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Review Article

Potential Neuroprotective Role of L-Citrulline in Parkinson's Disease: Mechanisms, Experimental Evidence and Future Perspectives

***Adediji Ebenezer Adisa and Oyebanjo Oyetola**

Babcock University, Ilishan-Remo, Ogun State, Nigeria
****Corresponding Author's email*: princeebenezerade@gmail.com, adediji0751@pg.babcock.edu.ng**

ABSTRACT

Parkinson's disease (PD), the second most common neurodegenerative disorder worldwide, remains without a disease-modifying treatment despite decades of pharmacological research. Mitochondrial dysfunction, oxidative stress, and neuroinflammation are implicated in its pathogenesis, prompting interest in naturally occurring compounds with neuroprotective potential. L-citrulline, a non-proteinogenic amino acid abundant in watermelon, is proposed as one candidate due to its capacity to enhance nitric oxide bioavailability, support antioxidant defence, attenuate inflammatory signalling, and preserve mitochondrial function. This review critically evaluates the mechanistic and experimental evidence for L-citrulline as a neuroprotective agent relevant to PD pathophysiology, and identifies gaps limiting its translational development. Preclinical and experimental literature was identified through structured searches of PubMed, Scopus, Web of Science, and Google Scholar using combinations of the terms "L-citrulline," "Parkinson's disease," "neuroprotection," "oxidative stress," "nitric oxide," and "rotenone." Studies were included if they reported experimental, mechanistic, or epidemiological data relevant to PD pathophysiology or to L-citrulline's neuroprotective actions, and excluded if they lacked verifiable bibliographic details or were unrelated to the proposed mechanisms. The epidemiological and pathological background of PD, the rotenone-induced model, and the SNCA/PINK1 pathways central to dopaminergic neurodegeneration are outlined alongside the evidence for L-citrulline's proposed mechanisms. Direct experimental evidence in PD-specific models remains limited; most supporting data derive from non-PD systems, including amyotrophic lateral sclerosis, metabolic, and inflammatory models. L-citrulline is thus a biologically plausible but currently unproven neuroprotective candidate in PD. Dedicated PD-model studies with integrated gene-expression endpoints, alongside pharmacokinetic and clinical investigation, are needed before its therapeutic value can be established.

Keywords: α-synuclein; L-citrulline; Neuroprotection; Nitric oxide; Oxidative stress; Parkinson's disease; PINK1; Rotenone

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INTRODUCTION

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder after Alzheimer's disease and constitutes a major and growing global public health burden (Sun *et al.*, 2024). The prevalence of PD is around 1% after the age of 60, escalating to 3% after 80 (Balestrino *et al.,* 2020). PD is characterised by motor symptoms: bradykinesia, resting tremor, muscular rigidity, and postural instability arising from the progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) and resultant depletion of striatal dopamine levels (Stocchi *et al.*, 2024). Non-motor symptoms, including cognitive decline, anosmia, sleep disturbances, autonomic dysfunction, and neuropsychiatric symptoms, frequently precede motor symptoms and substantially reduce quality of life (Kakimoto *et al.*, 2023).

Global estimates indicate that more than 7 to 10 million individuals live with PD, a figure that has risen sharply over recent decades, and the disease affects men approximately 1.5 times as often as women (Zirra *et al.*, 2022). The prevalence among individuals aged 65 years and older is approximately 1.6% (Ou *et al.*, 2021). Future projections suggest prevalence may exceed 12–14 million people worldwide by 2040 (Dorsey & Bloem, 2018). In West Africa specifically, hospital-based studies indicate that PD constitutes between 6.0% and 8.3% of neurological admissions (Quarshie *et al.*, 2021).

Despite the availability of conventional dopamine-replacement therapies, most notably levodopa and dopamine agonists. They are associated with significant long-term complications, including motor fluctuations, levodopa-induced dyskinesias, and neuropsychiatric adverse effects (Dujardin & Sgambato, 2020). No approved therapy currently exists that halts or reverses the progressive dopaminergic neurodegeneration that underlies PD. This unmet therapeutic need has driven the search for neuroprotective agents capable of targeting the cellular and molecular mechanisms of disease.

