional imaging studies have reliably

confirmed these findings [29].The cellular energy supply necessary for synaptic transmission, long-term potentiation, and neurotransmitter modulation is compromised by mitochondrial malfunction in the PFC. Furthermore, synaptic degeneration and dendritic shrinkage brought on by elevated ROS production in the PFC eventually contribute to deficiencies in working memory, attention, and affective inhibition. Brain-derived neurotrophic factor (BDNF), a crucial regulator of synaptic plasticity and neuron survival, is suppressed by inflammatory signaling, which also impairs mitochondrial function and raises cytokines like interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP)[6].

Links to Oxidative Stress, Inflammation, and Neuroplasticity in Depression

An interrelated pathophysiological trio of oxidative stress, inflammation, and poor neuroplasticity leads to the onset and persistence of Major Depressive Disorder (MDD). Excess reactive oxygen species (ROS), which are mostly produced in mitochondria, overwhelm antioxidant systems like SOD, GPx, and catalase, damaging proteins, lipids, and DNA, especially in the prefrontal cortex (PFC) and hippocampus, which are important areas for mood regulation [25]. By promoting transcription factors like NF-κB and raising cytokines like IL-6, TNF-α, and IL-1β, ROS also trigger inflammatory pathways that interfere with neurotransmitter balance and HPA axis function [6].Consequently, chronic inflammation inhibits the expression of brain-derived neurotrophic factor (BDNF), which hinders dendritic development, neurogenesis, and synaptic plasticity, particularly in the hippocampus and PFC[30]. This leads to a vicious loop whereby inflammation is fueled by oxidative stress, which in turn impairs neuroplasticity and prolongs depressed symptoms. The brain's ability to adapt is further weakened by mitochondrial malfunction, which results in decreased ATP generation. Thus, there is potential for treatment of MDD by focusing on this triad, particularly with mitochondria-focused nutraceuticals.

Key Mitochondria-Targeted Nutraceuticals in Depression: Detailed Overview

Coenzyme Q10 (CoQ10)

A lipid-soluble substance called coenzyme Q10, sometimes referred to as ubiquinone, is essential to the mitochondria's electron transport chain (ETC), which promotes the oxidative phosphorylation process that produces ATP. Apart from its function in bioenergetics, CoQ10 is a strong endogenous antioxidant that scavenges reactive oxygen species (ROS) and stabilizes mitochondrial membranes. Studies have shown markedly lower plasma CoQ10 levels in patients with depression, especially those with chronic fatigue and treatment-resistant types, which may indicate systemic mitochondrial dysfunction. CoQ10 supplementation has shown positive benefits on inflammatory state, mood, and fatigue. For instance, [21]found that daily 200 mg CoQ10 supplementation for 8 weeks significantly decreased oxidative stress indicators and depressed symptoms. It is an effective adjuvant in the treatment of depression with metabolic or fatigue-related components due to its good safety profile and systemic mitochondrial support.

Acetyl-L-Carnitine (ALCAR)

A naturally occurring derivative of amino acids, acetyl-L-carnitine (ALCAR) helps move long-chain fatty acids into mitochondria, where they are converted to ATP by β-oxidation. Additionally, by upregulating brain-derived neurotrophic factor (BDNF), altering NMDA receptors, and boosting

synaptic plasticity, ALCAR increases mitochondrial enzyme activity and has neuroprotective and neurotrophic effects. The use of ALCAR for mood disorders is supported by a substantial amount of clinical evidence. ALCAR was found to be as effective as fluoxetine in lowering depression symptoms, especially in older patients and those with dysthymia, according to a meta-analysis conducted in 2018 by Veronese et al. Remarkably, ALCAR has been shown to work more quickly than SSRIs, with mood enhancements observed as soon as one week of supplementation. Furthermore, its involvement in epigenetic modification (such as histone acetylation) points to a more extensive neurological effect. ALCAR has dual therapeutic efficacy for depression because of its neurotrophic activity and mitochondrial stimulation.

