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Review

Curcumin for parkinson´s disease: potential therapeutic effects, molecular mechanisms, and nanoformulations to enhance its efficacy

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Abstract: Parkinson's disease (PD) is one of the most prevalent neurodegenerative disorders worldwide. It is caused by the degeneration of dopaminergic neurons from the substantia nigra pars compacta. This neuronal loss causes the dopamine deficiency that leads to a series of functional changes within the basal ganglia, producing motor control abnormalities. L-DOPA is considered the gold standard for PD treatment, and it may alleviate its clinical manifestations for some time. However, its prolonged administration produces tolerance and several severe side effects, including dyskinesias and gastrointestinal disorders. Thus, there is an urgent need to find effective medications, and current trends have proposed some natural products as emerging options for this purpose. Concerning this, curcumin represents a promising bioactive compound with high therapeutic potential. Diverse studies in cellular and animal models have suggested that curcumin could be employed for the treatment of PD. Therefore, the objective of this narrative mini-review is to present an overview of the possible therapeutic effects of curcumin and the subjacent molecular mechanisms. Moreover, we describe several possible nanocarrier-based approaches to improve the bioavailability of curcumin and enhance its biological activity.

Key words: Curcumin; Parkinson´s disease; Natural products; Nanoparticles; Neurodegeneration; Neurodegenerative diseases.

Introduction

Parkinson's disease (PD) is one of the most prevalent neurodegenerative disorders worldwide. It is caused by the irreversible degeneration and loss of dopaminergic neurons from the substantia nigra pars compacta. This neuronal loss produces a dopamine deficiency that leads to a series of functional changes within the basal ganglia circuit. Consequently, the activity of substantia nigra pars reticulata neurons is increased, which inhibits the thalamic nuclei and motor cortex. Collectively, these alterations produce motor control abnormalities (1).

There is no definitive cure for PD to date; however, several pharmacological compounds may alleviate its clinical manifestations. L-DOPA is considered the gold standard for PD treatment, and it is efficacious for some time (2). However, its prolonged administration produces tolerance and several severe side effects, including dyskinesias, gastrointestinal disorders, nausea, hives, chest pain, and weakness (3). Thus, numerous attempts to find effective medications have been undertaken, and current trends have proposed some natural products as emerging options for this purpose (4–8).

In this regard, curcumin represents a promising bioactive compound with high therapeutic potential. Curcumin is a polyphenolic compound extracted from Curcuma longa, a plant widely utilized in traditional medicine (9). In the last years, curcumin has attracted grow-

ing attention because it exhibits a plethora of beneficial properties, such as antioxidant, anti-cancer, antibiotic, and anti-inflammatory activities (10–14). Furthermore, this substance can regulate a variety of cell signaling pathways through numerous molecular targets, including growth factors, receptors, transcription factors, adhesion molecules, enzymes, and genes (15).

Diverse studies in cellular and animal models have suggested that curcumin could be employed for the treatment of PD (16,17). Therefore, the objective of this narrative mini-review is to present an overview of the possible therapeutic effects of curcumin and the subjacent molecular mechanisms. Moreover, we describe several possible nanocarrier-based approaches to improve the bioavailability of curcumin and enhance its biological activity.

Beneficial effects of curcumin in PD models and underlying molecular mechanisms

The pathogenesis of PD is related to mitochondrial dysfunction, oxidative stress, neuroinflammation, and α-synuclein aggregation (18). As mentioned above, curcumin possesses a wide variety of biological properties; thus, it may act at the molecular level through diverse cell signaling pathways against PD pathological mechanisms. For example, curcumin may reduce oxidative stress through direct scavenging of reactive oxygen species (ROS), suppression of NADPH oxidase, and upregulation of glutathione peroxidase and superoxide dismutase (19,20). Curcumin may also suppress glial cells' activation, inhibit cyclooxygenase-2, and prevent protein and DNA oxidation (21).

Numerous research groups have explored the possible therapeutic use of curcumin to treat PD. A pioneering study evaluated the potential neuroprotective effect of curcumin in rats lesioned with 6-hydroxydopamine (6-OHDA) (22). The authors found that curcumin significantly reduced dopamine neurons' death in the substantia nigra pars compacta; moreover, it prevented the decrease of dopamine levels in the striatum. The authors speculated that this effect was due to the antioxidant activity of curcumin. In support of this hypothesis, Siddique et al. (23) analyzed the effect of curcumin in a drosophila PD model. Their results indicated that curcumin significantly decreased oxidative stress, cell death, lipid peroxidation, and protein carbonyl contents; moreover, it prolonged the life span of experimental subjects. Another study assessed the effects of curcumin in PC12 cells expressing mutant α-synuclein. The authors found that curcumin prevented cell death induced by the mutant α-synuclein (24). According to that report, the neuroprotective effect was mediated by decreases in: ROS levels, mitochondrial membrane depolarization, release of cytochrome c, and activation of caspases. Remarkably, very similar results in SH-SY5Y cells were found by Wang et al. (25), indicating that antioxidant and anti-apoptotic effects of curcumin in PD models are not cellular type-dependent artifacts. On the other hand, Chen et al. (26) evaluated the cytoprotective activity of curcumin in a model of apoptosis induced by 1-methyl-4-phenylpiridinium (MPP^+) in the PC12 cell line. According to the authors, curcumin decreased apoptosis through the overexpression of Bcl-2 and iNOS, as well as the attenuation of the mitochondrial membrane potential loss. Utilizing a similar approach, Chakraborty et al. (27) found that curcumin prevented the toxic effect of MPP^+ by reducing levels of ROS in differentiated PC12 cells. Interestingly, another study described that curcumin inhibited the MPP^+-induced cytotoxicity through upregulating HSP90 in SH-SY5Y cells (28).

