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REVIEW ARTICLE

CURCUMIN SUPPLEMENTATION AS A POTENTIAL FACTOR INFLUENCING THE PROGRESSION OF PARKINSON'S DISEASE

SUPLEMENTACJA KURKUMINY JAKO POTENCJALNY CZYNNIK WPŁYWAJĄCY NA POSTĘP CHOROBY PARKINSONA

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ABSTRACT

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder. The number of affected people is increasing, still there is no curative agent. Dopamine replacement therapies such as levodopa remain the cornerstone of PD treatment, but prolonged use leads to dyskinesia and does not halt neurodegeneration. Epidemiologic data suggesting the lower incidence of PD among the Southeastern Asian population in comparison to Western populations, warrants detailed analysis of dietary tendencies and allopathic treatments that may partially contribute to such discrepancy. A product that is widely used within Southeast Asia is turmeric, containing curcumin – an extensively researched phytochemical. Curcumin has been proposed to alleviate PD symptoms and possibly slow disease progression through its multifaceted biological activities.

Aim

This review examines the mechanisms by which curcumin may modulate the progression of PD, with emphasis on recently elucidated pathogenic pathways. Additionally, it summarizes the findings of clinical trials involving both animal and human subjects.

Materials and methods

Relevant literature – three human clinical studies and several animal investigations – was identified via PubMed and Google Scholar.

Results

Curcumin was observed to attenuate dopaminergic denervation and motor dysfunctions in mice, while also improving the state of gastrointestinal barrier and possibly inhibiting ferroptosis in dopaminergic neurons of affected rodents. Moreover, curcumin mitigated pathological changes in the rat cerebellum, a structure recently associated with PD. Two human studies demonstrated improvements in non-motor symptoms, whereas the third one reported no significant alleviation of motor dysfunction by curcumin therapy.

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Conclusions
Data from animal studies indicate that curcumin has a mitigating effect on PD pathomechanisms such as oxidative stress, inflammation and ferroptosis, while also restoring gastrointestinal barrier. However, evidence from human studies is limited and inconclusive. Further investigation is required.

Keywords: curcumin, gut-brain axis, Parkinson's disease, neurodegeneration, turmeric, oxidative stress, ferroptosis

STRESZCZENIE
Wstęp
Choroba Parkinsona (PD) jest postępującym schorzeniem neurodegeneracyjnym. Liczba pacjentów stale rośnie, a wciąż nie istnieje leczenie o działaniu przyczynowym. Terapie oparte na substytucji dopaminy, takie jak levodopa, stanowią podstawę leczenia, jednak ich długotrwałe stosowanie prowadzi do dyskinezji i nie zatrzymuje procesu neurodegeneracji. Dane epidemiologiczne wskazujące na niższą zapadalność na PD w populacjach południowo-wschodniej Azji w porównaniu z populacjami zachodnimi skłaniają do bardziej wnikliwej analizy nawyków żywieniowych oraz terapii stosowanych w tych regionach, które mogą częściowo tłumaczyć tę rozbieżność. Produktem szeroko wykorzystywanym w Azji Południowo-Wschodniej jest kurkuma zawierająca kurkuminę, intensywnie badany związek fitochemiczny. Przypisuje się jej zdolność do łagodzenia objawów PD, a nawet spowalniania postępu choroby dzięki wielokierunkowym mechanizmom działania.
Cel
Niniejsza praca analizuje mechanizmy, dzięki którym kurkumina może modulować przebieg PD, ze szczególnym uwzględnieniem ostatnio zidentyfikowanych szlaków patogenetycznych. Dodatkowo podsumowuje wyniki badań klinicznych prowadzonych zarówno na zwierzętach, jak i u ludzi.
Materiały i metody
Odpowiednie publikacje – trzy badania kliniczne z udziałem ludzi oraz liczne badania na zwierzętach – zostały wyszukane w bazach PubMed oraz Google Scholar.
Wyniki
W modelach zwierzęcych kurkumina łagodziła uszkodzenie układu dopaminergicznego i zaburzenia motoryczne, a także poprawiała stan bariery jelitowej oraz prawdopodobnie hamowała ferroptozę w neuronach dopaminergicznych. Ponadto wykazano, że kurkumina zmniejszała patologiczne zmiany w móżdżku szczurów – strukturze coraz częściej wiązanej z patogenezą PD. W dwóch badaniach z udziałem ludzi odnotowano poprawę objawów pozaruchowych, natomiast trzecie nie wykazało istotnego wpływu kurkuminy na funkcje motoryczne.
Wnioski
Dane z badań na zwierzętach wskazują, że kurkumina może łagodzić kluczowe mechanizmy patogenetyczne PD, takie jak stres oksydacyjny, stan zapalny i ferroptoza, a także poprawiać funkcjonowanie bariery jelitowej. Jednak dowody pochodzące z badań klinicznych są ograniczone i niespójne. Konieczne są dalsze badania.