Alpha-Lipoic Acid (ALA)

An important mitochondrial coenzyme for energy metabolism and enzymatic activities, especially oxidative decarboxylation, is alpha-lipoic acid (ALA) [31].ALA is a universal antioxidant that can regenerate other antioxidants like glutathione, vitamin C, and vitamin E, in addition to scavenging free radicals that are soluble in both water and lipids[32,33]. ALA also lowers proinflammatory cytokine levels and promotes mitochondrial enzyme function[34]. ALA has demonstrated synergistic effects when taken with ALCAR, despite the fact that it has not been thoroughly investigated as a stand-alone antidepressant [35]. According to preclinical research, ALA can improve mitochondrial respiration and lower lipid peroxidation, which may help neuropsychiatric disorders that involve oxidative stress [36].ALA may also be helpful for depression in people with concurrent metabolic disorders, as it has been shown to improve mood in patients with diabetes and metabolic syndrome [37]. Because of its mitochondrial and antioxidant functions, ALA is a desirable option for supplementary treatment in depression connected to oxidative stress.

Nicotinamide Riboside (NR)

Nicotinamide adenine dinucleotide (NAD+), a crucial coenzyme involved in DNA repair, mitochondrial energy production, and epigenetic control through sirtuins (particularly SIRT1), is derived from nicotinamide riboside (NR). Age, stress, and long-term disease all naturally lower NAD+ levels, which are risk factors for depression. By increasing intracellular NAD+ levels, NR supplementation improves ATP synthesis, neural resilience, and mitochondrial biogenesis. Pilot human trials have demonstrated decreased physical exhaustion, greater NAD+ bioavailability, and improved mitochondrial function, despite the paucity of clinical investigations on NR in depression [38]. In animal models, NR supplementation cures behavioral impairments linked to chronic stress, lowers inflammation, and increases hippocampus mitochondrial density. These results imply that NR might be especially helpful for neurodegenerative or fatigue-dominant types of depression.

Pyrroloquinoline Quinone (PQQ)

Redox cofactor and strong antioxidant pyrroloquinoline quinone (PQQ) activates peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) to promote mitochondrial biogenesis. PQQ enhances the quantity and quality of mitochondria in neural tissues, lowers apoptosis, and guards against mitochondrial oxidative stress. According to preclinical studies, PQQ supplementation improves hippocampal mitochondrial density and reduces depressive-like behavior in mice exposed

to long-term stress [18].PQQ has demonstrated advantages in energy metabolism, sleep quality, and cognitive performance in tiny trials, though human data is still being collected. PQQ is a unique possibility for treating depression because of its capacity to upregulate mitochondrial gene expression and reduce neuroinflammation, particularly in individuals who have cognitive symptoms or mitochondrial fragility.

Curcumin (as a Mitochondrial Protector)

The main polyphenol in turmeric (Curcuma longa), curcumin, is well known for its antioxidant and anti-inflammatory qualities. According to recent research, curcumin also functions as a modulator of the mitochondria, enhancing mitochondrial function by stabilizing mitochondrial membranes, regulating mitophagy, and inhibiting ROS. Curcumin has been demonstrated to downregulate inflammatory cytokines, inhibit NF-κB, and increase BDNF expression—all of which are dysregulated in depression. Curcumin's antidepressant effectiveness in mild-to-moderate depression is supported by numerous randomized controlled studies and meta-analyses [39].According to one study, curcumin worked particularly well for people with unusual symptoms, excessive inflammation, or depression brought on by obesity.

Mechanistic Insights of Mitochondria-Targeted Nutraceuticals in Depression

Antioxidant Defense and Redox Signaling

Antioxidant defense and redox signaling are two of the main interrelated processes by which mitochondria-targeted nutraceuticals produce their antidepressant effects[40,33]. The overproduction of reactive oxygen species (ROS) in Major Depressive Disorder (MDD) is largely caused by mitochondrial dysfunction. This overproduction results in oxidative stress, lipid peroxidation, and DNA damage in neurons, especially in vulnerable brain regions like the prefrontal cortex and hippocampus[25,41]. These oxidative assaults worsen depression symptoms by reducing neurogenesis, activating proinflammatory pathways, and impairing neural plasticity [42].

