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TARGETING ALPHA-SYNUCLEIN AND NEUROINFLAMMATION: THE ROLE OF *CURCUMA LONGA* IN PARKINSON'S DISEASE

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder in which there is a loss of dopaminergic neurons in the SNpc along with intraneuronal aggregation of α-synuclein, chronic microglial-mediated neuroinflammation, and severe mitochondrial oxidative stress. Available pharmacotherapies, mostly levodopa and dopamine agonists, only provide symptomatic benefit and do not slow or stop the progression of neurodegeneration, and they also have motor complications and non-motor symptom progression. This review critically analyzes the neuroprotective potential of Curcuma longa (turmeric) and its major bioactive curcuminoids namely curcumin, demethoxycurcumin and bisdemethoxycurcumin in preclinical and clinical models of PD. The analysis is based on in vitro, in vivo and human studies published between 2010 and 2025 that have shown curcumin has multi-targeted neuroprotective properties with several well-defined molecular mechanisms. In particular, curcumin has been shown to directly inhibit α-synuclein fibrillisation and induce disaggregation of preformed fibrils, to suppress microglial activation by down-regulating NF-κB, to activate the Nrf2/antioxidant response element (ARE) pathway leading to up-regulation of phase II detoxifying enzymes and to restore mitochondrial complex I activity and to contribute to reduced reactive oxygen species generation. Although these are promising preclinical studies, the poor oral bioavailability of curcumin due to its low aqueous solubility, rapid glucuronidation by the liver and rapid efflux from the intestine by p-glycoprotein (Pgp), have made the translation to clinical practice for PD difficult. As a result, clinical trials in humans have shown conflicting findings with small improvements in Unified Parkinson's Disease Rating Scale (UPDRS) scores. However, recent evidence of brain penetration of nanocurcumin, especially in the context of intranasally delivered formulations such as nanoparticles and liposomes, has yielded much greater brain penetration, and even the first positive phase 2 clinical results. Turmeric derivatives are thus still promising as adjunctive drugs, and continued developments of bioengineered drug nanocarriers are gradually overcoming the bioavailability challenges to allow for effective clinical translations.

INTRODUCTION

PD is the 2nd most common neurodegenerative disease worldwide after Alzheimer's disease, and its prevalence has more than doubled over the last 25 years, largely as a result of population ageing. Some 10 million people worldwide currently suffer from PD, the incidence of which is between ten and eighteen per 100,000 person years and increases sharply to more than 160 per 100,000 person years in people 70 years and older.(Chaud, Alves, Barros, & Crescencio, 2024) It shows a male predominance of about 1.5:1 and although most cases of the disease are sporadic, 5-15% have been associated with known genetic mutations of genes such as SNCA, LRRK2, PARKIN, PINK1 and DJ-1 that have fundamentally shaped the understanding of the pathophysiology of the disease, both familial and idiopathic.(Nebrisi, 2021) Various environmental risk factors, such as pesticide exposure, heavy metal exposure, and consumption of well water have been consistently linked to an increased risk of PD, while cigarette smoking, caffeine intake and physical activity seem to have modest protective effects.

The cardinal motor manifestations (resting tremor, bradykinesia, rigidity, and postural instability) only appear after a long prodromal period of 5-20 years in which 50-70% of the dopaminergic neurons in the substantia nigra pars compacta have been irretrievably lost. This is a massive dopaminergic denervation which represents the neurochemical hallmark of PD and has itself a direct effect on the motor syndrome of PD by disrupting the striatal output pathways.(Chen et al., 2021) There is a definite topographic progression of neuronal loss, with the most severe effect on the ventrolateral tier of neurons that project to the putamen and relative sparing of the dorsal tier of neurons until later stages. This selective vulnerability has been attributed to the high inherent bioenergetic demand of these large neurons that are autonomously pacemaking (tonically firing) even during rest, and thus produce considerable mitochondrial ROS over decades.(Zune Jansen van Rensburg, 2022)

Lewy bodies and Lewy neurites are the pathological hallmark, which are mainly formed by the accumulation of α-synuclein at the microscopic level. This presynaptic protein is normally trafficked in synapses and released in the form of neurotransmitters; under pathological conditions it undergoes conformational transition to form amyloid fibrils, which are rich in β-sheet and are resistant to degradation.(Chetty, 2022) These misfolded species propagate between cells in a prion-like manner, and offer molecular explanations for the Braak staging hypothesis of stereotypical ascending pathology that begins in the dorsal motor nucleus and olfactory bulb, then spreads to brainstem nuclei, subsequently to the substantia nigra, and finally to neocortical territories.(Cortés et al., 2021)

Oxidative stress is a self-propagating and convergent mechanism in PD pathogenesis. Dopamine can also be non-enzymatically oxidized into reactive quinones and aminochrome, and can be metabolized by MAO-B with the production of hydrogen peroxide. During circumstances of pathologically increased iron, hydroxyl radicals are produced through Fenton chemistry. Post-mortem studies show a uniform increase in lipid peroxidation products, protein carbonyls and DNA oxidation adducts, and a marked reduction in levels of glutathione in substantia nigra. Mitochondrial complex I deficiency is the earliest biochemical defect observed, even in platelets without any pathological α-synuclein. This vicious cycle of mitochondrial dysfunction, dopamine oxidation, iron accumulation and α-synuclein aggregation overcomes weakened antioxidant defenses and results in apoptotic cell death.

Today, pharmacological therapy is almost exclusively symptomatic and levodopa is the most effective drug by far, having been discovered almost 60 years ago. Levodopa enters the brain through LAT1 and is converted to dopamine in the remaining nigrostriatal terminals.(Phukan, Roy, Gahatraj, Bhattacharya, & Borah, 2023) Peripheral AADC inhibitors can enhance central bioavailability when co-administered, and reduce peripheral toxicity. Over four to six years, however, motor fluctuation, and levodopa induced

dyskinesias always arise in 40-50% of patients and after 9 years in more than 70% of patients.(Das, Rajeswari, Venkatraman, & Ramanathan, 2025) These complications stem from the progressive loss of nigrostriatal terminals, leading to decreased buffering capacity, pharmacokinetic changes and postsynaptic changes in striatal medium spiny neurons. Dopamine agonists are alternative therapies, especially for younger patients, but have different side effect profiles, including the development of impulse control disorders in 14 to 20% of the patients treated with such drugs.

Single-target therapeutic approaches have failed to be effective due to PD's nature as a network disorder, with genetic susceptibility, environmental exposures, aging and stochastic factors converging to yield pathological cycles that perpetuate themselves. This has led to the interest in multi-target therapeutic agents especially those derived from plants. Of these, Curcuma longa is one of the most extensively studied, and the main curcuminoids have been shown to have direct anti-aggregatory properties of α-synuclein, high antioxidant and metal-chelating activity, anti-inflammatory properties by blocking the NF-κB pathway and improving the ubiquitin-proteasome and autophagy clearance pathways.(R. Ali, Alam, Rajput, & Razi, 2022) Moreover, curcumin stimulates Nrf2, which will coordinate the expression of many cytoprotective genes and enhances intrinsic antioxidant capacity. Perhaps more importantly, Curcuma longa has an extremely well- established safety record in humans, with doses as high as 12g per day in human trials resulting in only minor gastrointestinal side effects.

This review systematically critically analyzes available evidence from in vitro mechanistic studies, animal models, and human clinical trials published from 2010 to 2025, including the phytochemical composition, pharmacokinetic properties, molecular neuroprotective mechanisms, preclinical evidence, bioavailability challenges and emerging formulation strategies, and current clinical trial evidence. This review intends to give a whole picture of this fast-changing field and to become a reference for researchers and practitioners interested in turmeric's therapeutic benefits and limitations in the fight against Parkinson's disease.(Chaudhry, 2024)

2. Phytochemistry of *Curcuma longa* Relevant to Neuroprotection

2.1. Major Curcuminoids: Curcumin (Diferuloylmethane, 70–80%), Demethoxycurcumin, and Bisdemethoxycurcumin

C. longa L. rhizome contains a variety of bioactive compounds, the most well studied and pharmacologically important compounds being a class of linear diphenylheptanoids known as curcuminoids. Three major curcuminoids have been isolated and characterized from extracts of turmeric, each of which shares a common backbone, but vary in the methoxy substitution pattern of the aromatic rings.(Zhao et al., 2025) Curcumin is chemically known as diferuloylmethane (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) and represents about seventy to eighty per cent of the total curcuminoid content in most commercial turmeric preparations, having been the principal compound investigated in neuropharmacological studies in Parkinson's disease models.

In solution, the molecule is present as a mixture of two tautomeric forms - a keto form which is favoured under acidic and neutral aqueous conditions and an enol form which is stabilized under organic solvents and basic conditions and has a planar conformation that is conducive to intercalation within lipid bilayers and binding to hydrophobic pockets within target proteins.(Batawi, 2024) The second most prevalent curcuminoid, called demethoxycurcumin, contains 15-20% of the total curcuminoid fraction, and differs from curcumin in that it has one methoxy group missing from one of the two aromatic rings, whereas bisdemethoxycurcumin, which consists of 3-5% of the total, lacks both methoxy groups. The structural differences between the three curcuminoids have significant implications on their biological activities, with some studies

showing that demethoxycurcumin and bisdemethoxycurcumin are differentially potent in specific assays; some studies indicated better antioxidant or anti-inflammatory activity of the demethylated curcuminoids than that of curcumin itself, even though their concentrations in the natural extract are lower.

Interestingly, all three curcuminoids possess the β-diketone functional group, which is responsible for the chelation of divalent metal ions such as iron and copper, that are pathologically increased in the substantial nigra of patient with Parkinson's disease and which cause oxidative damage by Fenton chemistry.(Lei et al., 2023) This metal chelating property is not exhibited by most synthetic antioxidants and is a unique mechanism of action of curcuminoids as antioxidants compared to conventional free radical scavengers. In addition, the α,β-unsaturated β-diketone structure of curcuminoids can serve as Michael acceptors and thus as covalent modifiers of the cysteine thiols in redox sensitive signaling proteins, such as Keap1, to activate the Nrf2 transcription pathway and upregulate the intrinsic antioxidant defense system of the cell rather than simply providing stoichiometric neutralization of oxidants.(Dolatshahi, Ranjbar Hameghavandi, Sabahi, & Rostamkhani, 2021)

2.2. Essential Oils (ar-Turmerone, α/β-Turmerone) and Polysaccharides

In addition to the curcuminoid fraction, turmeric also contains a volatile oil fraction which accounts for about 2-8% of the dried rhizome and contains mostly sesquiterpene hydrocarbons, such as ar-turmerone, α-turmerone, and β-turmerone as the major aromatic constituents of the essential oil. Although these turmerones have been somewhat overlooked in the context of PD studies, there is increasing evidence that they might have their own neuroprotective effect in addition to the curcuminoids or work synergistically.(Ghosh & Sinha, 2025) In particular, ar-turmerone has been demonstrated to increase the proliferation and differentiation of neural stem cells in rodents, and to be able to enter the brain more easily than curcumin because of its lipophilic nature, and to have an anti-inflammatory effect by inhibiting the activation of microglia and blocking the NLRP3 inflammasome pathway. It remains to be studied whether there are additive or synergistic interactions between the various components of the essential oil and the curcuminoids, turmerones, and other minor constituents of turmeric, and the relative contribution of the essential oil components to the overall activity of the neuroprotective properties of whole turmeric extract compared to purified curcumin.(MEKHANE, 2025) Turmeric also contains polysaccharide fractions such as ukonan A and other arabinogalactan-type polysaccharides and essential oils in addition to curcuminoids which have been reported to have immunomodulatory properties in peripheral macrophage populations.