Słowa kluczowe: oś jelitowo-mózgowa, choroba Parkinsona, stres oksydacyjny, neurodegeneracja, kurkuma, kurkumina, ferroptoza

Introduction

Parkinson's disease (PD) ranks as the second most prevalent chronic, progressive neurodegenerative disorder [1]. According to the Global Burden of Disease Study 2015, PD has the fastest-growing prevalence and disability rate of any neurological disorder [2] and its worldwide impact is expected to double by 2040 [3]. PD is characterized primarily by the degeneration of dopaminergic neurons in the *substantia nigra* pars compacta and the pathological aggregation of α-synuclein into Lewy bodies on a cellular level [4,5]. These processes are closely linked to oxidative stress, neuroinflammation, and mitochondrial dysfunction, all of which exacerbate synaptic failure and neuronal death [6].

Although current pharmacological treatments – most notably levodopa (L-DOPA) – effectively alleviate motor symptoms, they do not prevent ongoing neurodegeneration, and long-term use is associated with complications such as motor fluctuations and dyskinesia [7,8]. Given these challenges, there is growing interest in identifying neuroprotective agents capable of slowing dopaminergic neuron degeneration [6]. A promising line of research centers on phytochemicals, a diverse group of bioactive compounds naturally occurring in plant-based foods. Remarkable progress has recently been made in exploring certain neuroprotective agents [9] and curcumin has attracted significant attention due to its potentially beneficial role in various neurodegenerative diseases.

Curcumin is a polyphenolic compound and an active ingredient extracted from turmeric rhizome (*Curcuma longa*), a dietary spice used in Indian and Southern Asian cuisine and medicine [10]. Among the various properties of polyphenols, such as curcumin [11–13] anti-inflammatory [14] and antioxidant effects are the most extensively studied considering their involvement in the pathogenesis of neurodegenerative diseases [10]. Multiple animal studies have evidenced that curcumin exerts potent neuroprotective and antioxidant effects, via the increased activity of detoxification mechanisms, thereby alleviating oxidative stress, which is a major cause of neuronal death [6,15]. In addition, in preclinical studies, curcumin has demonstrated an ability to disrupt the clumping of α-synuclein, possibly mitigating the formation of Lewy bodies [6,16]. Collectively, these neuroprotective mechanisms indicate that curcumin could potentially serve as an adjunctive treatment agent for PD symptoms [6].

The main therapeutic problem is the very low oral bioavailability of curcumin and minimal cerebrospinal fluid penetration [17]. Strategies to overcome this matter include lipid-based formulations like nanomicelles and phospholipid complexes [18], which can increase uptake in various tissues, including several parts of the brain, suggesting passage across the blood–brain barrier [19]. Piperine, the main active component of black pepper, also enhances plasma curcumin concentration by blocking its biotransformation [20]. According to recent analysis, the majority of the curcumin formulations evaluated in clinical studies showed no concerns with safety, tolerability, or efficacy [21]. However, to better understand the mechanisms underlying curcumin nanoparticles' selective absorption, further research is necessary.

Aim

This review aims to evaluate how curcumin may serve to alter the progression of PD. Specifically, the article examines curcumin's proposed mechanism of action, with an emphasis on emerging pathogenic pathways of interest, including ferroptosis, the gut-brain axis, and the contribution of the cerebellum to PD symptomatology. In addition, we synthesise evidence from animal and *in vitro* studies, while also including available human clinical data to assess curcumin's potential neuroprotective effects in PD.