Nutraceuticals that support the cell's antioxidant defense system include curcumin, alpha-lipoic acid (ALA), and coenzyme Q10. While ALA regenerates other antioxidants like glutathione, vitamin C, and vitamin E and lowers mitochondrial lipid peroxidation[32,43], CoQ10 directly participates in the mitochondrial electron transport chain and stops ROS leakage . Because of its polyphenolic structure, curcumin suppresses oxidative enzymes like xanthine oxidase and increases nuclear factor erythroid 2–related factor 2 (Nrf2), a transcription factor that boosts the expression of endogenous antioxidants like glutathione peroxidase (GPx) and heme oxygenase-1 (HO-1) [44]. These nutraceuticals not only neutralize ROS but also alter signaling pathways that are susceptible to redox. For example, NF-κB, a redox-sensitive transcription factor that promotes inflammation, is activated by oxidative stress. Agents like ALA and curcumin diminish neuroinflammation, a major factor in treatment-resistant depression, by attenuating NF-κB activation [34,43]. This lowers the downstream production of proinflammatory cytokines, such as TNF-α and IL-6. Additionally, redox balance promotes ATP synthesis, mitochondrial biogenesis, and mitochondrial membrane integrity—all of which are critical for preserving neural resilience and synaptic function [45].

Therefore, a key way that mitochondria-targeted nutraceuticals preserve neuronal function and lessen depressive pathology is by restoring redox

equilibrium and bolstering endogenous antioxidant defenses.

Regulation of Apoptosis and Synaptic Plasticity by Mitochondria-Targeted Nutraceuticals in Depression

Particularly in stress-sensitive areas like the hippocampus and prefrontal cortex, dysregulated apoptosis and poor synaptic plasticity are important neurobiological alterations that contribute to neuronal shrinkage and functional abnormalities in Major Depressive Disorder (MDD). In intrinsic apoptotic pathways, mitochondria are essential because they control the permeability of the outer membrane of the mitochondria. Mitochondrial instability caused by oxidative stress or chronic stress triggers caspase-3 activation, cytochrome c release, and ultimately programmed cell death [11]. Furthermore, people with depression frequently exhibit pro-apoptotic signaling in the Bax/Bcl-2 ratio, which establishes the apoptotic threshold .By stabilizing mitochondrial membranes, inhibiting pro-apoptotic gene expression, and boosting anti-apoptotic signaling, mitochondria-targeted nutraceuticals such as pyrroloquinoline quinone (PQQ), coenzyme Q10 (CoQ10), and acetyl-L-carnitine (ALCAR) aid in reversing this imbalance [21,18].

These substances support synaptic plasticity, which includes the brain's ability to adaptively rearrange its synaptic architecture in response to stress and environmental stimuli, in addition to regulating apoptosis. Redox balance, ATP availability, and mitochondrial health are all necessary for this process. Brain-derived neurotrophic factor (BDNF), whose expression is frequently decreased in MDD and is intimately associated with antidepressant response, is a crucial modulator of neuroplasticity [30].It has been demonstrated that nutraceuticals like curcumin and ALCAR increase BDNF expression by activating TrkB signaling pathways, which leads to improved dendritic development and neurogenesis[20,39]. Additionally, by increasing NAD^+ levels, nicotinamide riboside (NR) activates SIRT1 and PGC-1α, improving mitochondrial biogenesis and plasticity [38].Together, these behaviors enhance mood stability, emotional resilience, and cognitive performance, especially in people with chronic or treatment-resistant depression.

Mitochondrial Biogenesis in Depression: Role of PGC-1α and SIRT1 Pathways

The creation of new mitochondria, or mitochondrial biogenesis, is an essential adaptive response to cellular stress and energy requirements. Strong mitochondrial function is necessary for preserving neuronal survival, synaptic activity, and plasticity in the brain. According to new research, Major Depressive Disorder (MDD) may be associated with impaired mitochondrial biogenesis, which could lead to decreased ATP levels, elevated oxidative stress, and impaired neuroplasticity, especially in the prefrontal cortex and hippocampus [11].

Sirtuin 1 (SIRT1) and peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) are two important modulators of mitochondrial biogenesis. The transcriptional coactivator PGC-1α controls the expression of genes related to antioxidant defense, oxidative phosphorylation, and mitochondrial replication. By deacetylating PGC-1α, SIRT1, a NAD^+-dependent deacetylase, connects mitochondrial biogenesis to cellular energy and redox conditions [46]. Both SIRT1 and PGC-1α activities are downregulated in depressed conditions, which results in mitochondrial depletion and functional deterioration.