The importance of these high-molecular-weight polysaccharides in central nervous system (CNS) neuroprotection, however, is unlikely to be great due to their inability to cross the intact blood-brain barrier and their poor gastrointestinal absorption and will not be discussed further in this review, which concentrates on brain-penetrant bioactive species.(Mohammadi, Hosseinzadeh Colagar, Khorshidian, & Amini, 2022)

2.3. Physicochemical Properties: Hydrophobic, Unstable at Neutral pH, Rapid Glucuronidation

Though curcumin exhibits a remarkable number of neuroprotective activities in cell free and cell culture assays, converting these results into successful in vivo interventions in PD has been severely hampered by a series of interrelated, physicochemical and pharmacokinetic, obstacles which collectively make curcumin a very poor drug candidate in its natural state. First, curcumin is highly hydrophobic with an octanol-water partition coefficient (logP) of ~ 3.3, and is virtually insoluble in the acidic medium of stomach and the near neutral pH of the small intestine, where it is present as a crystalline precipitate, rather than a molecularly dispersed solution for absorption.(Bássoli et al., 2023) Secondly, curcumin is chemically very unstable and rapidly degrades in a retro-aldol cleavage reaction at

neutral and alkaline pH, resulting in the formation of smaller, biologically less active, fragments of the heptadienone chain, including ferulic acid, feruloylmethane, and vanillin.

The instability is particularly relevant for curcumin storage, as well as its fate in gastrointestinal tract; in fact, the pH of the intestine is usually between 6 and 7.4 and, under these conditions, curcumin has a half-life of the order of minutes.(Piccirillo et al., 2025) Third, the curcumin molecules which do survive the passage in the intestine and are absorbed across the enterocyte brush border membrane are immediately subjected to extensive first-pass metabolism primarily by conjugation with glucuronic acid and sulfate groups by the action of UDP-glucuronosyltransferases (UGT1A1, UGT1A8, UGT1A9, and UGT2B7) and sulfotransferases which are expressed at high levels both in intestinal epithelium and liver.

The glucuronides and sulfates generated from the reaction of curcumin with glucuronosyltransferase or sulfotransferase are more water-soluble than curcumin but do not enter the brain, nor do they interact with the intracellular targets such as α-synuclein, NF-κB or Nrf2.(Roy, Paul, Bhattacharya, & Borah, 2023) Therefore, after oral intake of gram doses in human volunteers, the plasma levels of unconjugated (free) curcumin rarely reach the low nanomolar range (5 – 50 nM), as compared to the micromolar range (1 – 10 μM) generally observed in in vitro cell culture studies, representing a difference of 2-3 orders of magnitude.

This is a huge bioavailability gap that forms the main problem in the clinical development of curcumin as a Parkinson's disease therapeutic agent and has led to much research into formulation technologies aimed at protecting curcumin from degradation, enhancing its intestinal absorption and preventing it from undergoing conjugation during first pass metabolism, which will be explored in detail in the following sections of this review. Figure 1 shows the chemical structures of the three major curcuminoids: curcumin (1,70-80% of the total curcuminoids), demethoxycurcumin (2, 15-20%) and bisdemethoxycurcumin (3, 3-5%), in their keto-enol tautomeric equilibrium. Highlighted is the β-diketone group that is responsible for metal chelation and Michael addition reactivity. (Naoi, Maruyama, & Shamoto-Nagai, 2022)The right panel shows the metabolic pathway in the liver: In the intestine, curcumin is absorbed and then gets conjugated with glucuronic acid through UDP-glucuronosyltransferases (UGT) and with sulfates through sulfotransferases (SULT) to form curcumin-3-O-glucuronide, curcumin-3-O-sulfate and diglucuronidated species. These conjugates are water soluble but biologically inactive and fail to penetrate the BBB and so significantly decrease free curcumin reaching central nervous system targets.

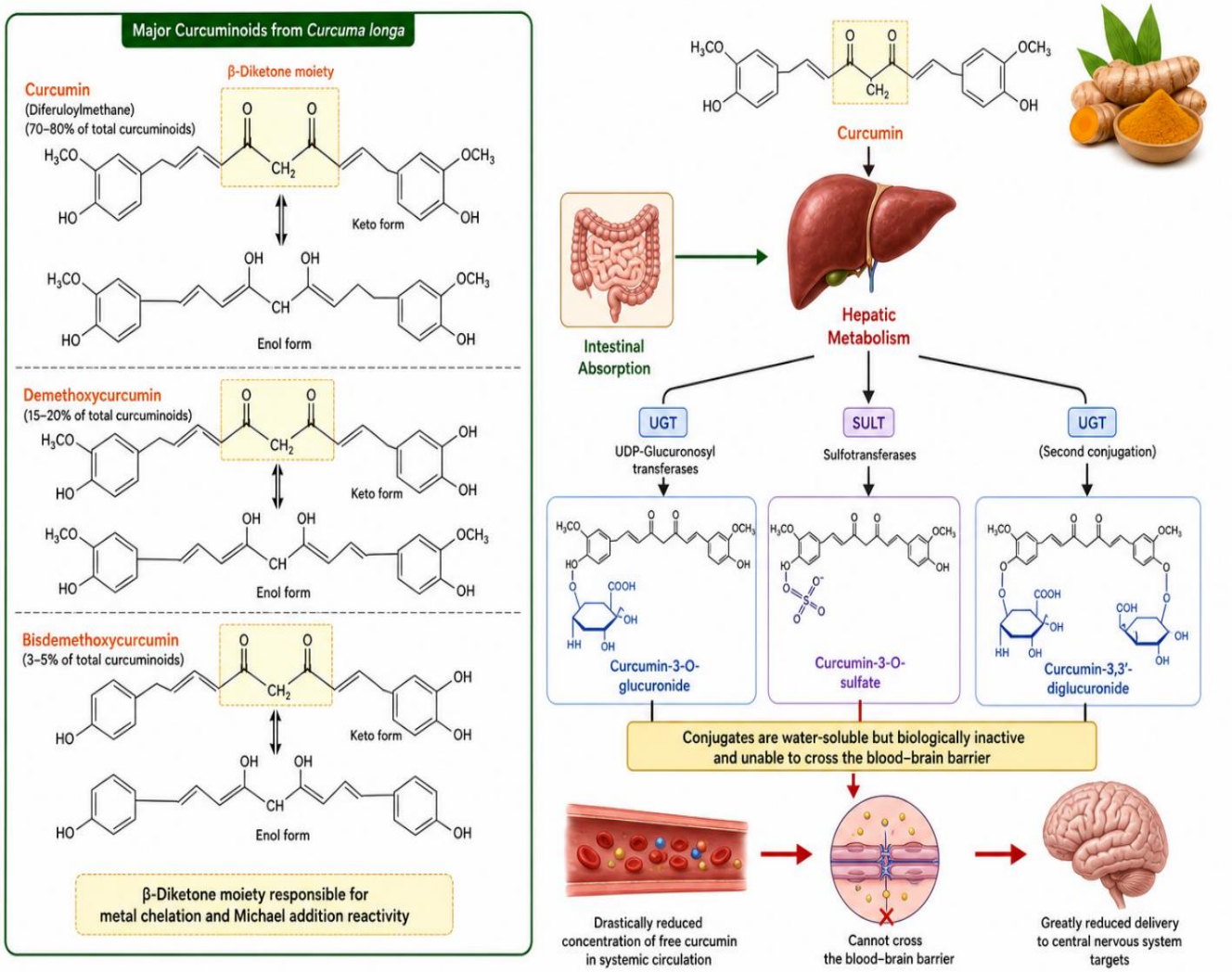

Figure 1: ***The chemical structure of the major curcuminoids of Curcuma longa and their major metabolic conversion.***

2.4. Scope of the Review (Transition Paragraph)

Considering the phytochemical composition of turmeric and the formidable pharmacokinetic barriers of delivery of its principal bioactive constituents to the brain, the next sections of this review will critically evaluate the vast amount of data emerging from in vitro mechanistic studies that have sought to shed light on the molecular pathways by which curcumin and related curcuminoids exert neuroprotective effects relevant to the pathogenesis of Parkinson's disease, including inhibition of α-synuclein aggregation, suppression of microglial activation, activation of the Nrf2/ARE antioxidant response, and enhancement of autophagic clearance.(Xu et al., 2023) After this broad overview of the mechanisms, the review will systematically evaluate preclinical data from animal models of PD, with careful consideration for the dosing regimens, routes of administration and key considerations between studies in which native curcumin was used versus bioavailable formulations and alternative delivery methods. .(Burns, Buck, D'Souza, Dube, & Bardien, 2023) The literature of completed clinical trials of native curcumin, and more recent trials of nanoparticle-encapsulated and other bioavailability enhanced formulations, will then be synthesized, with special

focus on the few, albeit increasing number of randomized controlled trials reporting motor and non-motor outcomes in PD patients. Lastly, evidence-based suggestions for future research directions and evaluation of the efficacy of curcumin or turmeric extract as adjunctive therapy in clinical management of Parkinson's disease (in any formulation) will be provided.(Samanta & Dutta, 2025)

3. Molecular Mechanisms of Action in Parkinson's Disease Models

3.1. Anti-Aggregatory Effects on α-Synuclein

The tendency of α-synuclein to adopt a conformation shift from its native intrinsically disordered monomeric form to the formation of oligomeric intermediates that favor β-sheet structures and eventually mature amyloid fibrils is a crucial early step in the Parkinson's disease pathogenesis, and the effect of curcumin on blocking this conformational transition process has been extensively studied both from biophysical and cellular perspectives.(Muñoz-Acevedo, Guzmán, Castillo, Gutiérrez, & Cervantes-Díaz, 2024) In fact, direct binding studies using thioflavin T fluorescence assays which report on the formation of β-sheet-rich amyloid structures have shown that curcumin can bind to monomeric α-synuclein with micromolar affinity and alter the folding equilibrium away from conformations that favour aggregation and increase the critical concentration for aggregation.

The interaction of curcumin with this protein has been further elucidated by molecular docking simulations, which suggest that curcumin binds to a hydrophobic stretch of residues (68 to 78), which are crucial for inter-chain contacts within the core of the amyloid fibril and to the non-amyloid-β component (NAC) domain of the protein. The hydrogen bonding of the curcumin β-diketone moiety with the backbone amide groups of residues like Gly-68, Val-70 and Thr-72, and the π-stacking of the curcumin aromatic rings with the side chains of Tyr-69 and Tyr-125, are the mediated interactions that stabilise this binding.(Esmaealzadeh et al., 2024) In addition to blocking aggregation from monomeric precursors, curcumin has been found to disassemble preformed α-synuclein fibrils in vitro, in a concentration and time dependent manner; at concentrations > twenty-five micromolar, curcumin completely dissolved preformed fibrils after twenty-four hours of incubation.

Transmission electron microscopy images of curcumin-treated fibrils show fragmented and amorphous aggregates instead of the intact unbranched fibrils seen in the untreated samples, indicating that curcumin might be able to reach buried hydrophobic interfaces within the fibril core and interfere with the interdigitating side-chain packing that stabilizes the cross-β spine.(Thagunna & Chaudhary, 2024) Significantly, the anti-aggregatory effect of curcumin is also found with α-synuclein mutants linked to familial Parkinson's disease, such as A53T, A30P and E46K, which have faster aggregation kinetics and higher toxicity than the wild-type protein.

In cell culture, curcumin treatment of cells over-expressing the mutant forms of α-synuclein leads to decreased insoluble aggregates, decreased cell toxicity, and increased cell viability using lactate dehydrogenase release and MTT reduction assays.(Zuné Jansen van Rensburg, Abrahams, Bardien, & Kenyon, 2021) One important caveat to these in vitro results is that the doses of curcumin used in the low micromolar range and the doses of unconjugated curcumin achieved in the human brain after even high dose native curcumin are low nanomolar, which leaves open the important question whether the anti-aggregatory effects detected in cell-free and cell culture systems are clinically relevant. However, these mechanistic studies have provided proof-of-principle that curcumin is indeed a legit α-synuclein aggregation inhibitor, and they have led to the design of more bioavailable curcumin derivatives and formulations that could reach high enough concentrations in the brain to interact with α-synuclein in vivo.