Moreover, a very recent study assessed the effects of curcumin in the PD cell model of rotenone-treated PC12 cells (29). The results indicated that curcumin decreased oxidized protein levels and activated the proteasome, suppressing the harmful effect of rotenone. Altogether, these studies suggest that curcumin might prevent neuronal death in PD models through different mechanisms that involve oxidative stress.

As previously mentioned, aggregates of α-synuclein are a neuropathologic feature of PD. These aggregates shape fibril structures hard to degrade by cellular mechanisms of protein degradation, and they exhibit cellular toxicity (30). Hence, α-synuclein aggregates represent a relevant target in PD. In this respect, numerous studies have indicated that curcumin may inhibit α-synuclein aggregation. For example, Ono et al. (31) used a combination of electron microscopy and fluorescence spectroscopy to explore the effect of curcumin on *in vitro* α-synuclein oligomerization. The results revealed that curcumin prevented the formation of α-synuclein fibrils; furthermore, it destabilized and dissociated preformed α-synuclein fibrils. Similarly, another study assessed the anti-aggregation activity of curcumin *in vitro* and in SH-SY5Y cells (32). Utilizing fluorescence microscopy and automated images capture, the authors demonstrated that curcumin inhibited the oligomerization of A53T mutant α-synuclein in the cell model, the effect also was dose-dependent. According to those reports, curcumin increased soluble α-synuclein species, facilitating their depuration through cellular mechanisms of protein degradation and avoiding proteolytic stress. Several other molecular mechanisms have been proposed to explain the effects of curcumin on α-synuclein oligomerization. Jiang. et al. (33) demonstrated that curcumin decreased the aggregation of A53T α-synuclein in cells SH-SY5Y by downregulating the mTOR/p70S6K signaling pathway and recovering the macroautophagy, indicating an indirect mechanism of action. A more recent study found that curcumin had neuroprotective effects and inhibited the accumulation of α-synuclein in a rat PD model produced by intra-nigral administration of lipopolysaccharide (34). The authors reported numerous molecular mechanisms responsible for these effects, including suppression of glial activation, inhibition of NADPH oxidase, prevention of iron deposition, and improvement in the glutathione system.

On the other hand, other studies have reported physical interactions between curcumin and α-synuclein (35–37). Singh et al. (35) reported that curcumin decreased the α-synuclein toxicity through its binding to preformed oligomers and fibrils, which changed their shape and hydrophobic surface exposure. Since curcumin exhibited more affinity for oligomeric intermediates than monomers, the authors concluded that curcumin might decrease the amount of cytotoxic soluble oligomers. Similarly, other studies found that the binding of curcumin to α-synuclein oligomers produces conforma-

tional changes that could be related to its neuroprotective effects (36,37).

Finally, Spinelli et al. (38) evaluated the effects of curcumin intake on α-synuclein protein aggregation in mice overexpressing human α-synuclein. Although curcumin did not modify the protein aggregation, it significantly attenuated motor and behavioral impairments. Moreover, curcumin promoted increases in phosphorylated α-synuclein in presynaptic areas of the cortex; thus, the authors concluded that dietary consumption of curcumin might be useful in PD and other synucleinopathies. However, the bioavailability of curcumin after its oral consumption remains a critical issue.

Nanoformulations to enhance the beneficial properties of curcumin

Despite the high therapeutic potential of curcumin, its clinical utilization has been hindered by diverse drawbacks, such as low solubility and limited permeability (39). Moreover, curcumin has a high rate of biotransformation after its ingestion, and it undergoes accelerated systemic elimination (20,40). As a consequence, curcumin has poor bioavailability and difficulties in crossing the blood-brain barrier (BBB). Due to these disadvantages, several approaches based on nanoparticles have been suggested to improve curcumin's limitations. The loading of curcumin into these nanocarriers comprises numerous theoretical advantages, including increased solubility, enhancement of bioavailability, and improvement of stability (16). Moreover, depending on their formulation and surface functionalization, the nanoparticles would provide an increased ability to cross the BBB (41).

Nanoformulations intended to biomedical applications include polymeric nanoparticles, liposomes, lipid nanoparticles, solid lipid nanoparticles, and polymeric micelles. It should be noted that nanosystems for brain diseases generally exhibit sizes <200 nm to facilitate their crossing through the BBB with minimal risk (2,3,16,41). Likewise, these nanoparticles may be fabricated with innocuous and natural materials to produce biocompatible, biodegradable, and non-toxic drug delivery systems. Furthermore, nanoparticles may be functionalized through surface chemical modifications or coupling of molecules to achieve optimal vectorization toward the basal ganglia (3,42,43).