By promoting mitochondrial biogenesis through the SIRT1–PGC-1α axis, mitochondria-targeted nutraceuticals including curcumin, pyrroloquinoline quinone (PQQ), and nicotinamide riboside (NR) have antidepressant-like effects. According to [38] NR increases NAD^+ levels, which in turn boost SIRT1 activity, which in turn encourages mitochondrial gene expression and energy restoration. In mouse models of depression, PQQ has also been demonstrated to increase PGC-1α in neural tissues, improving mitochondrial density and function [47]. Additionally, curcumin promotes neuroplastic enhancement and mitochondrial protection by activating the AMPK and PGC-1α pathways [39].When taken together, these nutraceuticals boost resilience against neuroinflammation and stress-induced damage in addition to restoring mitochondrial number and efficiency. By promoting mitochondrial biogenesis, these substances aid in reversing the energy and metabolic deficiencies that underlie MDD, providing a mechanism-based supplemental approach to enhance mood, cognitive function, and treatment results.

Cross-Talk Between Mitochondrial Dysfunction, Neuroinflammation, and the HPA Axis in Depression

Neuroinflammation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and mitochondrial dysfunction interact intricately in the pathophysiology of depression. In addition to producing energy, mitochondria play a crucial role in controlling immunological signals and stress reactions. Neuroinflammatory cascades, including the upregulation of proinflammatory cytokines like interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β), can be directly activated by mitochondrial impairment in Major Depressive Disorder (MDD), which is characterized by decreased ATP production, excessive ROS generation, and disrupted mitophagy [6]. A vicious cycle of inflammation and energy failure is maintained by these cytokines, which also hinder mitochondrial oxidative phosphorylation and biogenesis.

Further enhancing the neuroimmune response are ROS produced from mitochondria and damaged mitochondrial DNA (mtDNA), which can activate pattern recognition receptors (PRRs) such as NLRP3 inflammasomes [27]. Hyperactivity of the HPA axis, a characteristic of depression, has been connected to this persistent low-grade inflammation. Increased inflammatory cytokines promote the production of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH), resulting in prolonged cortisol secretion. This increases mood symptoms, damages the hippocampus, and inhibits the expression of BDNF[48].

Crucially, this cycle can be broken by nutraceuticals that target the mitochondria, including curcumin, CoQ10, PQQ, and ALCAR. ALCAR and CoQ10 enhance mitochondrial integrity, which lowers ROS leakage and consequent cytokine activation, while curcumin inhibits NF-κB activation and lowers IL-6 and TNF-α levels [39,21]By restoring cellular energy and preventing oxidative damage, these substances may also aid in normalizing HPA axis reactivity, thereby fostering psychological stress resilience. Therefore, focusing on mitochondrial health has systemic effects that go beyond cellular bioenergetics. These nutraceuticals provide a multimodal approach to reverse underlying diseases in depression by modifying neuroinflammation and HPA axis feedback.

Clinical and Preclinical Evidence of Mitochondria-Targeted Nutraceuticals in Depression

Since mitochondria-targeted nutraceuticals improve energy metabolism, lower oxidative stress, and improve neuroplasticity, they have drawn a lot of interest in preclinical and clinical research for their potential to treat depressed symptoms. Their effectiveness is being supported by an increasing number of human trials and animal models, particularly in the treatment of chronic stress, treatment-resistant depression, and mood disorders associated with aging.

Summary of Preclinical and Clinical Studies

Numerous nutraceuticals have shown notable antidepressant-like benefits in mouse models of lipopolysaccharide-induced depression and chronic unpredictable stress (CUS). While pyrroloquinoline quinone (PQQ) increased mitochondrial density and decreased inflammation-induced neurotoxicity, acetyl-L-carnitine (ALCAR) reversed behavioral despair and restored BDNF levels in the hippocampus [49,20,50]. Through mitochondrial biogenesis and SIRT1-PGC-1α activation, nicotinamide riboside (NR) has been demonstrated to cure depressive-like behaviors in rats and enhance NAD^+ availability [38].