Materials and methods

A literature search was conducted using the PubMed and Google Scholar databases.

Articles were identified using combinations of the keywords "turmeric" or "curcumin" with "Parkinson's disease," "gut-brain axis," "ferroptosis," or "cerebellum." The search was limited to English-language publications with available full text, published between 2010 and 2025. Earlier studies were also included when they provided foundational evidence relevant to PD pathology, such as early findings on lipid peroxidation in the *substantia nigra* or on the contribution of cerebellar function to disease symptomatology. This review focuses primarily on mechanistic evidence derived from animal and in vitro studies; however, three human clinical studies were also included.

Results

Overview of ferroptosis mechanisms and human *post-mortem* findings in PD

Ferroptosis is an iron-dependent form of regulated cell death that is distinct from apoptosis and necrosis [22,23]. It is characterized by elevated intracellular iron levels, impaired clearance of lipid peroxides (LPO), excessive production of reactive oxygen species and uncontrolled lipid peroxidation [22,24].

Mechanistically, ferroptosis is driven by the dysregulation of iron metabolism, resulting in the accumulation of free Fe^{2+} (ferrous ions). Through the Fenton reaction Fe^{2+} reacts with hydrogen peroxide (H_2O_2) to generate highly reactive hydroxyl radicals [23,25]. These radicals subsequently peroxidize polyunsaturated fatty acids (PUFAs) within cellular membranes, compromising membrane integrity and inducing cell death [23,26–29].

Crucially, ferroptosis arises when cellular mechanisms responsible for detoxifying LPO become impaired. This is most prominently associated with the dysfunction of glutathione peroxidase 4 (GPX4), a key enzyme that reduces LPO to non-toxic lipid alcohols [25,30]. Deficiencies in other antioxidant defenses, such as superoxide dismutase (SOD), further exacerbate oxidative stress and promote ferroptotic cell death [23,31,32].

Human ***post-mortem*** studies suggest that ferroptosis may be involved in the pathogenesis of PD, with reports of elevated iron levels [24,33], increased malondialdehyde (a marker of lipid peroxidation), and reduced PUFAs [24,34] in the *substantia nigra* of patients with PD. Collectively, these findings are consistent with ferroptosis-related neurodegeneration.

An unresolved sequence between ferroptosis and α-synuclein aggregation in PD: insights from *in vitro* studies

It remains unclear whether iron accumulation, the key event in ferroptosis, precedes the transformation of α-synuclein into its insoluble forms or results from it [35]. *In vitro* evidence indicates that lipid peroxidation products generated during ferroptosis, such as 4-hydroxy-2-nonenal promote pathological α-synuclein aggregation [24,36,37]. Conversely, other in vitro studies suggest that α-synuclein may enhance ferroptosis by reducing Fe (III) to Fe (II) via its iron-reductase activity, thereby facilitating the Fenton reaction [24,38].

Curcumin as a potential therapeutic agent counteracting ferroptosis – findings from animal and *in vitro* studies

Curcumin has the potential to modulate ferroptotic pathways through multiple mechanisms. It has been proposed to possess strong free radical scavenging capacity [10], primarily relying on proton donation from its phenolic groups [35,39] and can neutralize hydroxyl radicals produced during the Fenton reaction [10,40]. Both *in vitro* and animal studies reveal that curcumin has been associated with the upregulation of key antioxidant enzymes involved in counteracting ferroptosis, including SOD and GPX4 [15,35,41]. Beyond its antioxidant effects, curcumin has also been reported to chelate iron [35]. This is a property of particular relevance given that iron chelation is known to inhibit ferroptotic pathways [24].

The support for this curcumin's effect comes from a study by Du *et al*. [42], which investigated the 6-hydroxydopamine (6-OHDA) rat model of PD. All rats were administered 6-OHDA in order to induce neurodegeneration, but one group was additionally pretreated with intragastric curcumin. By day 21 post-lesion, the affected controls showed a marked loss of tyrosine-hydroxylase (TH) positive neurons. In contrast, curcumin-treated rats retained significantly more TH-positive cells, indicating protection of dopaminergic neurons, as TH is the rate-limiting enzyme in dopamine synthesis and is reduced in PD [42,43].