L-citrulline, a naturally occurring non-proteinogenic amino acid abundant in watermelon (*Citrullus lanatus*) and a critical intermediate in the nitric oxide-urea cycle, has been proposed as a candidate for neuroprotection based on its capacity to enhance nitric oxide (NO) biosynthesis, modulate antioxidant defence, attenuate neuroinflammatory signalling, and support mitochondrial bioenergetics (Stykel & Ryan, 2022; Allerton *et al.*, 2018). At present, however, direct evidence for L-citrulline in PD-specific experimental systems is scarce; the rationale for its inclusion in this review rests principally on the mechanistic convergence between its known biochemical properties and the three pathogenic axes, mitochondrial dysfunction, oxidative stress, and neuroinflammation most consistently implicated in dopaminergic neurodegeneration, together with a small but growing body of pesticide-induced Parkinsonism studies discussed in the Results. This convergence is presented here as a scientific rationale for further investigation rather than as evidence of established efficacy.

The objectives of this review are therefore to:

summarise the epidemiological and pathological background of PD, notably the rotenone-induced rodent model and the SNCA/PINK1 molecular pathways relevant to dopaminergic neurodegeneration; synthesise the available preclinical and mechanistic evidence for L-citrulline's proposed neuroprotective actions; critically appraise the strength, source, and PD-specificity of this evidence; and identify the research priorities that must be addressed before L-citrulline can be considered a validated neuroprotective candidate in PD.

METHODOLOGY

This is a narrative (non-systematic) literature review. It does not follow a PRISMA-type protocol, was not pre-registered, and did not involve dual independent screening or formal risk-of-bias/quality appraisal of included sources. It is intended to synthesise and critically discuss the available literature on L-citrulline's neuroprotective potential in the context of Parkinson's disease, rather than to provide an exhaustive or fully systematic account of the evidence base. This limitation is discussed further in the Discussion section.

Search databases: PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar.

Search terms: Combinations of the following terms were used: "L-citrulline" OR "citrulline"; "Parkinson's disease" OR "Parkinsonism" OR "neurodegeneration"; "neuroprotection"; "oxidative stress"; "nitric oxide"; "rotenone"; "paraquat"; "mitochondrial dysfunction"; "mitophagy"; "SNCA" OR "alpha-synuclein"; "PINK1"; "neuroinflammation". Terms were combined using AND/OR operators (for example, "L-citrulline" AND "Parkinson's disease"; "rotenone" AND "SNCA"; "L-citrulline" AND "oxidative stress").

Inclusion criteria: Peer-reviewed original research and review articles, published in English, reporting experimental, mechanistic, or epidemiological data relevant either to PD pathophysiology or to L-citrulline's biochemical and neuroprotective actions in any experimental system.

Exclusion criteria: Conference abstracts and non-peer-reviewed preprints; articles not published in English; sources whose bibliographic details (authorship, journal, volume, or DOI) could not be independently verified against the publisher or an indexing database; and studies unrelated to the biological themes above.

Time frame: Literature published primarily between 2013 and 2025, with emphasis on studies from the preceding five years; foundational or highly cited older sources were retained where directly relevant.

Because this is a narrative rather than a systematic review, the literature discussed below should be understood as a representative rather than an exhaustive account of the evidence base, and the

absence of formal quality appraisal means that the methodological rigour of individual cited studies has not been uniformly assessed.

RESULTS

Overview of Parkinson's Disease Pathophysiology

PD is fundamentally a synucleinopathy characterised by the intraneuronal aggregation of misfolded α-synuclein into proteinaceous inclusions known as Lewy bodies and Lewy neurites. These aggregates, predominantly distributed within dopaminergic neurons of the SNpc, are neurotoxic and disrupt vesicular trafficking, mitochondrial homeostasis, and protein degradation pathways (Rissardo *et al.*, 2023). The loss of dopaminergic input to the striatum underlies the motor symptoms of PD. The motor symptoms do not typically emerge until approximately 60–70% of SNpc dopaminergic neurons have been lost, owing to compensatory increases in dopamine turnover and receptor upregulation in the striatum (Zhou *et al.*, 2023).