ALCAR has demonstrated encouraging outcomes in a number of clinical trials. In older patients with dysthymia, a meta-analysis found that it was just as effective as fluoxetine, with a quicker beginning of action and fewer adverse effects .In a randomized controlled trial, patients with MDD, especially those with increased oxidative stress, showed substantial improvements in fatigue and depression levels after taking 200 mg/day of Coenzyme Q10 (CoQ10) supplements [21].In a similar vein, curcumin has shown antidepressant effects in a number of RCTs, particularly when administered as an adjuvant, improving HAM-D and BDI scores [39]. Nevertheless, PQQ and NR are still in the early stages of clinical development, with promising pilot results but few documented psychiatric outcomes to far.

Dosing and Bioavailability Challenges

These drugs' bioavailability is a significant barrier to converting preclinical success into clinical results. Curcumin, for instance, has limited oral bioavailability because of poor absorption and fast metabolism, even though it possesses potent antioxidant and anti-inflammatory qualities. As a result, improved formulations have been created, such as liposomal or nano-curcumin and curcumin-piperine complexes, which greatly raise plasma concentrations [39].Similar absorption restrictions apply to CoQ10 and ALA, although lipid-based administration methods can help.

Additionally, dosage differs greatly between trials. While CoQ10 usually ranges from 100 to 300 mg/day, clinical dosages of ALCAR range from 500 to 2000 mg/day. Depending on the formulation, investigations have shown that effective doses of curcumin range from 250 to 1000 mg/day. Although NR has been demonstrated to raise NAD^+ levels at doses of 250–500 mg/day, psychiatric outcome data are still necessary. For clinical dependability and comparability, standardization of dosage and formulation is still essential.

Safety Profiles and Tolerability

In both preclinical and clinical trials, the majority of mitochondria-targeted nutraceuticals have shown outstanding safety profiles. Even in older adults, ALCAR is well tolerated, with a few minor side effects including unsettled stomach. Up to 1200 mg per day, CoQ10 is regarded as safe and has a strong safety margin. Despite being generally safe, greater dosages of curcumin may produce minor nausea or diarrhea. Although there aren't many long-term mental safety studies, NR hasn't

caused any notable side effects in healthy volunteers over a few months [38]. Although there is currently little information on PQQ's effects on depressed human populations, it is thought to be non-toxic at dietary amounts.Crucially, these nutraceuticals don't have the potential side effects of standard antidepressants, like dependence, weight gain, or sexual dysfunction. As a result, they are particularly appealing as preventative or supplemental treatments for at-risk groups, such as those suffering from fatigue-dominant depression, mitochondrial diseases, or chronic inflammation.

Limitations and Challenges in the Use of Mitochondria-Targeted Nutraceuticals for Depression

The use of mitochondria-targeted nutraceuticals in the treatment of depression is fraught with a number of significant restrictions and difficulties that impede broad clinical adoption and the incorporation of guidelines, despite encouraging data from preclinical models and early-phase clinical trials.

Few High-Powered Human Studies

The scarcity of large-scale, well powered randomized controlled trials (RCTs) is one of the biggest obstacles. Small sample sizes, brief durations, or open-label designs are used in the majority of clinical trials conducted to date, which limit generalizability and statistical power. For example, while substances such as curcumin and acetyl-L-carnitine (ALCAR) have demonstrated promising outcomes in small-to-moderate RCTs, these results need to be replicated in multi-center trials with standardized outcome measures, including both objective (such as mitochondrial biomarkers, inflammatory cytokines) and subjective (such as HAM-D, BDI) endpoints. Furthermore, because of insufficient stratification in trials, patient subgroups that are most likely to benefit—such as those with depression caused by fatigue or inflammation—remain poorly described [39,20].