In addition, *substantia nigra* of the control group rats contained more iron-positive cells compared with substantia nigra of rats who had received curcumin pretreatment. This fact led the authors to attribute curcumin's neuroprotective effects to its iron-chelating properties [42].

However, whether anti-feroptotic effects observed in these preclinical trials can also occur in human patients suffering from PD remains unproven.

Curcumin and cerebellar modulation PD

Clinical observations show that many PD symptoms cannot be explained solely by dopaminergic degeneration in the *substantia nigra* [44]. A region that is increasingly recognized as contributing to PD motor and non-motor symptoms is the cerebellum [45,46]. This is supported by positron emission tomography study showing that reduced acetylcholinesterase (AChE) activity in both the midbrain and cerebellum correlated with gait disturbances and impaired balance in PD patients [47]. Relevant human trials investigating curcumin's impact on AChE were not identified.

Nevertheless, in the rotenone-induced rat PD model, neuropathological changes have also been detected in the cerebellum and notably curcumin restored cerebellar AChE activity to near-control levels [46].

Intestinal inflammation and the gut-brain axis in PD

Intestinal inflammation may contribute to PD, although its role in neurodegeneration is not yet fully established [48]. Li *et al*. [48] note that pathological features of Inflammatory Bowel Disease (IBD) could also influence PD. They highlighted mechanisms including chronic intestinal inflammation, disruption of gut barrier proteins, and alterations in the gut microbiome. Shared genetic factors between IBD and PD further support the connection between the two [48]. Patients with PD exhibit a shift in the gut microbiome toward a more pro-inflammatory composition [49]. A meta-analysis by Nie *et al*. [50] demonstrated that PD patients show reduced abundances of taxa with anti-inflammatory potential and increased levels of bacteria associated with pro-inflammatory activity. Such dysbiosis may disrupt epithelial tight junctions. It may also stimulate the production of cytokines, such as tumor necrosis factor-alpha (TNF-α), further increasing intestinal permeability [50–52].

Increased intestinal permeability may allow microbial products to reach enteric neurons, activating glial cells and triggering inflammation [49]. This weakens the gut barrier further and may promote the formation of pathological α-synuclein within the enteric nervous system [49, 53]. Forsyth *et al*. [53] demonstrated the aforementioned mechanisms in patients with PD still in its early stages. These individuals showed elevated urinary sucralose levels after oral ingestion, indicating increased gut permeability. Intestinal biopsies revealed greater staining for *E. coli*, α-synuclein, and nitrotyrosine, a marker of oxidative stress. Plasma lipopolysaccharide binding protein (LBP) was reduced in PD subjects and correlated with higher nitrotyrosine and *E. coli* staining relative to control subjects. Lower plasma LBP concentrations are associated with heightened exposure to Gram-negative bacterial endotoxin [53–55]. Together, these findings support a model

whereby microbial endotoxins drive glia-mediated oxidative stress and α-synuclein aggregation in genetically susceptible individuals [53]. Once α-synuclein aggregates within the enteric nervous system, it is thought to migrate retrogradely along the vagus nerve to the central nervous system [49]. After reaching the brain, pathological α-synuclein spreads across interconnected regions, driving the degeneration of nigrostriatal dopaminergic neurons and ultimately contributing to the onset of motor symptoms characteristic of PD [49].

Curcumin and gut-brain axis in PD: insights from animal studies

Curcumin may ameliorate the gastrointestinal inflammatory processes associated with neurodegeneration in PD. In a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse model, Zhong *et al*. [56] demonstrated that curcumin improved motor performance and exerted neuroprotective effects through activation of the SIRT1/NRF2 signaling pathway. This axis regulates cellular stress responses and modulates both intestinal and central inflammation [56,57]. Similarly, a rat model of ulcerative colitis showed that SIRT1/FoxO3a/NRF2 activation reduced oxidative stress and intestinal inflammation [58]. Zhong *et al*. further reported that curcumin lowered intestinal TNF-α levels, preserved tight junction proteins such as ZO-1 and occludin, improved motor function, and attenuated nigral TH loss. Notably, inhibition of SIRT1 abolished these benefits, underscoring the central role of this pathway [56].