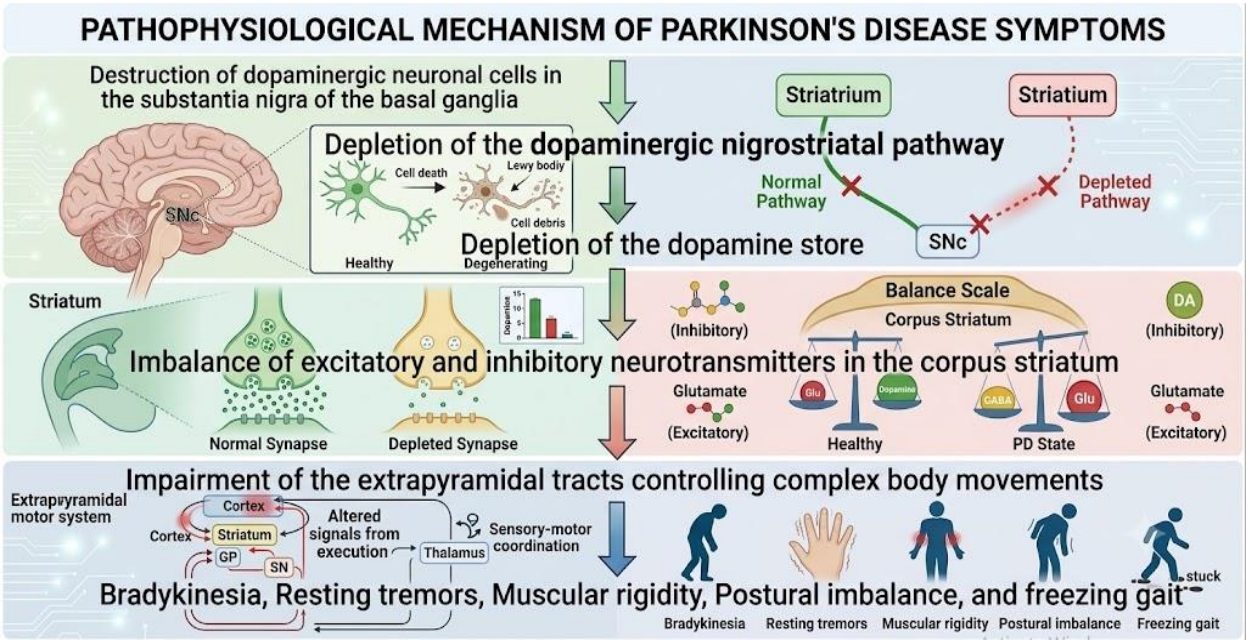

Figure 1: Pathophysiological Mechanism of Parkinson`s Disease

The aetiology of PD is multifactorial, involving interactions between genetic and environmental exposures. Key genetic determinants include mutations in SNCA (encoding α-synuclein), LRRK2, PINK1, and PRKN, among others; familial PD accounts for approximately 5–10% of cases (Morato Torres *et al.*, 2020). Environmental risk factors, including pesticide exposure, heavy metal accumulation, and traumatic brain injury, are thought to contribute to disease pathogenesis by exacerbating mitochondrial dysfunction, oxidative stress, and neuroinflammation (Huang *et al.*, 2022).

Mitochondrial dysfunction is widely regarded as a central pathological mechanism in PD. Neurons of the SNpc are exquisitely dependent on mitochondrial oxidative phosphorylation for their high metabolic demands. In PD, inhibition of mitochondrial complex I results in impaired ATP synthesis, increased reactive oxygen species (ROS) production, and loss of mitochondrial membrane potential (Borsche *et al.*, 2021). This mechanistic picture is strengthened by the observation that rotenone, a naturally occurring complex I inhibitor, reproduces core PD neuropathology in animal models (Prasuhn *et al.*, 2021; Innos & Hickey, 2021). Mitophagy, the selective autophagic elimination of damaged mitochondria, is an important quality-control mechanism, and the PINK1/Parkin pathway is its principal mediator. Under physiological conditions, PINK1 is imported into functioning mitochondria and degraded; upon mitochondrial depolarisation, PINK1 accumulates on the outer membrane, phosphorylates ubiquitin, and recruits Parkin to initiate mitophagy (O'Callaghan *et al.*, 2023). Mutation of PINK1 causes autosomal recessive PD by impairing this activity, leading to accumulation of dysfunctional mitochondria, increased ROS, and enhanced α-synuclein toxicity (Hou *et al.*, 2024).