Standardization of Formulations and Dosages

The absence of consistent formulations, bioavailability improvements, and dosage guidelines across research is another significant obstacle. Numerous nutraceuticals have issues with rapid metabolism and variable absorption. For instance, curcumin has a notoriously low bioavailability in its natural form, which leads to the use of various modified formulations that are not directly comparable, such as curcumin-piperine, liposomal curcumin, and nanocurcumin[39]. Likewise, there are significant differences in the pharmacokinetics of Coenzyme Q10 and NR between preparations and populations. It becomes challenging to evaluate study results or determine clinically appropriate dosage recommendations in the absence of established procedures. Additionally, nutraceuticals are subject to less rigorous regulatory scrutiny than pharmaceuticals, which leads to inconsistent products in both clinical and over-the-counter contexts.

Absence of Longitudinal and Multi-Nutraceutical Comparisons

It is still unclear how mitochondria-targeted nutraceuticals will affect depression in the long run. The majority of current trials are 4–12 weeks lengthy and offer no information about neuroprotective, relapse prevention, or longterm efficacy. ALCAR + ALA or curcumin + CoQ10 are two examples of nutraceutical combos that may have synergistic benefits by addressing many pathways at once, as depression is a complex condition (e.g., antioxidant defense + BDNF overexpression + HPA axis modulation). Few research, nevertheless, have investigated these

combinations in carefully monitored environments. Prioritizing therapies based on patient profile, cost, or bioavailability is further limited by the absence of comparative effectiveness trials among various mitochondrial enhancers.

Future Directions in Mitochondria-Targeted Nutraceutical Therapy for Depression

Precision, integrative, and synergistic treatment approaches are gaining traction as knowledge about the role of mitochondrial dysfunction in depression grows. Future strategies will probably focus on lifestyle-based co-treatments, combination therapies, and tailored biomarker-guided interventions that comprehensively address the neuroinflammatory and bioenergetic foundations of mood disorders.

1. Personalized Mitochondrial Therapy Based on Biomarkers

Creating frameworks based on biomarkers to customize nutraceutical therapies is a crucial frontier. Clinical indicators such as fatigue, cognitive impairment, and resistance to treatment may indicate underlying inflammatory or mitochondrial problems [27].In order to determine which people might benefit most from substances like ALCAR, NR, or PQQ, biomarkers like mitochondrial DNA (mtDNA) copy number, oxidative stress markers (such 8-OHdG, MDA), NAD^+ levels, and cytokines (like IL-6, TNF-α) may be used. Such indicators should be used in future studies to track response and stratify individuals, which could improve clinical efficacy and cost-effectiveness.

2. Combined Use with Standard Antidepressants

The use of mitochondria-targeted nutraceuticals in conjunction with first-line antidepressants like SSRIs and SNRIs is another exciting avenue. Numerous antidepressants fail to treat mitochondrial, inflammatory, or neuroplastic deficiencies and have delayed onset. When taken together, a number of nutraceuticals, such as CoQ10, curcumin, and ALCAR, have demonstrated synergistic benefits that improve mood, energy levels, and cognitive function more quickly or effectively than when taken alone[39,21]. Subpopulations with high levels of inflammation, metabolic syndrome, or fatigue-dominant presentations should be the focus of future clinical trials that assess the best combinations, sequencing, and duration.

3. Lifestyle Synergy: The Role of Exercise, Diet, and Sleep

Lifestyle factors have a significant impact on mitochondrial health. Through the AMPK-SIRT1-PGC-1α pathways, aerobic exercise, circadian sleep alignment, and anti-inflammatory diets (like Mediterranean) naturally promote mitochondrial biogenesis and lower oxidative burden. These practices may work in concert with nutraceuticals such as NR or curcumin to improve neuroplasticity and stress tolerance [46].To improve patient outcomes, future studies should investigate multimodal therapies that combine structured behavioral programs with nutraceuticals. Wearable technology and digital health technologies may help with biomarker response, energy levels, and sleep quality monitoring in real time.