Another mechanism through which curcumin may modulate gastrointestinal inflammation involves its regulatory effects on the gut microbiota. Cui *et al*. [59] demonstrated that 100 mg/kg curcumin significantly improved motor outcomes and preserved dopaminergic neurons in an MPTP mouse model. Strikingly, these neuroprotective effects disappeared when mice underwent antibiotic-mediated microbiota depletion prior to curcumin administration, indicating that curcumin's efficacy is microbiota-dependent. Beyond behavioral and dopaminergic outcomes, curcumin also mitigated central α-synuclein pathology in the same model. Curcumin treatment substantially reduced α-synuclein aggregation in the *substantia nigra* and striatum [59].

To further elucidate the microbial contribution to these effects, Cui *et al*. then performed 16S rRNA sequencing. Curcumin treatment increased the relative abundances of Muribaculaceae, Lactobacillaceae, Lachnospiraceae, and Eggerthellaceae, and decreased Aerococcaceae and Staphylococcaceae. Higher *Aerococcus* levels were associated with worse motor outcomes, lower dopaminergic neuron survival, and stronger microglial activation. *Staphylococcus* taxa were elevated in the MPTP group but normalized following curcumin pretreatment. In addition, Staphylococcus abundance positively correlated with increased glial mobilization [59].

Curcumin additionally increased the abundance of *Lactobacillus*, which prevents glial hyperactivation in PD models of other studies [59–61].

Curcumin also restored Lachnospiraceae, a family notable for short-chain fatty acid (SCFA) production by some of its members [59,62]. This is important because PD is often associated with a reduction in SCFAs, reflecting a more pro-inflammatory microbiome [56,63–66]. SCFAs such as acetate, butyrate and propionate play crucial anti-inflammatory roles in the gut, in part by promoting interleukin-10 (IL-10) expression [67,68]. Another mice study demonstrated that SCFA levels were markedly depleted in the MPTP mice group, but significantly restored with curcumin treatment indicating another potential path of its influence on gut-brain axis in PD [66].

In the study by Cui *et al*. [59], curcumin strongly reduced brain inflammation in the studied animals. The authors attributed this effect mainly to modulation

of the gut microbiota, rather than direct brain penetration, which is limited by curcumin's poor bioavailability. Microglia are key drivers of PD-related neuroinflammation via the secretion of cytokines such as TNF-α, interleukin-1β (IL-1β), interleukin-4 (IL-4), and interleukin-6 (IL-6) [59,69]. Accordingly, the observed decline in ionized calcium-binding adapter molecule 1 (Iba1) immunostaining in curcumin-treated mice indicates a suppression of microglial activation. Consistent with this, MPTP administration substantially elevated striatal cytokine levels, whereas curcumin significantly reduced these inflammatory mediators. Together, these results suggest that curcumin mitigates MPTP-induced microglial activation and neuroinflammation, likely through a microbiota-dependent mechanism [59].

Overall, these observations support the hypothesis that curcumin modulates gut inflammation and microbial composition, which in turn influences α-synuclein pathology, neuroinflammation, and dopaminergic neuron survival through the gut-brain axis. It is important to note however, that these findings are derived exclusively from animal models, and whether curcumin exerts comparable gut-brain axis-mediated effects in human PD remains unclear.

Human studies

We analyzed two randomized human controlled trials and one human cohort study which in total included 125 participants.

Maghbooli *et al.* [70] conducted a double-blind placebo-controlled trial. PD patients were given 160 mg of curcumin nanomicelle supplementation for 3 months. It turned out to significantly improve sleep quality and overall quality of life compared with placebo, though no significant effect was observed on fatigue severity. Measurement tools were accordingly: the Pittsburgh Sleep Quality Index, the PD questionnaire (PDQ) and the Fatigue Severity Scale.