Oxidative stress, arising from an imbalance between ROS generation and antioxidant defence, plays a

pivotal role in PD pathogenesis. Dopaminergic neurons of the SNpc are intrinsically susceptible to oxidative injury because of their high metabolic activity, the pro-oxidant metabolism of dopamine itself, and their relatively reduced antioxidant capacity (Monzio Compagnoni *et al.*, 2020). Elevated iron levels in the SNpc additionally promote ROS generation through the Fenton pathway (Devos *et al.*, 2020). Excess ROS causes lipid peroxidation, protein oxidation, DNA strand breaks, and mitochondrial damage; oxidative modification of α-synuclein accelerates its misfolding, while α-synuclein oligomers in turn impair mitochondrial respiratory function, creating a self-reinforcing cycle (Picca *et al.*, 2020). Antioxidant enzyme activities, including superoxide dismutase (SOD) and catalase (CAT), are characteristically reduced in the SNpc of PD patients and experimental models (Bej *et al.*, 2024).

The third major etiology of PD is Neuroinflammation. Activated microglia accumulate within the SNpc of PD patients and release pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, which exacerbate dopaminergic neurodegeneration (Marogianni *et al.*, 2020). Microglial overactivation also generates NO via inducible nitric oxide synthase (iNOS) and superoxide via NADPH oxidase, producing peroxynitrite and consequent nitrative stress (Ebadpour *et al.*, 2024). The relationship between neuroinflammation and α-synuclein pathology appears bidirectional: α-synuclein aggregates activate microglia, while inflammatory mediators are reported to promote α-synuclein misfolding (Hirsch & Standaert, 2020).

The Rotenone-Induced Parkinson's Disease Model

The rotenone-induced PD model in rodents, particularly the Wistar rat, is one of the most extensively used preclinical platforms for studying PD pathophysiology (Ibarra-Gutiérrez *et al.*, 2023). Rotenone is a naturally derived, highly lipophilic complex I inhibitor that crosses the blood–brain barrier readily (Sherer *et al.*, 2007; Hirst, 2013). Systemic rotenone administration reproduces several core neuropathological features of human PD, including nigrostriatal dopaminergic degeneration, α-synuclein aggregation, motor dysfunction, and markers of oxidative stress and neuroinflammation (Monzio Compagnoni *et al.*, 2020).

Mechanistically, rotenone inhibits electron transfer from complex I to ubiquinone, causing electron leakage and partial reduction of oxygen to superoxide, initiating oxidative injury, bioenergetic failure, and α-synuclein misfolding (Rocha *et al.*, 2022). Rotenone-exposed Wistar rats consistently show motor deficits on behavioural tests such as the pole test, open field test, and hanging-wire test, accompanied by striatal dopamine depletion, elevated malondialdehyde (MDA), reduced SOD/CAT activity, and molecular evidence of SNCA upregulation with PINK1 downregulation (Chen *et al.*, 2022; Stykel & Ryan, 2022).

The major importance of the rotenone model is its construct validity for mitochondrial complex I pathology, its capacity to replicate α-synuclein aggregation, and its reproducibility across laboratories (Dovonou *et al.*, 2023; Picca *et al.*, 2020). Notable limitations include inter-animal variability, potential peripheral organ toxicity that may confound systemic biochemical analyses, and incomplete replication of the progressive, age-related course of human PD (Jagaran & Singh, 2021); cell-to-cell propagation of α-synuclein, as described in Braak staging, is also not fully recapitulated. Despite these limitations, the model remains a widely used tool for investigating mitochondrial and oxidative mechanisms of dopaminergic neurodegeneration.