Intending to improve curcumin bioavailability, and therefore, its therapeutic activities, several research groups have developed nanosystems aimed to treat PD (Figure 1). For example, Siddique et al. (44) devised a nanocomposite of curcumin and alginate and assessed its possible therapeutic effect in a PD fly model after 24 days of dietary intake. The nanocomposite showed antioxidant and anti-apoptotic effects; furthermore, it significantly improved motor impairment. Hence, the authors concluded that their formulation represents an exciting approach.

In another study, Taebnia et al. (45) fabricated mesoporous silica nanoparticles functionalized with 3-(2-aminoethyl amino) propyltrimethoxysilane and loaded with curcumin. The nanoparticles exhibited good entrapment efficiency and high drug loading. Interestingly, although the formulation inhibited the α-synuclein fibrillation *in vitro*, it did not significantly affect cytotoxicity in PC12 cells.

On the other hand, a research group developed nanoparticles of glyceryl monooleate loaded with curcumin-piperine and evaluated their antiparkinsonian effect *in vitro* e *in vivo* (46). Their formulation was effective *in vitro*, inhibiting the formation of α-synuclein oligomers and fibrils, reducing toxicity induced by rotenone, activating the autophagic pathway, and decreasing oxidative stress and apoptosis. Remarkably, *in vivo* tests demonstrated that the nanoformulation crossed the BBB, improved motor impairment, and decreased neuronal death in mice treated with rotenone. Therefore, this approach represents an exciting prospect to treat PD, and further studies are warranted.

Likewise, Bollimpelli et al. (47) prepared a lactoferrin nanocarrier loaded with curcumin and assessed its neuroprotective effect against rotenone-induced cytotoxicity in SK-N-SH cells. Using different experimental strategies, the investigators demonstrated that their nanoparticles had higher intracellular uptake and enhanced neuroprotective effect that curcumin alone; thus, these might be an encouraging drug delivery system for the treatment of PD.

Lastly, in a recent and sophisticated study, Zhang et al. (48) designed polysorbate 80-decorated cerasomes loaded with curcumin. The authors reported that the formulation produced an extended circulation time. Moreover, the combination of the nanohybrid cerasomes and microbubbles destruction targeted by ultrasound markedly reduced motor deficits, normalize dopamine levels, and prevented α-synuclein aggregation in a PD mouse model. Although these findings are encouraging, the long-term utilization of ultrasound is an issue that should be carefully analyzed to avoid side effects.

Conclusion

The side effects of current treatments for PD have encouraged the pursuit of new effective medications. In

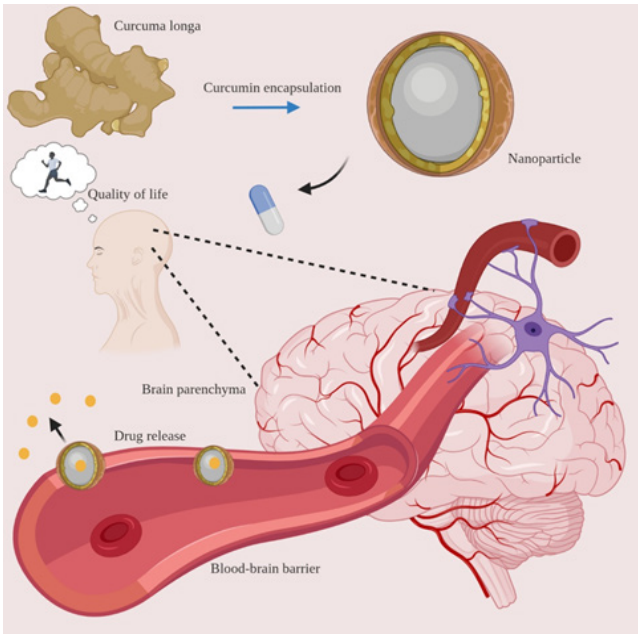

Figure 1. Curcumin encapsulation onto nanoparticle for brain targeting and controlled release.

this regard, it has been well established that curcumin is a bioactive compound that exhibits multiple health benefits. Likewise, numerous studies have demonstrated its therapeutic usefulness for innumerable diseases, including PD. Unlike synthetic compounds that usually act only through single molecules, curcumin may simultaneously modulate different targets and cell signaling pathways; thus, curcumin might be more efficacious than current drugs. Moreover, since its natural origin, curcumin's safety profile is suitable and could be administered for prolonged periods without significant harmful effects. It is noteworthy that curcumin may be consumed as a dietary supplement, which might help to prevent the appearance of PD and other neurodegenerative diseases. Finally, the encapsulation of curcumin in nanoparticles may solve its low solubility, poor availability, and limited crossing through the BBB, which represent critical obstacles for its use in PD.

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Conflicts of interest
The authors declare that there are no conflicts of interest.

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