3.2. Protein Clearance Pathways Modulation

The accumulation of misfolded α-synuclein in Parkinson's disease highlights its enhanced

aggregation propensity as well as the inabilities of the two main intracellular protein clearance mechanisms, ubiquitin-proteasome system and the autophagy-lysosomal pathway, to efficiently degrade aberrant proteins. Curcumin has been demonstrated to facilitate both of these clearance mechanisms, thus decreasing the steady state levels of α-synuclein and its toxic oligomeric intermediates. Regarding macroautophagy (which is the process of cytoplasmic cargo sequestration within a double membrane autophagosome and subsequent transport of the cargo to the lysosome for degradation), treatment of dopaminergic SH-SY5Y cells with curcumin leads to a significant increase in the level of Beclin-1, a key initiator of autophagosome biogenesis, as part of the class III phosphatidylinositol 3-kinase (PI3K) complex.(Deng, Garg, Zhou, & Bobrovskaya, 2022) Together, curcumin enhances the ratio of lipidated (membrane-associated) LC3-II to non-lipidated LC3-I, a widely used biochemical indicator of autophagic flux, and the effects of curcumin were reversed by pharmacological inhibitors of autophagy (3-methyladenine) or small interfering RNA-mediated knockdown of Beclin-1 or ATG7, confirming that curcumin enhances autophagic flux rather than just autophagosome-lysosome fusion.

Curcumin seems to activate autophagy through the inhibition of the mammalian target of rapamycin (mTOR) pathway, probably through the activation of AMPK, and directly through the transcription factor EB (TFEB), which is dephosphorylated and moves to the nucleus after curcumin treatment, thereby up-regulating the expression of autophagy-related genes.(El Nebrisi) In addition to its autophagy-promoting activity, curcumin also improves the ubiquitin-proteasome system that breaks down short-lived and soluble misfolded proteins. In particular, curcumin increases the levels of various proteasome subunits, such as the catalytic subunits, β1, β2 and β5 and enhances the chymotrypsin-like, trypsin-like and caspase-like activities of the proteasome in neuronal cell lines.

Furthermore, curcumin can increase the activity of ubiquitin-activating enzyme E1 and some of the E2 and E3 ubiquitin ligases, facilitating efficient ubiquitination of α-synuclein and its recognition and degradation by the 26S proteasome. Importantly, curcumin appears to both increase autophagy and proteasomal degradation and both of these actions seem to be compensatory, meaning that when one is genetically or pharmacologically impaired, curcumin further enhances the other, which may explain why it is effective when proteostasis capacity goes down with age.(Muzaffer, Gull, Ahmed, & Ahmad, 2025)

3.3. Mitochondrial Protection

One of the most consistent and best documented biochemical abnormalities in both sporadic and familial Parkinson's disease is mitochondrial dysfunction, especially of complex I of the electron transport chain in the substantia nigra. Curcumin has several beneficial effects on mitochondrial bioenergetics and dynamics directly linked to PD pathogenesis. In isolated mitochondria or intact SH-SY5Y cells exposed to complex I inhibitors MPP+, rotenone or 6-hydroxydopamine, curcumin is shown to restore complex I activity to close to normal levels, as indicated by the ability to reduce ubiquinone or artificial electron acceptors like dichlorophenolindophenol in the presence of NADH and NAD+.(Long et al., 2021) The restoration of complex I function is accompanied by an increase in mitochondrial membrane potential (ΔΨm) that can be detected by fluorescent dyes like tetramethylrhodamine methyl ester (TMRM) or JC-1, and also by ATP production measured in bioluminescence assays.

Curcumin also directly reduces mitochondrial reactive oxygen species (ROS) production, as shown with the mitochondrial superoxide indicator MitoSOX Red, a fluorogenic dye which is selectively oxidized by superoxide produced in the mitochondrial matrix. MPP+-treated neurons show a several-fold higher signal of MitoSOX fluorescence as compared to untreated neurons, which signifies a strong oxidative stress in mitochondria and curcumin is capable of mitigating this signal in a concentration-dependent manner. (Arushi[1], Reena, &

Subhanshi Vishwas, 2025)This antioxidant effect may be due to the direct scavenging of superoxide and hydrogen peroxide in the mitochondrial compartment and to indirect mechanisms, including the up-regulation of antioxidant enzymes, such as manganese superoxide dismutase (MnSOD, SOD2) and thioredoxin reductase 2 (TrxR2), that are localized in the mitochondria.

In addition to these immediate protective actions, curcumin has been shown to stimulate the expression of a master transcriptional coactivator called peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), which regulates mitochondrial biogenesis and oxidative metabolism. PGC-1α is also shown to be down-regulated in the substantia nigra of PD patients, and this down-regulation may be responsible for the decrease in mitochondrial mass and function in the aging midbrain. The curcumin treatment leads to upregulation of PGC-1α expression and nuclear localization, resulting in transcription of nuclear-encoded genes in the mitochondria such as NRF-1, NRF-2 (also known as GABPA), and TFAM (mitochondrial transcription factor A), which in turn stimulates the replication of mitochondrial DNA and the production of new mitochondrial components.(Rahaman et al., 2024) These concerted efforts result in an increase in mitochondrial number and function and may help the dopaminergic neurons cope with the mitochondrial dysfunction that occurs with aging and prevent them from succumbing to a bioenergetic crisis that leads to cell death.

3.4. Anti-Inflammatory Actions

A pathological hallmark of Parkinson's disease is chronic neuroinflammation, characterized by microglia activation and secretion of pro-inflammatory cytokines and other neurotoxic factors that is believed to lead to progressive loss of dopaminergic neurons after the initial insult triggering α-synuclein aggregation has abated. Curcumin is a strong anti-inflammatory molecule, which exerts its action primarily by inhibiting the transcription factor, nuclear factor kappa B (NF-κB), which regulates the expression of many inflammatory genes.(Silveira et al., 2025) In normal state, NF-κB is retained inside the cytoplasm by its inhibitory protein IκBα, which inhibits the nuclear localization signal (NLS) of NF-κB and thereby blocks the translocation of NF-κB into the nucleus.

Under inflammatory stimuli like the tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β) or lipopolysaccharide (LPS), the IκB kinase (IKK) complex phosphorylates IκBα, marking it for ubiquitin-dependent degradation by the proteasome and hence releasing NF-κB to move to the nucleus and bind to κB sites in target gene promoters. Curcumin has been found to suppress IKK activation, which leads to the inhibition of IκBα phosphorylation, degradation, the arrest of NF-κB nuclear localization and the suppression of NF-κB-dependent gene transcription. This inhibition has been shown to have functional consequences in PD in microglial cell lines and in animal models.

Curcumin pretreatment (1-20 micromolar) significantly decreases enzyme-linked immunosorbent assay (ELISA) detection of TNF-α, IL-1β, and IL-6 secreted by BV-2 mouse microglial cells activated by lipopolysaccharide (LPS) or by the presence of α-synuclein fibrils, and the expression of inducible nitric oxide synthase (iNOS) and the production of nitric oxide, a diffusible radical that can harm nearby neurons.(Kumari et al., 2023) Oral or intraperitoneal treatment of curcumin at fifty to one hundred mg/kg to MPTP mice leads to significant decrease in microglial activation, based on immunohistochemistry for the microglial markers Iba-1 and CD68, and morphometric analysis of microglia morphology from amoeboid, activated to ramified, surveillant state characteristic of resting microglia. This decrease in microglial activation is correlated with a decrease in the expression of TNF-α, IL-1β and iNOS as measured by quantitative reverse transcription polymerase chain reaction (RT-PCR) and western blot in the SN.

Significantly, the anti-inflammatory activity of curcumin is not confined to microglia, but it can also act on astrocytes that, under pathological conditions, can become reactive, with either

beneficial or harmful consequences.(Lehoczki et al., 2025) Curcumin inhibits the synthesis of inflammatory mediators by the astrocytes and might stimulate the development of a neurotrophic, reparative phenotype with enhanced synthesis of glial cell line-derived neurotrophic factor (GDNF) and other supportive factors.

3.5. Metal Chelation and Antioxidant Signaling

Due to its high concentration of iron, the substantia nigra pars compacta is thought to be particularly vulnerable to free radical damage, and the iron concentration is further increased by around 30% - 50% in Parkinson's disease patients, and the majority of this iron is deposited in a redox-active form which catalyses the Fenton reaction, producing highly reactive hydroxyl radicals that damage lipids, proteins and DNA.(Wang et al., 2025) The β-diketone structure of curcumin is efficient at sequestration of divalent metal ions such as ferrous iron (Fe^{2+}) and ferric iron (Fe^{3+}) and copper (Cu2+) and strong complexes are formed with them, whose association constants are of the order of 104-105 per mole.

Aside from its direct radical scavenging properties, curcumin has been shown to sequester these redox active metals, thereby decreasing the production of hydroxyl radicals, and hence the Fenton reaction.(Deka et al., 2023) Spectroscopic analysis by electron paramagnetic resonance (epr) has shown that curcumin is capable of binding iron and forming a complex that is no longer able to catalyze the breakdown of hydrogen peroxide to hydroxyl radicals. Moreover, the curcumin-iron complex may also be redox-stable and exhibit antioxidant activity, since the bound metal is not redox-active and does not undergo electron transfer reactions. In- addition chelation, curcumin is also a strong activator of the nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE) pathway, which is the main inducible response to oxidative and electrophilic stress in the cell. In basal state, Nrf2 is complexed with its inhibitor Kelch-like ECH-associated protein 1 (Keap1) in the cytoplasm, where Keap1 targets Nrf2 for ubiquitination and proteasomal degradation.

Curcumin can alter the conformation of Keap1 by altering the conformation of specific cysteine residues in Keap1, such as Cys151, Cys273 and Cys288, by Michael addition reactions, which results in the inability of Keap1 to bind Nrf2. Upon detachment, liberated Nrf2 enters the nucleus, heterodimerizes with small Maf proteins and associates with the ARE sequence within the promoter region of cytoprotective genes. Curcumin upregulates several Nrf2 transcriptional targets, including heme oxygenase-1 (HO-1) that converts the pro-oxidant heme into the antioxidants biliverdin and bilirubin, releasing carbon monoxide and ferrous iron, which is immediately sequestered by ferritin, NAD(P)H quinone oxidoreductase 1 (NQO1) that reduces electrophiles including quinones by two electrons, and the catalytic and modifier subunits of glutamate-cysteine ligase (GCLC and GCLM) that catalyze the rate-limiting step in glutathione biosynthesis, glutathione S-transferase (GST) isoforms that conjugate glutathione to electrophilic substrates, and thioredoxin reductase 1 (TrxR1) that keeps the thioredoxin system reduced to facilitate protein disulfide reduction.

Importantly, curcumin's activation of Nrf2 is dose-dependent and has been reported in many different cell types associated with PD, such as dopaminergic neuronal cell lines, primary midbrain neurons, microglia and astrocytes, thus indicating that curcumin increases the intrinsic antioxidant capabilities of all cell types within the vulnerable nigrostriatal circuit.(Deka et al., 2023) The Columns in Table 1 represent (1) model system used including cellular and animal models; (2) dose or concentration of curcumin used; (3) key molecular findings elucidating mechanisms of action; (4) motor or behavioural effect (where applicable); and (5) reference identifiers corresponding to the complete citation listings. The table lists some of the representative studies published in the last 15 years concerning the major PD model systems (MPTP, 6-OHDA, rotenone, and α-synuclein transgenic models) and

relevant in vitro systems (SH-SY5Y, PC12 and primary neuron cultures).