Molecular Markers of Neurodegeneration: SNCA and PINK1

The SNCA gene encodes α-synuclein, a 140-amino-acid presynaptic protein involved in synaptic vesicle trafficking and dopamine biosynthesis regulation. In PD, oxidative modification, Ser129 phosphorylation, and nitration promote its misfolding and fibril formation (Zalon *et al.*, 2024; Morato Torres *et al.*, 2020), impairing the ubiquitin–proteasome system and autophagy–lysosome pathway. Point mutations (A53T, A30P, E46K) and gene multiplication cause early-onset familial PD (Huang *et al.*, 2022), and in sporadic PD and rotenone models, oxidative stress upregulates SNCA transcription (Freeman & Wang, 2020). Elevated α-synuclein has further been reported to inhibit damaged mitochondria clearance, linking SNCA overexpression to defective PINK1/Parkin-mediated mitophagy (Kinnart *et al*., 2024).

PINK1 encodes a mitochondrially targeted kinase that serves as the principal initiator of selective mitophagy. Under normal conditions, PINK1 is imported and degraded; upon depolarisation, as occurs during rotenone-induced complex I inhibition, PINK1 stabilises on the outer membrane and activates Parkin-mediated ubiquitination of damaged mitochondria (O'Callaghan *et al.*, 2023; Narendra & Youle, 2024). Loss-of-function PINK1 mutations cause autosomal recessive early-onset PD (PARK6); in rotenone-treated animals, PINK1 is characteristically downregulated, resulting in defective mitophagic clearance and enhanced α-synuclein aggregation

(Zhang *et al.*, 2024). The interplay between SNCA upregulation and PINK1 downregulation has been described as a self-amplifying cycle (Hou *et al.*, 2023), and restoring PINK1 function is considered a mechanistically grounded therapeutic target in PD.

L-Citrulline: Biochemistry and Proposed Neuroprotective Mechanisms

L-citrulline is a non-essential, non-proteinogenic amino acid and a key intermediate in the urea cycle. It is abundant in watermelon (*Citrullus lanatus*), present in both flesh and rind (Gu *et al*., 2023). In the urea cycle, it is synthesised from ornithine and carbamoyl phosphate in hepatic mitochondria, and is also produced within the cytoplasm during the conversion of L-arginine to NO by nitric oxide synthase (Allerton *et al.*, 2018). Oral L-citrulline is reported to offer a pharmacokinetic advantage over direct L-arginine supplementation, bypassing first-pass hepatic metabolism and intestinal arginase catabolism (Lv *et al.*, 2025; Porto *et al.*, 2023).

The conversion of L-citrulline to L-arginine via argininosuccinate synthase and lyase increases the arginine available for NO synthesis by endothelial and neuronal NOS. NO has roles in vasodilation, cerebrovascular regulation, and synaptic plasticity (Allerton *et al.*, 2018). In PD, where cerebrovascular dysfunction and reduced cerebral perfusion have been proposed to contribute to neuronal vulnerability, enhanced NO bioavailability has been suggested, though not directly demonstrated in PD models, as a possible route to hemodynamic neuroprotection (Ivanovski *et al.*, 2023; Wal *et al.*, 2023).

It is important to acknowledge the dual nature of NO in neurodegeneration. Excessive NO production via iNOS in activated microglia reacts with superoxide to form peroxynitrite, a potent oxidizing and nitrating species (Teleanu *et al.*, 2022). The neuroprotective versus neurotoxic effects of NO therefore depend heavily on cellular source, local redox environment, and the NOS isoform engaged; L-citrulline is proposed to preferentially support eNOS/nNOS activity over iNOS-driven pathways, although this nuance has not been directly tested in PD-relevant tissue (Porto *et al.*, 2023).

L-citrulline also exhibits antioxidant properties that appear independent of its role in NO metabolism. Experimental studies report that L-citrulline supplementation reduces MDA levels while augmenting SOD and CAT activity in tissues under oxidative stress (Chowdhury *et al.*, 2022; Sarandy *et al.*, 2023), possibly through hydroxyl radical scavenging and enhanced expression of Nrf2-regulated antioxidant genes such as HO-1 and GCL (Porto *et al.*, 2023). Zhao *et al.* 2024 additionally reported that L-citrulline activated the AMPK pathway in an iron-overload model, improving mitochondrial dynamics and reducing iron-induced oxidative stress, a finding of indirect relevance given the established role of nigral iron accumulation in PD.

