Review

A State of the Art of Antioxidant Properties of Curcuminoids in Neurodegenerative Diseases

Serena Silvestro [†] ⬤, Cinzia Sindona [†], Placido Bramanti and Emanuela Mazzon *

IRCCS Centro Neurolesi "Bonino-Pulejo", Via Provinciale Palermo, Contrada Casazza, 98124 Messina, Italy; serena.silvestro@irccsme.it (S.S.); cinzia.sindona@irccsme.it (C.S.); placido.bramanti@irccsme.it (P.B.)
* Correspondence: emanuela.mazzon@irccsme.it; Tel.: +39-090-60128172
† These authors contributed equally as first author.

Abstract: Neurodegenerative diseases represent a set of pathologies characterized by an irreversible and progressive, and a loss of neuronal cells in specific areas of the brain. Oxidative phosphorylation is a source of energy production by which many cells, such as the neuronal cells, meet their energy needs. Dysregulations of oxidative phosphorylation induce oxidative stress, which plays a key role in the onset of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). To date, for most neurodegenerative diseases, there are no resolute treatments, but only interventions capable of alleviating the symptoms or slowing the course of the disease. Therefore, effective neuroprotection strategies are needed. In recent years, natural products, such as curcuminoids, have been intensively explored and studied for their therapeutic potentials in several neurodegenerative diseases. Curcuminoids are, nutraceutical compouns, that owen several therapeutic properties such as anti-oxidant, anti-inflammatory and neuroprotective effects. In this context, the aim of this review was to provide an overview of preclinical and clinical evidence aimed to illustrate the antioxidant effects of curcuminoids in neurodegenerative diseases. Promising results from preclinical studies encourage the use of curcuminoids for neurodegeneration prevention and treatment.

Keywords: neurodegenerative diseases; curcuminoids; anti-oxidant properties

1. Introduction

Neurological diseases affect millions of people around the world [1]. The environmental alterations in the central nervous system (CNS) induce the activation of microglia and astrocytes, cells involved in maintaining homeostasis of the CNS. Following damage, these cells activate a response that induces the release of pro-inflammatory cytokines responsible for a local inflammatory reaction [2]. Furthermore, once active, microglia and astrocytes can produce reactive oxygen species (ROS). However, the brain, despite accounting for only 2% of total body weight, consumes about 20% of the body's oxygen (O_2); thus, it is rich in the antioxidants involved in preventing the formation of ROS. Excessive ROS production, if not effectively counteracted by cellular constituents, causes pathological conditions such as neurodegenerative diseases [3–5]. This is particularly relevant in neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). Indeed neuroinflammation and oxidative stress are common features of neurodegenerative diseases [6,7]. Although therapies that delay or control symptoms are available for these disorders, there are currently no effective treatments available. Therefore, there is a growing interest in natural compounds that possess antioxidant and anti-inflammatory properties [8,9].

Curcuma is a spice extracted from the rhizomes of *Curcuma Longa*, belonging to the Zingiberaceae family, cultivated in India and in southeast Asia [10]. The main constituent of Curcuma is curcumin, a yellow pigment commonly used as a spice and food coloring. It is used as a natural medicine for the treatment of inflammatory diseases [11]. Indeed,

curcumin is a nutriceutical compound that possesses numerous therapeutic properties against various diseases, including neurodegenerative diseases [12].

Among the several properties of curcuminoids [13–15], the anti-inflammatory [16,17] and antioxidant activities [18,19] are the most investigated due to their role in the pathogenesis of neurodegenerative diseases [20]. Indeed, curcuminoids play a key role in the inhibition of enzymes such as p38 Mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (c-JNK) and transcription factors (such as nuclear factor-κB, NF-κB) related to inflammatory processes. Also, they decrease the expression of several pro-inflammatory cytokines [21,22]. Moreover, many of curcumin's beneficial effects can be associated with its antioxidant properties [23]. Since oxidative stress, caused by excessive production of reactive oxygen species, lipid peroxidation and oxidative damage to DNA and proteins, is responsible for many pathological complications such as neurodegenerative diseases, curcumin could play an important role in these conditions.

Curcumin has been extensively investigated due to its beneficial properties against several neurological diseases such as PD [24], AD [25] and ALS [26].

The purpose of this review is to describe the antioxidant properties of curcuminoids associated with the efficacy in neurological disease. In the present review, preclinical and clinical evidence highlighting the curcuminoids' antioxidants effects in neurological disorders are summarized.

2. Curcumin

Curcuminoids are the active compounds found in turmeric and include curcumin (diferuloyl methane), demethoxycurcumin and bisdemethoxycurcumin (Figure 1). Several in vitro and in vivo evidence describes the anti-inflammatory [27] and antioxidant properties [28] of curcuminoids. Among the curcuminoids, curcumin makes up about 90% of the curcuminoids present in turmeric. Curcumin is a polyphenol, with the molecular formula $C_{21}H_{20}O_6$, characterized for the first time in 1910 [29].
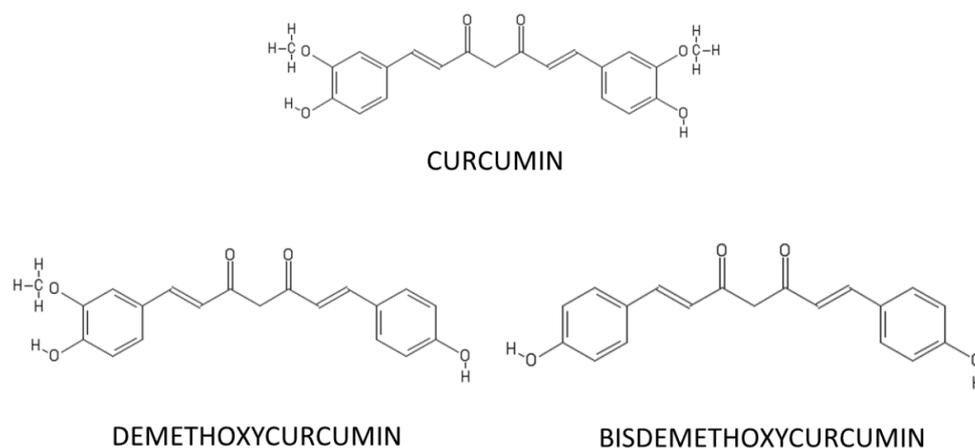