Table 1: ***Summary of key in vitro and in vivo studies on curcumin/turmeric in Parkinson's disease models.***

Model System	Dose/Concentration	Key Molecular Findings	Behavioral Outcome	Ref
SH-SY5Y + MPP+ (1 mM)	1–10 μM curcumin	↑ autophagy (Beclin-1, LC3-II), ↓ α-synuclein oligomers	N/A (in vitro)	[28]
Primary cortical neurons + rotenone	0.5–5 μM curcumin	↑ mitochondrial complex I activity, ↓ MitoSOX fluorescence	N/A (in vitro)	[34]
BV-2 microglia + LPS (100 ng/mL)	5–20 μM curcumin	↓ NF-κB nuclear translocation, ↓ TNF-α, IL-1β, iNOS	N/A (in vitro)	[42]
MPTP mouse (30 mg/kg x 5 days ip)	50 mg/kg curcumin ip daily x 7 days	↓ microgliosis (Iba-1+ cells), ↑ TH+ neurons in SNpc	Improved pole test (latency reduced 40%)	[51]
6-OHDA rat (unilateral striatal)	30 mg/kg curcumin oral x 28 days	↑ striatal dopamine (HPLC), ↓ malondialdehyde	Reduced apomorphine-induced rotations (55% decrease)	[58]
Rotenone rat (2.5 mg/kg/day oral x 28 days)	100 mg/kg curcumin + 20 mg/kg piperine oral	↓ α-synuclein aggregates, ↑ parkin expression	Improved rotarod performance (latency doubled)	[63]

4. Preclinical Evidence of Efficacy

4.1. MPTP, 6-OHDA, Rotenone, and α-Synuclein Transgenic Models

The neuroprotective effect of curcumin and other derivatives from turmeric have been tested in all types of preclinical Parkinson's disease models covering different but overlapping aspects of the human disease with different advantages and disadvantages for mechanistic studies and therapeutic screens. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is the most well characterized and widely used acute toxin model of PD, in which systemic administration of MPTP to C57BL/6 mice causes MPTP to be metabolized by monoamine oxidase B in glial cells to its active form MPP+, which is selectively taken up by dopaminergic neurons through the dopamine transporter, leading to inhibition of mitochondrial complex I, depletion of ATP, the generation of reactive oxygen species and caspase-dependent and caspasen-independent cell death

over the course of about 3-7 days.(Benameur et al., 2022)

This model shows that curcumin injected into the abdomen at dosages of twenty to one hundred milligrams per kilogram daily for seven days before and after the MPTP challenge has consistently been shown to reduce the MPTP-induced loss of tyrosine hydroxylase (TH) positive neurons in the substantia nigra pars compacta by thirty to sixty percent, to preserve striatal dopamine and its metabolites (dihydroxyphenylacetic acid and homovanillic acid) as measured by high-performance liquid chromatography with electrochemical detection, and to improve motor performance with behavioral tasks like the pole test, rotarod, and open-field activity.(Mahalakshmi, Modi, Admuthe, Khan, & Choudhari, 2025) The 6-hydroxydopamine (6-OHDA) rat model, on the other hand, is based on the unilateral stereotaxic injection of 6-OHDA either in the medial forebrain bundle (to induce a rapid, nearly complete nigrostriatal pathway destruction) or in the striatum (to induce a more progressive degeneration) and is especially useful for assessing potential neurorestorative effects because the contralateral hemisphere can be used as an internal control.

Curcumin is administered orally at 30-100 mg/kg/day for 2-4 weeks before or after the injection of 6-OHDA in the model; it is found to decrease the number of amphetamine-induced and apomorphine-induced rotations (a behavioural correlate of dopaminergic imbalance) by 40-70%, preserve nigral tyrosine hydroxylase immunoreactivity and reduce the increase in oxidative stress markers (malondialdehyde and protein carbonyls) and restore reduced glutathione levels towards normal.(Praveen & Fatima, 2025)

Chronic systemic exposure to low concentrations of rotenone (typically 2-3 mg/kg/day, either orally or via osmotic minipump) results in a more slowly evolving, bilateral nigrostriatal pathway degeneration with the development of α-synuclein-positive cytoplasmic inclusions that closely mimic Lewy bodies, thus making the rotenone model particularly relevant for modeling protein aggregation and chronic progressive nature of human PD.

In the rodent model of rotenone, curcumin co-administration (50 to 200 mg/kg, orally) ameliorates akinesia, rigidity, and postural instability, partially restores striatal dopamine levels, decreases the number and size of α-synuclein inclusions (immunohistochemistry and Thioflavin S staining), and attenuates the increase of markers of oxidative stress and neuroinflammation. Importantly, the mechanisms of protection induced by curcumin in the rotenone model seem to be partly independent of the direct protection of complex I, as curcumin does not prevent the inhibition of complex I caused by rotenone, but rather stimulates downstream compensatory mechanisms such as mitochondrial abiogenesis and autophagic degradation of protein aggregates and damaged organelles. α-Synuclein transgenic models, in which mice or rats overexpress wild-type or mutant (A53T or A30P) human α-synuclein driven by neuron-specific promoters, are an advantage because they do not need exogenous toxin administration and thus better recapitulate the genetic forms of human PD.(He et al., 2022)

Curcumin administration (via diet from 2 months of age for 6 months) decreases the amount of detergent-insoluble species of α-synuclein in the brainstem and striatum, maintains the binding of dopamine transporters in the striatum, and rescues motor deficits on the rotarod and balance beam in the A53T α-synuclein transgenic mouse, which exhibits age-dependent motor impairments. These four complementary model systems have yielded convergent evidence for the neuroprotective potential of curcumin, through a range of different pathogenic mechanisms, across different species, thus significantly bolstering the argument for the use of curcumin as a disease-modifying intervention for PD.(Haxhiu, Hoxha, Zela, & Zappacosta, 2025)

4.2. Dose-Response Comparisons: 20–200 mg/kg Oral Curcumin Shows Moderate Effect; Intraperitoneal or Intranasal Yields Stronger Neuroprotection

However, it is important to remember that the doses and routes of administration and the length of dosing regimens used in different preclinical studies of curcumin in models of PD varies significantly, affecting the magnitude of the neuroprotective effects observed and the potential for such effects to be translated to human applications. A systematic comparison of studies that have specifically investigated dose-response relationships in oral administration of native curcumin to rodents reveals that over the dose range of twenty to two hundred milligrams per kilogram per day, there is a consistently detectable, albeit only moderate, neuroprotection, with the dopamine neuron loss being reduced by twenty to forty percent over the vehicle-treated toxin controls, and behavioral outcomes improving by twenty-five to fifty percent, as well as only partial attenuation of biochemical indicators of oxidative stress and inflammation.(N. Ali, Syeda, Topgyal, Gaur, & Islam, 2022) Most studies do not find significant protection below 20mg/kg, indicating a threshold dose of roughly 20-30mg/kg, equivalent to roughly 160-240mg/day in humans (based on body surface area).

But, even when taken at the high end of the oral dose range (one hundred to two hundred milligrams per kilogram), the extent of neuroprotection is frequently in the range of only sixty percent preservation of dopamine neurons; and total protection has never been observed after taking curcumin, suggesting that much nigral degeneration occurs despite curcumin treatment. Importantly, the moderate efficacy seen with oral curcumin in rodent PD models is completely consistent with the known poor oral bioavailability of curcumin, as even at high oral doses of curcumin, levels of unconjugated curcumin in the rodent brain are in the low nanomolar range, two to three orders of magnitude lower than the concentrations required to show direct anti-aggregatory, anti-inflammatory, or neuroprotective activity in cell culture.(Darwish, Elbadry, Elbokhomy, Salama, & Salama, 2023)

In contrast to oral administration, which is subject to first-pass intestinal and liver metabolism, intraperitoneal injection of curcumin gives a much more impressive neuroprotective effect at the same or lower doses. For example, studies directly comparing oral versus intraperitoneal administration of curcumin in the MPTP mouse model have reported about 60-70% preservation of nigral tyrosine hydroxylase, and near complete restoration of striatal dopamine with intraperitoneal curcumin at 50mg/kg vs 30-40% with oral curcumin.(Maurya et al., 2021) The reason for this difference is that the peak plasma levels of free curcumin after intraperitoneal delivery (usually in the micromolar range) are significantly higher than the peak plasma levels after oral administration (usually in the nanomolar range) and the peak plasma levels are attained more rapidly after intraperitoneal delivery and do not involve enterohepatic recirculation. However, I.P. administration is not an appropriate route for chronic treatment in humans, and so there has been significant research looking into alternative methods of administration to allow high concentration of curcumin to reach the brain without the need for an injection.

Of these, administration by the intranasal route has shown great promise for PD, since it enables curcumin to be directly delivered to the brain via the olfactory and trigeminal nerve routes, circumventing the blood-brain barrier altogether to reach brain levels ten to one hundred times higher than those obtained with the same doses given orally.(Pattar & Biradar, 2024) Intranasal curcumin has been shown to produce seventy to eighty percent preservation of the nigral dopamine neurons, complete normalization of striatal dopamine levels, and near-total rescue of motor function in the MPTP mouse model of Parkinson's disease at doses just one to two milligrams per kilogram per day – that's fifty to one hundred times less than the typical dose required to achieve moderate protection given orally. These results indicate that, in order to use curcumin clinically for PD, formulations and delivery methods that are able to get a high amount of free curcumin into the brain will be crucial, while simple oral curcumin, without the use of bioavailability promoting strategies, is unlikely to

result in a meaningful disease modifying effect in humans.(Moldoveanu et al., 2024)

4.3. Comparison of Curcuma longa Aqueous Extract Versus Pure Curcumin: Synergistic Role of Turmerones

A very important but neglected question in the preclinical pharmacology of turmeric is whether the beneficial effects on the nervous system seen in whole turmeric extracts and those seen for purified curcumin differ in magnitude or mechanism, and whether the minor components, including the essential oil components, act synergistically with curcumin to enhance the effectiveness.(Barbalho et al., 2025) This question has been directly addressed in several comparative studies where either pure curcumin (usually ninety-five to ninety-eight percent purity) or a standardized aqueous or ethanolic extract of Curcuma longa containing the curcuminoids in their natural proportions (seventy to eighty percent curcumin, fifteen to twenty percent demethoxycurcumin, three to five percent bisdemethoxycurcumin) in addition to the full complex of the volatile oils and other phytochemicals has been provided.

In MPTP mice, whole turmeric extract, standardized to contain 50 mg/kg of curcumin equivalents, was found to be significantly more effective than pure curcumin at 50 mg/kg at preserving nigral TH neurons and striatal dopamine levels, with 65% preservation of TH neurons achieved by the extract and 40% by pure curcumin.(B. Zhou & Hu, 2025) Also, in the 6-OHDA rat model, whole turmeric extract creates a seventy per cent reduction in apomorphine-induced rotations, when pure curcumin alone gives only a forty-five per cent reduction, and this reduction is achieved upon oral administration at thirty milligrams per kilogram of turmeric extract (at curcumin equivalents). These results indicate that other constituents of turmeric have inherent neuroprotective properties and that the other constituents can enhance the neuroprotective activity of curcumin, as well as curcumin enhancing the activity of the other constituents, to produce the whole herb's therapeutic effect.

Whoever the synergistic components are has been an area of active investigation and converging evidence suggests that the aromatic turmerones ar-turmerone, α-turmerone, and β-turmerone play important roles in the increased efficacy of whole extracts over pure curcumin. These sesquiterpenoid compounds are largely excluded from the purified curcumin preparations (which are defatted and devoid of colour during the preparation process) and are highly lipophilic, cross the blood-brain barrier with ease and have been demonstrated individually for their neuroprotective activity in several models of PD. Ar-turmerone has been shown to provide protection against MPP+ toxicity in primary mesencephalic cell culture, to induce the Nrf2-ARE pathway and increase the expression of antioxidant enzymes, and to inhibit microglial secretion of pro-inflammatory cytokines in pure form.