Neuroinflammation propagates dopaminergic neurodegeneration through microglial activation and cytokine release. In non-PD systems, L-citrulline has been reported to attenuate inflammatory responses: in a neonatal rat model of lipopolysaccharide-induced lung injury, treatment reduced circulating pro-inflammatory cytokines and oxidative stress markers (Ivanovski *et al.*, 2023), an effect proposed to operate through eNOS-derived NO suppressing iNOS expression and NF-κB-mediated transcription (Porto *et al.*, 2023; Ebadpour *et al.*, 2024). In other experimental models, L-citrulline supplementation has been associated with reduced microglial activation and TNF-α/IL-6 releases (Troshev *et al.*, 2021), although these studies were not conducted in PD models.

Beyond antioxidant and anti-inflammatory actions, L-citrulline-derived NO has been reported to regulate mitochondrial bioenergetics through PGC-1α activation and to modulate the opening of the mitochondrial permeability transition pore (mPTP), an event implicated in apoptotic neuronal death (Bagheripour *et al.*, 2023). L-Citrulline increases nitric oxide bioavailability, which may influence redox signalling and mitochondrial homeostasis. Since mitochondrial dysfunction induced by rotenone disrupts the PINK1/Parkin-mediated mitophagy pathway, it has been hypothesised that improving cellular redox balance may indirectly preserve PINK1 function, although direct experimental evidence for L-citrulline remains limited (Narendra & Youle, 2024).

L-citrulline supplementation has also been shown to modulate brain monoamine metabolism in non-PD experimental models. In broiler chickens subjected to heat stress, oral L-citrulline altered brain free amino acid profiles and monoamine neurotransmitter levels, including dopamine and serotonin (Chowdhury *et al.*, 2022). A possible mechanism involves L-citrulline's influence on tetrahydrobiopterin (BH4) availability, a cofactor for both NOS and the aromatic amino acid hydroxylases involved in catecholamine biosynthesis; whether this translates to a meaningful effect on dopaminergic neurotransmission in PD remains to be investigated.

Preclinical Evidence for L-Citrulline in Neurodegeneration

Studies by Gyawali *et al.* (2021) reported that reduced L-citrulline levels and citrulline transporter activity in transgenic SOD1-G93A mice, a model of amyotrophic lateral sclerosis (ALS), implicate impaired NO metabolism in motor neuron degeneration. ALS shares several pathophysiological mechanisms with PD, including oxidative stress, mitochondrial dysfunction, and protein aggregation, which have been used to argue by extrapolation rather than direct investigation that L-citrulline supplementation might confer neuroprotective benefits in PD.

In an iron-overload model of oxidative stress in mice, Zhao *et al.* (2024) reported that L-citrulline activated the AMPK pathway, improved mitochondrial quality-control dynamics, reduced intracellular iron deposition, and modulated gut microbiota composition. Vincenzi *et al.* (2021) separately investigated citrullinemia-related metabolites and cerebral energy metabolism in rats; while this addressed a metabolic enzyme deficiency rather than neurodegeneration, it has been cited as indirect support for the importance of citrulline–arginine–NO flux in cerebral bioenergetics.

Haramipour *et al.* (2022) reported that prenatal L-citrulline exposure improved reflexive motor function in newborn mice. This developmental finding has been used to suggest that L-citrulline supports motor circuitry of relevance to PD, though the study did not involve a neurodegenerative or adult model and this extrapolation should be treated with caution.

Anti-inflammatory effects were further reported by Ivanovski *et al.* (2023) in a neonatal rat model of lipopolysaccharide-induced injury, and Uyanga *et al.* (2022) demonstrated L-citrulline's support of NO bioavailability under heat stress in broiler chickens. Neither study involved a PD or general neurodegeneration model; their relevance to PD is inferential, based on shared downstream pathways (cytokine signalling, oxidative stress) rather than direct evidence.

The most directly relevant evidence identified relates to pesticide-induced Parkinsonism models. A 2025 study using paraquat-induced Parkinsonism in adult male Wistar rats reported that L-citrulline administration reduced lipid peroxidation, improved antioxidant enzyme activity, and improved short-term memory performance relative to paraquat-only controls (Umar *et al.*, 2025), findings broadly consistent with the pro-oxidant, complex-I-adjacent mechanisms shared by paraquat and rotenone. This paraquat study represents the most direct experimental evidence currently available for L-citrulline in a Parkinsonism model. No published study using the rotenone model specifically, combining motor, biochemical, and SNCA/PINK1 gene-expression endpoints, was identified.