A cohort study by Donadio *et al.* [71] assessed both motor and non-motor symptoms and performed skin biopsies to detect phosphorylated α-synuclein deposits, proposed as a biomarker of neurodegeneration in PD. Researchers administered 2 g of curcumin phospholipids daily and measured progression of the disease across the follow-up period of 12 months using the Movement Disorder Society – Unified PD Rating Scale (MDS-UPDRS), Hoehn and Yahr Scale (H&Y), Non-Motor Symptoms Scale (NMSS) and Composite Autonomic Symptom Score-31 (COMPASS-31). The curcumin-supplemented group maintained a stable L-DOPA dosage, while the control group received progressively higher doses over 12 months. The curcumin group showed an increase only in MDS-UPDRS and H&Y scores and the increases were lower than those in the untreated group. COMPASS-31 and NMSS decreased over the follow-up with an opposite trend compared to the untreated group. That means patients who were supplemented with curcumin showed an improvement in non-motor symptoms, including autonomic system function, and although they worsened in terms of motor symptoms, the progression was smaller than in the control group. Skin nerve biopsy showed reduced phosphorylated α-synuclein load compared with the unsupplemented group.

A triple-blind placebo-controlled trial by Ghodsi *et al.* [72] evaluated 80 mg of curcumin nanomicelle given as an add-on therapy in PD. Statistical analysis demonstrated that supplementation of curcumin did not induce significant improvement in motor function or quality of life, based on MDS-UPDRS and PDQ-39 scores across 9 months. The study by Ghodsi *et al.* [72] is the only one of the three which reports adverse effects of curcumin supplementation, most significant being nausea and vomiting.

To summarize, the human studies are inconclusive – some suggest curcumin may improve non-motor symptoms of PD, while

others did not observe the same effect. Moreover, they have several serious limitations.

Limitations of human studies

In his systematic review, Chang [6] highlights several drawbacks of the included studies, most notably their small sample sizes. The studied populations were also highly heterogeneous and stratified analyses by disease duration and stage, or comorbidities were not conducted. Researchers applied different observation periods, measuring scales, doses, and formulations.

It is also worth noting that in Donadio *et al.*'s investigation [71], patients selected their own treatment, either ingesting curcumin combined with a stable dose of L-DOPA or receiving increasing doses of L-DOPA. Since patients selected their own treatment, those who chose curcumin may have had prior expectations or optimism that could have influenced outcomes. Moreover, the clinical relevance of changes in skin p-synuclein deposition relative to central neurodegenerative processes remains to be fully established [6].

Safety of curcumin

Said trials also do not cover well the possibility of adverse effects and drug interactions. Review by Fuloria *et al.* [73] lists possible side effects of excessive turmeric consumption such as: hindering of iron absorption, delayed blood clotting, pain in individuals with gallstones (due to cholekinetic effect [74]), reduced testosterone levels and sperm movements in men, contact urticaria, uterine contraction in pregnancy. In contrast, Cheng *et al.* [75] consider daily intake of curcumin up to 8 g safe.

Conclusions and future perspectives

Animal and *in vitro* studies consistently demonstrate curcumin's neuroprotective potential in PD through multiple mechanisms, including its inhibitory effect on ferroptosis, modulation of toxin-induced cerebellar pathology and impact on the gut-brain axis. However, substantial uncertainties remain when translating these findings to human PD. Clinical evidence is limited to three small, heterogeneous studies employing different curcumin formulations, doses, outcome measures, and follow-up durations. While some findings suggest potential benefits for non-motor symptoms, others report no significant effects. Collectively, the available human data are insufficient to support firm clinical recommendations or to conclude that curcumin alters disease progression in PD.

Ideally, future research should involve larger study populations and adopt a prospective design, unified across many centers, applying substantially longer follow-up periods. A more homogeneous cohort – with respect to comorbidities, disease stage, and ongoing therapeutic regimens – would also help produce more reliable and interpretable results. Additionally, it would be valuable to include a Parkinson's-free population to determine whether curcumin supplementation influences the incidence of PD or just its progression.

It could also be beneficial to clarify the role of dietary turmeric, to conduct a study in which turmeric is consumed in its natural culinary form, combined with black pepper (which contains piperine) to enhance absorption. It would provide important insight into how real-world dietary patterns may affect neuroprotective outcomes. Lu *et al.* [76] showed that turmeric-rich curry consumption has an inverse association with cognitive decline.

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