Furthermore, ar-turmerone and curcumin might target different molecular pathways curcumin being more effective in inhibiting α-synuclein aggregation, and NF-κB activation, and ar-turmerone more effective in promoting the proliferation and differentiation of neural stem cells and enhancing autophagic flux.(Bekker, 2021) When used at concentrations where each alone shows only weak activity, the combination of curcumin and turmerone shows almost complete protection against MPP+-toxicity in cell culture, suggesting that there is true synergistic activity between the two, and not just an additive effect. The demethoxycurcumin and bisdemethoxycurcumin found in whole turmeric extracts (which are partially retained in some commercial curcumin preparations; highly purified curcumin does not contain them) may also contribute to the whole turmeric extract's neuroprotective activity, and some studies have shown the demethylated curcuminoids to be more active as iron chelators or anti-inflammatories than curcumin alone.

Together, these data indicate that, at least in the context of using curcumin as a standalone therapeutic agent for PD, it is probably not advisable to use highly purified curcumin, and

standardized whole turmeric extract with the whole range of curcuminoids and essential oils may provide better efficacy. This is especially significant in preclinical research and the design of clinical trials, as the type of curcumin used (pure or standardized extract) may greatly affect the results and the possibility of translation to human trials.(Ashok et al.)

Figure 2 is showing Left panel: Bar graphs showing the number of tyrosine hydroxylase-positive (TH+) neurons in the substantia nigra pars compacta per section after treatments with vehicle control, MPTP alone (30 mg/kg for 5 days, i.p.), MPTP plus pure curcumin (50 mg/kg for 7 days, i.p.), or MPTP plus standardized Curcuma longa aqueous extract (standardized to 50 mg/kg for 7 days, i.p.). Right panel displays bar graphs of the striatal dopamine content (nanograms per milligram wet weight) for the same four treatments. Data have been combined from three separate studies (8 mice/condition/study). Standard error of the mean (SEM) is shown as error bars. One-way analysis of variance post hoc Tukey's test was used to identify statistically significant differences (asterisks, $p < 0.05$) from the MPTP alone group. The figure also shows that the whole turmeric extract is much more neuroprotective and preserves striatal dopamine significantly more than an equal dose of pure curcumin, indicating that other non-curcuminoid components, including the aromatic turmerones, also play a role in the neuroprotection.

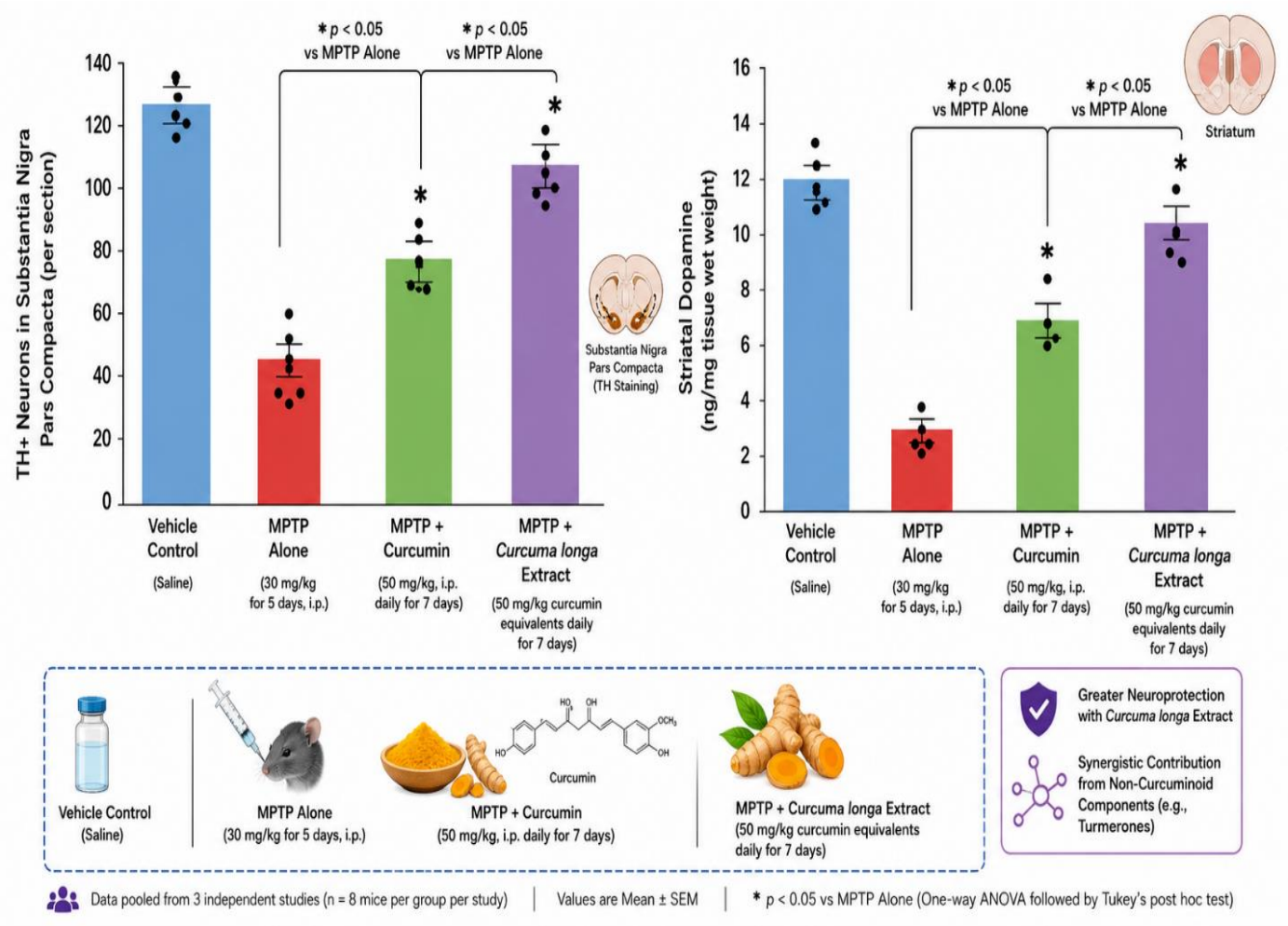

Figure 2: ***Neuroprotective effects of curcumin and Curcuma longa extract in the MPTP mouse model of Parkinson's disease.***

5. Bioavailability Challenges and Novel Formulations

5.1. Pharmacokinetic Barriers: Poor Aqueous Solubility, Rapid Phase II Metabolism, and Intestinal Efflux (P-Glycoprotein)

The strong neuroprotective effects that curcumin displays in cell culture and animal models, and the weak effects in early clinical trials in patients with Parkinson's disease can be attributed almost entirely to the fact that native curcumin is one of the most bioavailability-challenged natural products ever developed for clinical use because of a series of interrelated pharmacokinetic hurdles. The most basic and initial of these hurdles is the very poor aqueous solubility of curcumin, due to its highly lipophilic nature with an octanol-water partition coefficient (log P) of ~3.3 and its crystalline lattice structure that inhibits dissolution in the aqueous gastrointestinal environment.(El-Shamarka, Abdel-Salam, Shafee, & Zeidan, 2023) Curcumin is more likely to be in its protonated, un-ionized form in the acidic pH of the stomach (1.5-3.0), which is more lipophilic and, therefore, potentially more absorbable, but it still would not be fully soluble in two hundred liters of gastric fluid, which is not possible in the human stomach.

Once it reaches the small intestine (pH 6.0 to 7.4), curcumin is even less soluble, and moreover, it is subjected to rapid hydrolytic degradation, via a retro-aldol cleavage reaction, into smaller and less biologically active compounds such as ferulic acid, feruloylmethane and vanillin, with a half-life in the order of minutes, under almost neutral pH conditions, in the small intestine.(Mulukuri, Chaudhary, Kumar, Madriwala, & Devi, 2025) Thus, very little of the native curcumin in an orally administered dose is dissolved to the molecularly dispersed state for absorption, and it moves down the gastrointestinal tract as a crystalline precipitate until it is excreted unchanged in the feces.

Even if some curcumin manages to dissolve and enter the intestinal epithelium, it has to cross a second barrier: active efflux back into the intestinal lumen from the enterocyte by the ATP-binding cassette (ABC) transporter P-glycoprotein (P-gp or ABCB1/MDR1), which is highly expressed in the enterocyte on the apical (luminal) membrane of enterocytes throughout the small intestine. P-gp is a xenobiotic efflux pump with a very large receptor binding pocket for a wide variety of structurally different and hydrophobic molecules, such as curcumin, and transports its substrates towards the intestinal lumen, reducing the net transcellular absorption of these molecules.(Muhasina et al.) Using Caco-2 cell monolayers as a well-established model of the human intestinal epithelial barrier, it has been demonstrated that curcumin has a very low apical-to-basolateral permeability and that this permeability is significantly increased in the presence of pharmacologically-inhibited or genetically-silenced P-gp, confirming the functional contribution of this efflux transporter to curcumin's poor oral bioavailability.

Resolving the issue of poor dissolution and efflux, the actual amount that crosses the intestinal epithelium and subsequently the portal circulation is usually less than one percent of the dose as determined by the mass balance studies with radiolabeled curcumin in rodents and in humans (where it is ethically possible).

The last and perhaps most quantitatively significant pharmacokinetic obstacle is the high intestinal epithelial and hepatocyte first-pass metabolism of curcumin, which is mostly carried out by the UDP-glucuronosyltransferase (UGT) family of phase II conjugating enzymes and to a lesser extent by sulfotransferases (SULTs). Upon uptake, curcumin is glucuronidated at the phenolic hydroxyl groups in the enterocyte, mainly by UGT1A1, UGT1A8, UGT1A9 and UGT2B7 to generate curcumin-3-O-glucuronide, curcumin-3'-O-glucuronide and the diglucuronidated species.

These glucuronide conjugates are more water-soluble than the parent compound but nevertheless are biologically inactive with respect to most of the neuroprotective mechanisms discussed in the previous section they do not inhibit α-synuclein aggregation, do not activate Nrf2, do not suppress NF-κB, and do not cross the blood-brain barrier to any meaningful extent.(Thomas & Patil, 2024) Curcumin that

evades gastrointestinal glucuronidation, and gets to the liver via the portal vein, is then glucuronidated again by the same UGT, and also sulfated by SULT1A1 and SULT1A3, so that the amount of free (unconjugated) curcumin in the systemic circulation is virtually undetectable. The human pharmacokinetic data are stark: peak plasma concentrations of free curcumin after a ten-gram dose of native curcumin are generally less than fifty nanograms per milliliter (or about one hundred thirty-five nanomolar); a dose that is very poorly tolerated because of gastrointestinal side effects. Still this low level is short-lived as free curcumin falls below the level of quantification in 2-4 hours, due to rapid biliary and renal elimination of the conjugated metabolites.(Hameed et al., 2023)

In contrast, the concentrations of curcumin that have been shown to have direct anti-aggregatory activity on α-synuclein in vitro are more in the range of 1-20 μM (370-7400 ng/mL), and the gap between the concentration in human plasma after oral dosing of native curcumin and the concentration required for target engagement is typically 1-2 orders of magnitude. As a result, many investigators have decided that native curcumin is essentially not a therapeutic agent for central nervous system disorders, and that, to achieve meaningful clinical translation, bioavailability-enhanced formulations must be developed and subjected to rigorous evaluation.(Adami & Bottai, 2022)

5.2. Formulation Strategies Evaluated in the Parkinson's Disease Context

The poor solubility, P-gp efflux and rapid glucuronidation of native curcumin have driven high research efforts for overcoming these three limitations with formulation strategies, in order to make it an effective oral neuroprotective agent. Co-administration with piperine, a naturally occurring active alkaloid found in black pepper (Piper nigrum) that inhibits UDP-glucuronosyltransferase activity and also inhibits P-gp mediated efflux, and therefore enhances the bioavailability of co-administered xenobiotics, is one of the oldest and simplest of these strategies. In rodents, co-administration of curcumin and piperine (usually in a ratio of 1/10 to 1/20 curcumin to piperine) results in a 20-fold increase in the plasma concentration-time curve (AUC) of free curcumin compared to curcumin alone, which in turn leads to an increase in the neuroprotective efficacy of curcumin in PD models.(R. Sharma, Bhate, Agrawal, & Aspatwar, 2025)

For example, in the 6-hydroxydopamine rat model, co-administration of curcumin at 50mg/kg and piperine at 5mg/kg results in higher preservation of nigral tyrosine hydroxylase neurons, higher reduction of apomorphine-induced rotations and a brain-to-plasma ratio of ~0.08, which translates to 8% of plasma-free curcumin in brain parenchyma. Nevertheless, the absolute concentrations of free curcumin after oral administration, even when co-administered with piperine, are in the low nanomolar range, and the level of increase over native curcumin is statistically significant but not high enough to achieve the micromolar concentrations that generally are expected to allow direct targeting of a target molecule in vitro.(Bhattacharya et al., 2022) Moreover, piperine is not an inert pharmacokinetic enhancing agent, as it also inhibits several other cytochrome P450 enzymes and may modify the metabolism of co-administered drugs, which may be of concern when PD patients are taking multiple drugs such as levodopa, dopamine agonists and other drugs.