DISCUSSION

Nature of the Current Evidence: Mechanistic versus Direct

Much of the evidence reviewed above is mechanistic rather than directly demonstrated in Parkinson's disease. A substantial proportion of the literature on L-citrulline's antioxidant, anti-inflammatory, and mitochondria-protective actions derives from non-PD systems cardiovascular models, poultry and livestock nutrition studies, developmental models, and a single ALS model, and the extension of these findings to PD-specific dopaminergic neurodegeneration is, in most cases, an inference rather than a demonstrated result. Statements elsewhere in this literature that describe L-citrulline as acting on "PD pathophysiology" should therefore be read as describing a plausible mechanistic overlap rather than confirmed disease-modifying activity.

Only one identified study (Umar *et al.*, 2025) directly examined L-citrulline in a Parkinsonism model (paraquat-induced), and no study using the rotenone model, the platform most extensively discussed elsewhere in this review, has yet to test L-citrulline. This is a critical gap: the mechanistic case for L-citrulline in PD rests heavily on reasoning by analogy across disease models rather than on a body of PD-specific replication.

Extrapolation from Non-PD Experimental Systems

Several of the studies drawn upon in this review involve experimental systems that are only loosely analogous to PD. The ALS model of Gyawali *et al.* (2021) shares some pathophysiological mechanisms with PD (oxidative stress, mitochondrial dysfunction) but differs substantially in the neuronal populations affected and the underlying genetic drivers; findings of altered citrulline transport in motor neurons cannot be assumed to generalise to nigral dopaminergic neurons. Similarly, the heat-stress studies in broiler chickens (Chowdhury *et al.*, 2022; Uyanga *et al.*, 2022) demonstrate that L-citrulline can modulate NO bioavailability and monoamine metabolism under a specific and non-neurodegenerative form of physiological stress; extrapolating these findings to the chronic, progressive, complex-I-driven neurodegeneration of PD requires caution. The developmental study of Haramipour *et al.* (2022) examined prenatal exposure and neonatal reflexes, which are mechanistically and temporally distant from adult-onset

neurodegeneration. In each of these cases, the studies are legitimate evidence for L-citrulline's general biochemical activity. Still, they do not constitute evidence for efficacy in PD, and this review's earlier framing of them as directly "relevant" to PD mechanisms should be understood in that qualified sense.

Blood–Brain Barrier Penetration and Pharmacokinetic Considerations

A major and largely overlooked gap in the current evidence base is the lack of data on L-citrulline's ability to cross the blood–brain barrier and its pharmacokinetic profile within the brain. The great majority of cited studies measured plasma, serum, or peripheral tissue concentrations of L-citrulline, arginine, or NO metabolites; very few report direct measurement of L-citrulline or its downstream metabolites within brain parenchyma, and none of the PD-relevant studies discussed above report cerebrospinal fluid or striatal/nigral tissue concentrations following oral administration. L-citrulline is a small, polar amino acid, and while some transport across the BBB via neutral amino acid transporters has been documented in other contexts (for example, in ALS cell-line and blood–brain barrier transport studies), the extent, saturability, and regional distribution of this transport in the intact PD-relevant brain, and whether it is sufficient to achieve mechanistically meaningful local concentrations, has not been established. This is particularly important in PD, where BBB integrity is itself compromised by neuroinflammation, which could alter both the rate and pattern of L-citrulline entry into affected brain regions in ways that peripheral pharmacokinetic data cannot predict. Until dedicated pharmacokinetic and brain-exposure studies are conducted, claims about L-citrulline's central neuroprotective potential should be regarded as provisional.