Table 1: Key Mitochondria-Targeted Nutraceuticals in Depression: Mechanisms and Evidence

Nutraceutical	Mechanism of Action	Key Effects in Depression	Evidence Type	Citations
Coenzyme Q10 (CoQ10)	Supports ETC, reduces ROS, stabilizes mitochondrial membranes	Reduces fatigue, oxidative stress, improves mood	Clinical & Preclinical	[21], [8], [11]
Acetyl-L-Carnitine (ALCAR)	Increases fatty acid transport into mitochondria, boosts BDNF, modulates NMDA receptors	Rapid antidepressant effect, improves cognition	Clinical & Preclinical	[20], [15], [39]
Alpha-Lipoic Acid (ALA)	Regenerates GSH, Vit C/E; reduces lipid peroxidation and inflammation	Antioxidant support, mood improvement in metabolic patients	Preclinical & Limited Clinical	[31], [32], [37]
Nicotinamide Riboside (NR)	Boosts NAD^+, activates SIRT1–PGC-1α, supports mitochondrial gene expression	Improves mitochondrial function, neural energy, resilience	Animal & Pilot Human Trials	[38], [46], [27]
Pyrroloquinoline Quinone (PQQ)	Stimulates PGC-1α, antioxidant, protects against ROS-induced damage	Enhances mitochondrial density, reduces depressive-like behavior	Preclinical & Limited Clinical	[18], [47], [21]
Curcumin	Inhibits NF-κB, reduces IL-6/TNF-α, increases BDNF, supports redox defense	Effective in mild-to-moderate MDD, improves cognition	RCTs & Meta-analyses	[39], [44], [30]

Table 2: Summary of Clinical Studies on Mitochondria-Targeted Nutraceuticals in Depression

Nutraceutical	Study Design	Population	Dosage & Duration	Main Findings	Citations
CoQ10	Randomized Controlled Trial (RCT)	MDD patients with high oxidative stress	200 mg/day for 8 weeks	↓ Depressive symptoms, ↓ oxidative markers	[21]
ALCAR	Meta-analysis of multiple RCTs	Older adults with dysthymia	500–2000 mg/day, various durations	Comparable to fluoxetine, faster onset, well tolerated	[20], [15]
Curcumin	Multiple RCTs, Meta-analysis	Mild-to-moderate MDD	250–1000 mg/day (with piperine)	Improved HAM-D & BDI scores; best in inflammation-linked depression	[39], [44]
ALA	Open-label & adjunct trials	Diabetics with depressive symptoms	300–600 mg/day for 12 weeks	↓ Depression in patients with metabolic syndrome	[37], [34]
NR	Pilot human trial	Healthy adults (fatigue, NAD+ focus)	250–500 mg/day for 6–12 weeks	↑ NAD^+ levels, improved energy; psychiatric outcomes still under study	[38]
PQQ	Small human study	Adults with stress/fatigue	20 mg/day for 8 weeks	Improved sleep, mood, and mitochondrial markers	[18], [47]

CONCLUSION

With its effects on energy metabolism, oxidative stress, neuroinflammation, apoptosis, and synaptic plasticity, mitochondrial dysfunction is becoming more widely acknowledged as a key factor in the pathogenesis of Major Depressive Disorder (MDD). In light of these extensive and interrelated functions, mitochondrial health becomes a viable target for the creation of novel, mechanism-based therapies for depression. Coenzyme Q10, Acetyl-L-carnitine, Alpha-lipoic acid, Nicotinamide riboside, PQQ, and curcumin are examples of mitochondria-targeted nutraceuticals that have shown promise in resolving the redox and bioenergetic imbalances linked to depression. These substances offer a multifaceted approach to mood stability by supporting neuroplasticity, mitochondrial biogenesis, and stress management in addition to their neuroprotective and antioxidant properties.

Crucially, the majority of the examined nutraceuticals have good safety records, little adverse drug reactions, and are well tolerated, which makes them appropriate for usage as a supplement to traditional antidepressants or as a preventative measure in high-risk groups. Even with encouraging preclinical and early clinical results, there are still significant obstacles in the sector. Large-scale, placebo-controlled studies that assess these drugs' effectiveness in a range of depressed individuals using mechanistic endpoints like HPA axis reactivity, oxidative stress metrics, and mitochondrial biomarkers are desperately needed. Clinical translation will also require longer-term outcome data and standardization of formulations and dosing procedures. All things considered, mitochondria-targeted nutraceuticals offer a fascinating and little-studied aspect of treating depression. Instead of just modifying neurotransmitter symptoms, these therapies target fundamental biological dysfunctions, which could revolutionize the future of individualized, integrated psychiatry with more study and improvement.

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