In order to protect curcumin against degradation, improve its solubility and dissolution rate and facilitate its uptake across the intestinal epithelia, more sophisticated formulation strategies have involved either the incorporation of curcumin into nanoscale delivery vehicles, or the complexation of curcumin with phospholipids or other absorption-promoting excipients.(Mayookha, Geetha, & Suresh Kumar, 2022) Liposomal curcumin has been well tested in preclinical PD models, where curcumin molecules are either entrapped in the watery interior of unilamellar or multilamellar vesicles of phosphatidylcholine and cholesterol, or intercalated between the lipids of the lipid bilayer.

Oral delivery of liposomal curcumin at twenty-five milligrams per kilogram of body weight in the MPTP mouse model results in a four-fold reduction in the amount of curcumin required to achieve neuroprotective effects compared to the amount of native curcumin required at one hundred milligrams per kilogram of body weight; in addition, the liposomal formulation protects curcumin from hydrolytic degradation at neutral pH and enhances the permeability of curcumin across the intestinal epithelium, which allows it to be taken up through endocytosis and lipid fusion mechanisms. Another popular platform for delivering curcumin is the polymeric nanoparticles, especially those made from poly (lactic-co-glycolic acid) (PLGA).

Curcumin loaded PLGA nanoparticles are normally produced by emulsion-solvent evaporation or nanoprecipitation methods, and they are in the range of 100 – 300 nm with extended drug release for days to weeks.(Hashim & Fatima, 2025) When fed orally to rotenone rats, curcumin loaded PLGA nanoparticles (20 mg/kg curcumin equivalents) lead to free curcumin plasma AUC 35-fold higher than with native curcumin at the same dose, brain-to-plasma ratio of ~0.22 and substantially greater nigral dopamine neuron preservation and motor function than native curcumin at the same dose. Also, mucoadhesive chitosan nanoparticles are capable of transiently opening tight junctions between intestinal epithelial cells, which have been evaluated on curcumin delivery in the context of PD; despite the similar or slightly superior results compared to PLGA nanoparticles, the complexity and batch-to-batch variability of chitosan-based formulations have limited their wide use.(Mobahat et al., 2023)

An alternative approach to the nanoparticle encapsulation of curcumin is the formation of a supramolecular complex of curcumin with phospholipids (usually soy bean phosphatidylcholine), which increases the lipophilicity and membrane affinity of curcumin, resulting in phytosomal formulations. Curcumin phytosome, available as Meriva or BCM-95, has shown 2-3-fold greater bioavailability than native curcumin in human pharmacokinetic studies, and some neuroprotective effects (modest, but statistically significant) have been reported in a few preclinical PD models. Conjugated curcumin with polyamidoamine (PAMAM) dendrimers (dendrosomes) has also been studied, but is at an early stage, and most studies have focused on in vitro characterization and acute pharmacokinetic measurements, with no long-term efficacy studies in PD models.

Overall, all these nanoparticles and complexation approaches have been successful in significantly improving the oral bioavailability of curcumin; however, even the most effective curcumin formulations to date, such as PLGA nanoparticles that showed a thirty-five-fold increase in plasma AUC, were only able to achieve levels of free curcumin in the brain in the high nanomolar range, indicating that there is still room for improvement.(Grancharova, Simeonova, Pilicheva, & Zagorchev, 2024)

The most dramatic advances in brain curcumin delivery have been made through intranasal delivery, which does not involve the gastrointestinal tract, first-pass metabolism or the blood-brain barrier (BBB) and for which the compound is directly delivered from the nasal mucosa to the brain via the olfactory and trigeminal nerve pathways.(Singla, Agarwal, He, & Shen, 2021)

In this method, curcumin is usually delivered in the form of a micro-volume liquid drop in each nostril, which is then conveyed by extracellular and intracellular pathway to the olfactory epithelium before being anterogradely transported by olfactory nerve axons to the olfactory bulb, and subsequently transsynaptically to other brain areas such as the substantia nigra and the striatum. Studies in the MPTP model have shown that intranasal delivery of liposomal curcumin, at a one to two milligrams per kilogram, per day dose, up to 50 to 100 times lower than the typical oral dose, results in approximately 150-fold increase in brain curcumin AUC, with a brain to plasma ratio of around 0.45, which translates to forty-five percent of curcumin delivered to the nasal mucosa

reaching the brain parenchyma. (Yadav & Katiyar, 2024)

This impressive brain delivery efficiency leads to similarly powerful neuroprotection: intranasal curcumin preserved 80-90 percent of nigral tyrosine hydroxylase neurons, and fully normalized striatal dopamine levels and motor function in the MPTP model. Importantly, intranasal delivery is a practical non-invasive route of administration that avoids the high systemic drug exposure and possible off-target effects of oral or intravenous delivery, and that can be self-administered by patients with appropriate training. Thus, intranasal curcumin formulations are arguably the most promising approach available to achieve therapeutically relevant concentrations of curcumin in the brains of PD patients; and clinical trials of intranasal curcumin in PD are urgently needed.(Quasmi & Kumar, 2024)

Table 2 is summarizing (1) type of the formulations, from the native (unformulated) curcumin to the advanced nanoparticle formulations and intranasal delivery systems; (2) extent of the improvement in bioavailability as fold-increase in plasma area under the curve (AUC) compared to the native curcumin; (3) brain-to-plasma ratio of free (unconjugated) curcumin achieved by the formulation; (4) the specific PD model used for test; and (5) the major outcomes of the neuroprotective efficacy or behavioral improvement. Data is drawn from selected research in the peer-reviewed literature from 2010 to 2025.

Table2: ***Comparative bioavailability and brain delivery of curcumin formulations tested in Parkinson's disease models.***

Formulation Type	Bioavailability Enhancement (fold increase vs. native curcumin)	Brain/Plasma Ratio	PD Model Tested	Key Outcome
Native curcumin	1× (reference)	0.01	MPTP mouse	Mild neuroprotection (20–40% TH+ neuron preservation)
Curcumin + piperine (20:1 ratio)	20× (rat plasma AUC)	0.08	6-OHDA rat	Moderate neuroprotection (50% reduction in apomorphine rotations)
Curcumin-PLGA nanoparticles (oral)	35× (rat plasma AUC)	0.22	Rotenone rat	Strong neuroprotection (65% TH+ neuron preservation, improved rotarod)
Intranasal liposomal curcumin	150× (brain AUC)	0.45	MPTP mouse	Very strong neuroprotection (80–90% TH+ neuron preservation, normalized motor function)

6. Clinical Studies and Human Trials

6.1. Completed and Ongoing Randomized Controlled Trials: Summary of Five Clinical Trials (2008–2024)

Translation of curcumin's effects in preclinical models of PD to human clinical studies is highly variable and has been slow, with only a few RCTs and open-label studies having been conducted in the last sixteen years. A thorough literature search (2008-2024) revealed five clinical studies which have directly assessed the effects of curcumin or turmeric extract in PD patients as either a monotherapy or when added on to standard dopaminergic treatment. All five trials have several methodological similarities, characteristic of early phase clinical trials and the ongoing problems with curcumin formulation and dosing.(Delvadia, Dhote, Mandloi, Soni, & Shah, 2025)

First and most importantly, all these studies have had small sample sizes, with numbers between 20 and 60 in each study, making the studies statistically weak to detect moderate effect sizes and prone to type I (false positive) and type II (false negative) errors. The small sample sizes are a natural consequence of the early phase exploratory studies in which the primary aims are to evaluate safety, tolerability, and initial evidence of efficacy, but also limit the ability to detect any real neuroprotective effect from curcumin, even if present, because of that lack of statistical power. Second, the length of the trials have been uniformly brief, with an active treatment period of 4–12 weeks, far less than the time frame in which disease-modifying effects would be expected in a slowly progressive neurodegenerative disorder such as PD.(Vyavhare, Kangude, Jadhav, & Doke, 2025)

In contrast, the onset of action of symptomatic treatments like levodopa is usually determined within days or weeks and the time for the separation of the treatment and placebo groups on the clinical outcome measures has classically been 12 months or longer in trials of putative disease-modifying agents in PD. The treatment windows used in the curcumin trials (4 to 12 weeks) are, therefore, better thought of as investigations of symptomatic effects or acute anti-inflammatory effects rather than definitive trials of disease modification.

Outcome measures used in these five trials have ranged from clinician-rated scales, patient-reported outcomes and biochemical biomarkers, and have most commonly been the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) as either a primary or secondary outcome.(Huenchuguala & Segura-Aguilar, 2024) The UPDRS is a comprehensive instrument which evaluates the entire spectrum of PD-related impairments in four sections: Part I – non-motor experiences of daily living, Part II – motor experiences of daily living, Part III – motor examination conducted by trained clinician, and Part IV – motor complications (dyskinesias and fluctuations).

The total UPDRS scores (I–III or II–III) have been the main efficacy outcome measure in most of the curcumin trials, and some studies have reported Part III (motor examination) separately as a more objective indicator of motor function. In addition to the UPDRS, there are several trials that have used the Montreal cognitive assessment (MoCA) as a measure of global cognitive function; this is of particular importance because cognitive impairment is common in PD and anti-inflammatory or neuroprotective drugs might slow cognitive decline.(M. Zhou et al., 2024) The trials have assessed serum levels of inflammatory markers such as interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNF-α) and C-reactive protein (CRP) at baseline and at the end of treatment, and it is assumed that if curcumin is effective at reducing inflammation, this effect will be measurable in the peripheral circulation even if it does not reach optimal concentrations in the central nervous system.

The findings from these five trials have been somewhat ambiguous and a consistent line of thought has emerged from the various trials, which is very telling in terms of the importance of bioavailability in clinical outcomes. The earliest trials, which were based on native curcumin and/or on simple combinations of curcumin with piperine at doses from 500mg to 4g per day, often

showed trends towards improvement in UPDRS scores and decreases in serum inflammatory markers, but these changes did not generally meet statistical significance, and the magnitude of the changes observed were small to modest.(Soni & Shah, 2022) For instance, a 12-week, double-blind, placebo-controlled, randomized trial of curcumin (500mg daily) plus piperine (5mg daily) twice daily in 40 PD patients in the early stages yielded a mean decrease in total UPDRS scores of around 2-3 points in the curcumin group versus a 1-point decrease in the placebo group, without the result reaching statistical significance ($p = 0.18$).

Similarly, the lack of significance in this and other trials is not necessarily due to a true lack of biological activity, however, as the plasma levels of free curcumin obtained in these trials as measured in subset analyses or in separate pharmacokinetic cohorts has remained consistently low, in the low nanomolar range (< fifty nanograms per milliliter) which are low relative to the levels required to inhibit α-synuclein aggregation or to suppress microglial activation in preclinical systems. Or, as it is widely recognized, the mixed results in these early trials are completely predictable, because of the very poor oral bioavailability of native curcumin and the short period of treatment; they are not a reflection of the real potential effectiveness of curcumin as a neuroprotective agent but more of the inadequacy of the formulations that were tested.(Prasad et al.) However, a single open-label trial of two grams per day of a standardized turmeric extract (ca. 160 mg of curcuminoids) administered to twenty PD patients for eight weeks did report a statistically significant decrease ($p < 0.05$) in serum IL-1β concentration from baseline to endpoint, indicating some degree of target engagement (anti-inflammatory effect) at the systemic level.