Comparison with Established Antioxidant and Neuroprotective Candidates

Placed alongside other antioxidant and neuroprotective candidates that have been investigated in PD, L-citrulline's evidence base is at an early, largely preclinical stage. Compounds such as coenzyme Q10 and creatine progressed to large-scale human clinical trials in PD. Still, they ultimately failed to demonstrate disease-modifying benefit, illustrating that promising preclinical antioxidant or bioenergetic mechanisms do not reliably translate into clinical efficacy. N-acetylcysteine and resveratrol have undergone early-phase clinical or PD-model testing with biomarker or pharmacokinetic endpoints, providing at least some direct human or PD-model data. By comparison, L-citrulline has not, to the knowledge of this review, been tested in any registered human PD trial, and PD-model data are limited to a single paraquat study. This does not diminish the biological plausibility of L-citrulline as a candidate. Still, it does mean that, relative to several established conventional agents, the evidence supporting its prioritisation for PD-specific development is currently unavailable.

Established Findings, Mechanistic Hypotheses, and Future Research Directions

To avoid overstating what is currently known, the evidence discussed in this review is classified below into three tiers.

Established findings (supported by direct, replicated evidence): mitochondrial complex I dysfunction, oxidative stress, and neuroinflammation are core, well-replicated features of PD pathology; the rotenone model reproduces key aspects of PD neuropathology; SNCA and PINK1 dysregulation are mechanistically linked to dopaminergic neurodegeneration; and L-citrulline reliably increases NO bioavailability and has demonstrated antioxidant and anti-inflammatory activity in a range of non-PD experimental systems.

Mechanistic hypotheses (biologically plausible but not directly tested in PD models): that L-citrulline's antioxidant and anti-inflammatory actions translate into meaningful neuroprotection against dopaminergic degeneration; that L-citrulline preserves PINK1 function via redox modulation; that L-citrulline's effects on monoamine metabolism have any bearing on dopaminergic neurotransmission in PD; and that findings from ALS, heat-stress, and developmental models predict L-citrulline's behaviour in a PD-relevant nigrostriatal system.

Future research directions: controlled studies of L-citrulline in the rotenone (and other PD-specific) model, combining behavioural, biochemical, and SNCA/PINK1 gene-expression endpoints within a single design; dedicated pharmacokinetic and brain-exposure studies, including measurement of BBB penetration under PD-relevant inflammatory conditions; dose–response characterisation; assessment of interactions with levodopa and dopamine agonists; and, contingent on positive preclinical findings, early-phase human trials with biomarker endpoints.

Limitations of This Review

This review has several limitations. First, as a narrative rather than a systematic review, it does not provide a fully exhaustive or independently reproducible account of the literature, and the

selection of sources, while guided by the criteria described in the Methodology, was not free of subjective judgement. Secondly, the evidence synthesised is overwhelmingly preclinical and, for L-citrulline specifically, overwhelmingly derived from non-PD systems, which limits the conclusions that can be drawn about clinical relevance.

CONCLUSION

Parkinson's disease represents an urgent unmet medical need, driven by its progressive nature, the absence of disease-modifying therapies, and its expanding global prevalence. Its multifactorial pathogenesis, notably mitochondrial dysfunction, oxidative stress, neuroinflammation, α-synuclein aggregation, defective mitophagy, and dopaminergic neurotransmitter deficiency, is well established in the literature and demands therapeutic strategies capable of engaging multiple pathological targets simultaneously.

L-citrulline is, based on the evidence reviewed here, a potential neuroprotective agent: it enhances NO bioavailability, has demonstrated antioxidant and anti-inflammatory activity, and has shown effects on mitochondrial bioenergetics and monoamine metabolism in a range of experimental systems. However, this evidence base remains largely circumstantial and inferential with respect to PD specifically. Direct experimental support is limited to a single paraquat-induced Parkinsonism study; no rotenone-model data exist, and no pharmacokinetic evidence establishes that orally administered L-citrulline enters the brain in concentrations sufficient for neuroprotection. Claims that L-citrulline is a "promising" or "multi-mechanistic" neuroprotective agent for PD should accordingly be read as describing a research hypothesis rather than an established finding. Structured research of PD preclinical investigation combining behavioural, biochemical, neuroinflammation, gene-expression, and pharmacokinetic endpoints, followed by a well-designed clinical investigation, is required before any conclusion can be drawn about L-citrulline's therapeutic value in Parkinson's disease. This review is intended to identify the research agenda rather than to argue for L-citrulline's clinical adoption.

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