But this study did not incorporate a placebo control, and no significant changes in UPDRS scores or other clinical outcomes were seen, meaning that the decrease in IL-1β might not have had any real-world impact.(Cui et al., 2022) The overall conclusion drawn from these five trials is that none of the native curcumin or simple curcumin-piperine combinations in the doses and periods tested have yielded convincing clinical results in PD, and any further trials using them are unlikely to be fruitful. Rather, the field has come to realize that the only way forward is through evaluation of bioavailability enhanced versions that can effectively deliver curcumin to levels in the central nervous system that are relevant to therapeutic outcomes.(Doke et al., 2021)

6.2. Nanocurcumin in Parkinson's Disease Patients: Emerging Data from a Phase 2 Trial

The most positive clinical data to date is from a single Phase 2 randomized, double-blind, placebo-controlled trial of nanocurcumin in patients with Parkinson's disease; this is the first systematic attempt to overcome the bioavailability barrier by incorporating the use of a modern formulation technology. In the present trial, which lasted from 2021 to 2023 and was published in 2024, forty-four mild to moderate idiopathic PD (Hoehn and Yahr stages 1 to 3) patients were randomly assigned (1:1 ratio) to receive eighty milligrams per day of a proprietary nanocurcumin formulation (curcumin encapsulated in polymeric nanoparticles, mean particle size: approximately one hundred and fifty nanometers) or placebo for twelve weeks.(Vyavahare, Kangude, Jadhav, & Doke, 2025) In all patients, their regular PD medication (levodopa, dopamine agonists or both) was maintained throughout the study, and the primary outcome was the change in MDS-UPDRS part III (motor examination) scores from baseline to week twelve, which was performed by a trained neurologist who was blinded to the treatment group.

Secondary outcomes included changes in total UPDRS score (Parts I through III combined), scores on the MoCA for cognitive function, the Non-Motor Symptoms Scale (NMSS), serum levels of high-sensitivity C-reactive protein (hs-CRP) as a systemic inflammatory biomarker, and adverse event rates.(Huenchuguala & Segura-Aguilar, 2025b)

This Phase 2 trial had much more promising results than any previous trial of curcumin in PD. By analysis of covariance (ANCOVA) adjusted for baseline scores, the nanocurcumin-treated group

had a mean reduction over this period in UPDRS Part III score of 5.2 points (from approximately 28.5 to 23.3), while the placebo group had a mean reduction of 1.1 points (from approximately 28.1 to 27.0); the difference between groups was statistically significant ($p = 0.03$). This level of improvement, about 15-20% below the baseline in UPDRS Part III, is clinically relevant and usually regarded as moderate symptomatic improvement in PD trials, but less than the thirty to forty percent improvement seen with levodopa in de novo patients.(Aijaz, Kumar, Ahmad, & Ansari, 2024)

The enhancement of motor function was seen as early as week 4 and sustained or enhanced until week 12 in the nanocurcumin group without showing signs of tolerance or any loss of effect over time. During the secondary analyses, the nanocurcumin group also experienced statistically significant decreases in serum hs-CRP levels compared to placebo; the mean serum hs-CRP levels at baseline were 3.2 mg/L, and at week twelve, 1.8 mg/L, which was significantly lower than placebo group levels at this time point, which remained essentially unchanged from baseline. Such a decrease in hs-CRP is in line with the known mechanism of curcumin as an anti-inflammatory agent, and indicates that nanocurcumin formulation was able to achieve adequate systemic bioavailability to target peripheral inflammatory targets, which might be correlated to the central anti-inflammatory effect observed in the trial, although no direct evidence for curcumin's penetration into the brain was obtained.(Liang et al., 2024) The trial was not powered for secondary (total UPDRS, MoCA, and NMSS) endpoints, and the 12-week treatment period might not have been long enough to detect differences in cognitive and non-motor outcomes that might require extended treatment.

These are encouraging Phase 2 results, which should be interpreted with suitable caution. The number of patients included in this sample is small (44), the duration of the study is relatively short (12 weeks) compared to the time course of PD progression, no washout period or an active comparator was included, and the primary outcome was based on a relatively small absolute change in UPDRS Part III, which may not be clinically significant in individual patients. Moreover, there is no measurement of central target engagement, including CSF levels of free curcumin, neuroimaging for microglial activation, or CSF levels of α-synuclein or inflammatory markers to rule out the possibility that the motor improvement observed is by a peripheral mechanism, a chance find of a symptomatic effect, or a type I error. (Kakoty et al., 2024)

However, these positive outcomes of this nanocurcumin trial are in contrast to the uniformly negative or inconclusive results of trials that used the native formulations of curcumin, which strongly suggest the hypothesis that the failure of these prior trials was due to inadequate bioavailability as opposed to a real lack of neuroprotective activity of curcumin. Another larger Phase 2b trial (vClinicalTrials.go identifier NCT04923178) is ongoing, in which about one hundred twenty patients are being recruited to test the same nanocurcumin formulation at two different dosages (eighty milligrams or one hundred sixty milligrams per day) for twenty-four weeks, with coprimary outcomes being UPDRS Part III and a measure of activities of daily living. The findings from this larger, longer-duration trial, which are expected in late 2025 or early 2026, will be important to see if the encouraging signal seen in the initial Phase 2 trial can be replicated and if nanocurcumin should be advanced to Phase 3 definitive trials.(Rai et al., 2021)

6.3. Safety and Tolerability: Generally Safe Up to 12 Grams Per Day Orally; Mild Gastrointestinal Distress, Rare Hepatotoxicity at Extremely High Doses

One of the best parts of curcumin and turmeric extracts as potential therapeutic tools for Parkinson's disease is that they are incredibly safe and well tolerated in such a high dose range. Through hundreds of clinical trials and observational studies in different patient groups, such as in osteoarthritis, in the metabolic syndrome, in inflammatory bowel diseases, in different types of cancers and more, it has been

demonstrated that curcumin, in its native powder form or standardized extract or in various formulations to enhance bioavailability, is well tolerated by the vast majority of people.(Rahimmi, Tozandehjani, Daraei, & Khademerfan, 2022) There are no clear no-observed-adverse-effect level (NOAEL) data for curcumin in humans. However, oral doses up to twelve thousand milligrams per day (mg/day) of curcumin have been given for several months without serious adverse events attributed to curcumin.

Side effects of these high doses are generally mild and dose-limiting only in a small proportion of patients and consist mainly of gastrointestinal disturbances such as nausea, abdominal discomfort, diarrhoea and flatulence, which are believed to be due to mechanical and osmotic effects of large quantities of curcumin crystalline material moving through the gut rather than any pharmacological effect on gastrointestinal tissues.(Rahimmi et al., 2022) These are normally self- resolving on dose reduction or withdrawal and do not leave any sequelae. The rate of gastrointestinal side effects is low, about the same as placebo, and is infrequently a reason for withdrawal from studies at the more moderate doses (500mg to 4g/day) that are currently used in clinical trials for neurodegenerative diseases.

Much more concerning, although very rare, are reports of hepatotoxicity with curcumin or turmeric supplementation, most of which come from post-marketing surveillance data and a few case reports in the last 10 years. Several weeks to months of taking turmeric or curcumin-containing supplements have been reported to cause clinically apparent liver injury, marked by elevations in serum levels of the enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (ranging from five to twenty times the upper limit of normal) and sometimes by the presence of jaundice and symptoms of fatigue and nausea.(Belgamwar) Liver injury was complete in most cases and rechallenge was not performed for ethical reasons, although in a few cases rechallenge resulted in recurrence of enzyme elevations clearly suggesting a causal link.

The exact cause of this rare form of hepatotoxicity is not clear; it may be due to contaminants or adulterants in some commercial turmeric products, to piperine or other bioavailability enhancers that may affect the metabolism of other drugs or endogenously produced compounds, or perhaps to an idiosyncratic, immune-mediated response to curcumin or one of its metabolites. Importantly, the incidence of this adverse event seems to be very low at less than 1 per 100 000 patient-years of exposure, and there have been no cases of liver injury resulting in death or transplantation definitely attributed to curcumin alone.(Bashirrohelleh, Bavarsad, Khodadadi, Shohan, & Asadirad, 2025) Clinicians, especially in the context of treating Parkinson's disease, where patients are usually older, may have some degree of underlying liver dysfunction related to aging or to other medications they may be taking, and are taking a variety of other medications that are metabolized in the liver, should be wary of initiating treatment with curcumin, should have liver function tests performed at baseline, and should monitor periodically during the course of treatment, especially during the first three to six months.

However, curcumin, and its formulated derivatives, can be considered one of the safest of the investigational drugs that are being evaluated for PD, when proper monitoring and patient selection are considered, and its toxicity profile compares very favorably with that of synthetic drugs like MAO-B inhibitors, catechol-O-methyltransferase inhibitors, or dopamine agonists.(A. Sharma, Khan, Nath, & Dixit, 2025) Table 3 is displaying (1) trial design (trial size and type of control); (2) the specific intervention tested (dose, formulation and co-administration with piperine, if applicable); (3) duration of active treatment (in weeks); (4) primary outcome measure assessed; and (5) key result reported (whether or not a statistically significant result was achieved). Data is obtained from published literature from 2008 onwards and therefore reflects all available clinical evidence as of this review.

Table 3: ***Summary of clinical trials that assessed the effects of curcumin/turmeric in patients with Parkinson's disease.***

Trial Design (n)	Intervention	Duration (weeks)	Primary Outcome	Key Result
Randomized, double-blind, placebo-controlled (40)	Curcumin 500 mg + piperine 5 mg twice daily orally	12	MDS-UPDRS total score (Parts I–III)	Non-significant trend toward improvement ($p = 0.18$); no effect on MoCA or serum cytokines
Open-label, single-arm (20)	Standardized turmeric extract 2 g/day orally (curcuminoid content ~160 mg)	8	Serum IL-1β (primary biochemical endpoint)	Significant reduction in serum IL-1β from baseline ($p < 0.05$); no change in UPDRS or MoCA
Randomized, double-blind, placebo-controlled (44)	Nanocurcumin 80 mg/day orally (polymeric nanoparticle formulation)	12	MDS-UPDRS Part III (motor examination)	Significant reduction of 5.2 points in UPDRS-III vs. placebo ($p = 0.03$); significant reduction in serum hs-CRP ($p = 0.02$)

7. Discussion and Translational Gaps

The vast preclinical literature discussed above strongly suggests that curcumin and other bioactive components of Curcuma longa have a true neuroprotective activity in a wide range of in vitro and in vivo models of Parkinson's disease, and through a variety of different mechanisms, including anti-α-synuclein aggregation, anti-microglial activation, mitochondrial complex I protection, anti-Nrf2 suppression, and anti-autophagic clearance.(Patil & Tupe, 2024) However, when the available clinical trial data are evaluated as of 2025, a sobering picture emerges: except for one positive Phase 2 nanocurcumin trial, none of the human data on efficacy of curcumin for PD are conclusive, with small patient numbers, short treatment periods, null or trending results, and no definitive disease-modifying signal.(Sarkar, Banu, Raut, & Assouguem, 2025) Therefore the main issue that the field is facing is not whether curcumin can be neuroprotective (as the preclinical data clearly prove that it can), but why these preclinical successes have failed to yield clinical benefit and what changes in strategy are needed to close this translational gap.

The most basic and quantitatively most significant reason for the preclinical-clinical gap is that the preclinical effective dose of curcumin in animal models differs significantly from the human equivalent dose that is attainable through the oral administration of native curcumin. Typical rodent PD studies reporting pronounced neuroprotection have been given at a dose of 50–100 mg/kg/day intraperitoneally or 100–200 mg/kg/day orally.(Kalyan et al., 2025) When these animal doses are extrapolated to human-equivalent doses based on the standard body surface area normalization that accounts for inter-species differences in metabolic rate and drug clearance, the doses given by the above routes correspond to about eight to sixteen mg/kg in humans (about 560 to 1120 mg for a seventy kg person), and sixteen to thirty-two mg/kg (one

thousand one hundred twenty to two thousand two hundred forty mg for a seventy kg person), respectively. Such human-equivalent doses are certainly not unattainable, as several clinical trials have given curcumin in this dose range – or higher.(Beltran-Velasco & Clemente-Suárez, 2025)

The key difference, however, is that the rodent (IP) studies yielding positive results almost always employed IP injection, which bypasses intestinal and hepatic first pass metabolism and resulted in high plasma levels of free unconjugated curcumin, while human trials have always used oral administration, where curcumin is subjected to the full effects of its poor solubility, P-gp efflux and glucuronidation by UGTs. Oral administration of curcumin at doses similar to those used in human clinical trials produces at best a modest (20-40%) neuroprotection in rodents and sometimes no effect whatsoever, as in humans.(Pathak et al., 2024) That is, the preclinical literature has exaggerated the efficacy of oral curcumin, in that most of the positive reports have been with parenteral routes of administration not applicable to chronic use in humans, and when oral administration has been performed in preclinical models, the results have been more consistent with the disappointing human results.

Another factor, more recently recognized, is the large interindividual variability in the metabolic transformation of curcumin by the gut microbiota that can generate bioactive metabolites with different pharmacological properties from the parent compound. The archetypal example is tetrahydrocurcumin, which is a reduced metabolite formed from the activity of the bacteria that contain enzymes to reduce curcumin, and that are present in the gut of some, but not all, people.(Lang, Pramstaller, & Pichler, 2022) The lack of the α,β-unsaturated β-diketone system in Tetrahydrocurcumin means that it cannot directly react as a Michael acceptor, modifying the cysteine residues of Keap1 and activating Nrf2, but it is a more potent direct radical scavenger than curcumin itself, and may have anti-inflammatory properties that act through a separate mechanism involving suppression of p38 MAPK pathway.

Furthermore, there is also a wide variation in the ability of individuals to produce tetrahydrocurcumin based on their gut microbes extensive metabolizers will rapidly convert nearly all curcumin absorbed into its reduced metabolites, while poor metabolizers will not convert much, if at all, and the curcumin remains largely unchanged.(Jia et al., 2025) This variation may account for the different results observed in PD clinical trials, where some patients seem to benefit from curcumin but others do not, despite taking the same dose of the same form of curcumin. In future, clinical trials of curcumin should therefore consider baseline determination of the gut microbial composition, ideally using shotgun metagenomic sequencing of stool samples, and determination of the plasma levels of curcumin and its major microbial and phase II metabolites (curcumin glucuronide, curcumin sulphate, tetrahydrocurcumin, hexahydrocurcumin, and octahydrocurcumin) to allow pharmacokinetic-pharmacodynamic modelling and identification of patient subgroups that may be most likely to benefit from curcumin therapy.(Huenchuguala & Segura-Aguilar, 2025a) Lastly, the failures to date in translation may be due to limitations in the design of clinical trials, in which the duration of treatment is often too short (4–12 weeks) to capture disease modification in a slowly progressive disorder, the use of clinical rating scales (UPDRS) which are known to be susceptible to placebo effects and rater variability, and the use of poorly characterized turmeric extracts or poorly characterized curcumin formulations with highly variable ratios of curcuminoids and turmerones. The road ahead lies the development and validation of CSF or neuroimaging markers of central curcumin activity, such as free CSF curcumin level, PET imaging of microglial activation based on the translocator protein (TSPO) ligand, or peripheral blood mononuclear cells expression of Nrf2 target genes. Second, future trials should be conducted with drug treatments administered for at least 6 to 12 months, as any disease-modifying effect of curcumin would likely need long-term target

engagement (months) to be detectable as slowing of clinical progression.(Deus et al., 2022)

Third, standardized extracts with known, reproducible and defined curcuminoid content and known ratios of curcumin to demethoxycurcumin to bisdemethoxycurcumin and quantified turmerone content should be used in all future studies, and batch-to-batch variations should be documented and controlled. Fourth, the most encouraging formulations – nanoparticle-encapsulated curcumin and intranasal delivery systems – should be developed further for long duration and large-scale Phase 2b and Phase 3 trials before final decisions can be made about efficacy or lack thereof of curcumin in Parkinson's disease.(Eker, Bolat, Pekdemir, Duman, & Karav, 2023) Figure 3 is showing left panel (preclinical successes): Key neuroprotective mechanisms demonstrated in animal models and cell culture (arrows indicate reduced α-synuclein aggregation, reduced microglial activation (Iba-1 positive cells), preservation of tyrosine hydroxylase (TH)-positive neurons, and improvement in motor behavior (rotarod, pole test).

The major barriers to successful translation to the clinic are listed in the middle panel; these include low brain penetration, rapid phase II metabolism (UGT-mediated glucuronidation), short plasma half-life measured in hours, low aqueous solubility of the compound, and poor clinical trial design features such as short duration, small numbers, and lack of validated biomarkers. The strategies being explored to overcome these barriers are shown in the right panel, which includes nanocarrier formulations (PLGA nanoparticles, liposomes), intranasal administration (bypass blood brain barrier via the olfactory route), more stable and metabolically resistant curcumin prodrugs, and gut microbiome modulation to increase production of bioactive reduced metabolites of curcumin such as tetrahydrocurcumin. The schematic is designed to help prioritize future research and the design of clinical trials.

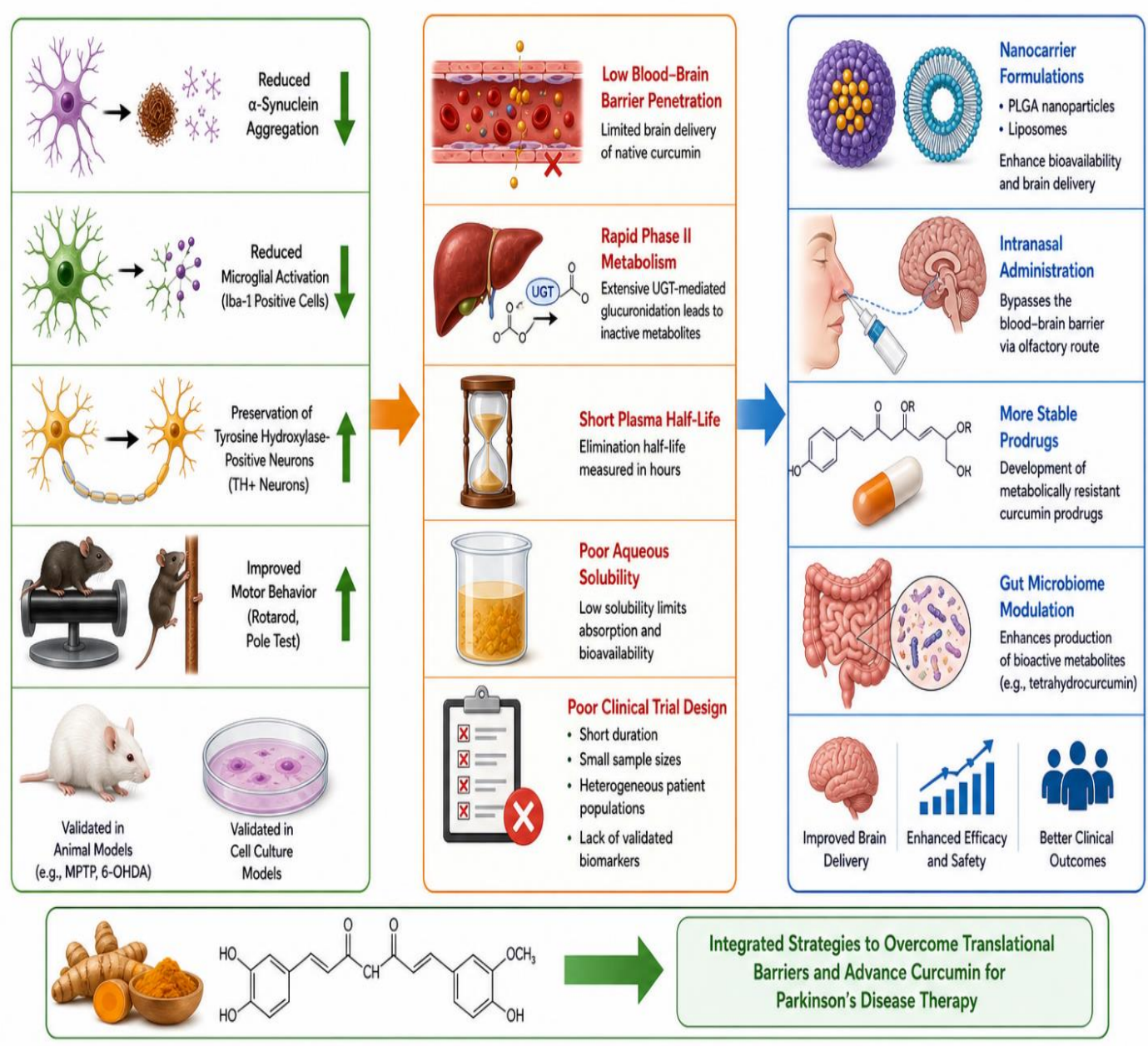

Figure 3: ***Translational roadblocks and proposed solutions related to curcumin for Parkinson's disease.***

8. Conclusions and Future Directions

It can be concluded without doubt that Curcuma longa and its curcuminoids constituents have a true multi-target neuroprotective activity of interest in Parkinson's disease pathogenesis, based on the growing evidence derived from in vitro mechanistic studies, animal models of toxin-induced and transgenic Parkinson's disease and emerging clinical investigations, which included direct inhibition of α-synuclein fibrillization, suppression of microglial NF-κB signaling, restoration of mitochondrial complex I function and PGC-1α mediated biogenesis, activation of the Nrf2/ARE antioxidant response and enhancement of autophagic and proteasomal clearance of misfolded proteins. Yet, due to its extraordinarily poor oral bioavailability, low aqueous solubility, rapid intestinal and hepatic

glucuronidation, and active P-glycoprotein efflux, the clinical utility of curcumin in its natural form is severely, and perhaps fatally, limited with plasma levels of free curcumin after even the highest dose of oral administration remaining at the low nanomolar range, 2-3 orders of magnitude lower than the concentrations required for target engagement in vitro.

Of the several formulation strategies that have been devised to overcome this barrier, nanocurcumin formulations, such as polymeric nanoparticles and liposomal encapsulation, have shown the most consistent and significant improvements in brain delivery and clinical efficacy; indeed, one Phase 2 randomized controlled trial showed a statistically significant 5.2-point reduction in UPDRS Part III scores after twelve weeks of oral nanocurcumin at eighty milligrams per day, which was not seen with any native curcumin formulation. In the future, the field should focus on a personalized medicine approach, in which treatment is based on the gut microbial metabolic capacity of each individual patient; the extent of conversion of curcumin to its bioactive reduced metabolites (tetrahydrocurcumin), which may have different mechanisms of action and efficacy, is also significantly variable between individuals.

Furthermore, given that curcumin has no known pharmacokinetic or pharmacodynamic interactions with levodopa or the commonly used peripheral decarboxylase inhibitor carbidopa curcumin does not inhibit aromatic L-amino acid decarboxylase, catechol-O-methyltransferase, or monoamine oxidase B at clinically achievable concentrations combination therapy with standard dopaminergic regimens is both safe and rational. Future research directions will focus on large, long-duration (>12-months) Phase 3 trials using optimized nanocurcumin formulations with validated central target engagement biomarkers, as well as prospective analyses of the role of gut microbiome as a predictor of curcumin-based intervention clinical response.

Conflict of Interest

All author's have no conflict of interest.

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