CURCUMIN

DEMETHOXYCURCUMIN

BISDEMETHOXYCURCUMIN

Figure 1. Chemical structure of curcumin and other curcuminoids such as Demethoxycurcumin and Bisdemethoxycurcumin, obtained from the rhizomes of *Curcuma Longa*.

Among them, curcumin is known to have neuroprotective effects and its antioxidant and anti-inflammatory power is widely studied. The diketone group and two phenolic rings in its chemical structure act as electron traps, thus preventing the production of hydrogen peroxide (H_2O_2), hydroxyl radical (OH·) and superoxide anion (O^{2-}·). Moreover, the b-diketone fraction and hydroxyl groups of curcumin are capable of complexing metals, such as copper (Cu^{2+}) and zinc (Zn^{2+}), ferrous iron (Fe^{2+}) [30]. Fe^{2+} is necessary for the Fenton reaction that generates OH· radicals; thus, curcumin by chelating the Fe^{2+} protects against metal-induced toxicity. Indeed, it is well known that curcumin contains antioxidant properties and it appears ten times more powerful than vitamin E as a free radical scavenger [31]. Due to the ability of curcumin to cross the blood–brain barrier [32],

it also decreases the ROS level [33], protects the brain from lipid peroxidation and reduces the neuron death induced by oxidative insults [34]. Furthermore, curcumin, in addition to acting as direct scavenging of ROS, exerts its antioxidant properties by increasing glutathione (GSH) levels [35], improving the activity of glutathione peroxidase (GSH-Px), glutathione reductase (GR), catalase (CAT) and superoxide dismutase (SOD) [36]. Furthermore, curcumin reduces mitochondrial damage and apoptosis mediated by lipid peroxidation [37].

Curcumin can inhibit the activation of several transcription factors including NF-κB [38], activated protein-1 (AP-1) [39], Notch-1 [40], β-catenin [41] and peroxisome proliferator-activated receptor-gamma (PPAR-γ) [42], all involved in different biological processes, including inflammation. NF-κB is localized in the cytosol—after activation, it is translocated to the nucleus, where it promotes the expression of different genes involved in cell proliferation and inflammation [43]. The dysregulated activity of NF-κB underlies several inflammatory diseases, such as neurodegenerative diseases [44]. Curcumin inhibits NF-κB activation by suppressing the translocation of p65 and the inhibitor κB (IκB) into the nucleus [45]. In this way, it inhibits the activation of numerous genes involved in cell survival, including Bcl-2, Bcl-xL, cyclin D1, cyclooxygenase 2 (COX-2) and matrix metallopeptidase (MMP)-9, thus promoting the arrest cell cycle, inhibiting proliferation and inducing apoptosis [46].

Many of curcumin's effects are also mediated by its ability to inhibit several protein kinases (PKs) involved in various cellular processes, such as autophosphorylation-activated (AK) protein kinase [47], Ca^{2+}-dependent protein kinase (CDPK) [48], Janus kinase (JAK) [49], mitogen-activated protein kinase (MAPK) [50,51], the mammalian target of rapamycin (mTOR) [52,53], phosphorylase kinase (PhK) [47], cytosolic protein kinase (cPK) [47], PKA [47], PKB/Akt [54], PKC [47]. Furthermore, the inhibitory action on the MAPK pathway and the inhibition of the phosphorylation of the extracellular receptor kinase (ERK), c-JNKs and p38 MAPKs are responsible for the powerful anti-inflammatory effects of curcumin [55]. Indeed, the inhibition of the NF-κB and MAPK pathways reduce the expression of numerous inflammatory interleukins (ILs) such as IL-1β, IL-6, Tumor necrosis factor-alpha (TNF-α) [56], IL-2 [57], IL-5 [58], IL-8 [59], IL-12 [60], IL-18 [61] and signal transducer and activator of transcription (STAT) proteins [49]. Therefore, curcumin by regulating transcription factors, such as NF-κB, inhibits the production of pro-inflammatory cytokines, thus exhibiting a powerful anti-inflammatory action [62].

These characteristic properties of curcumin make it a valid neuroprotective compound. Indeed, epidemiological studies show that in the Indian population, the consumption of turmeric is closely correlated with the low incidence of neurodegenerative diseases such as AD and PD, compared to the Caucasian population [63,64].

3. Methodology

The aim of this manuscript was to provide an overview of experimental and clinical studies that report the antioxidant effects of curcuminoids in neurodegenerative diseases, such as PD, AD and ALS. In order to write this review, a search was carried out in PubMed using the following keywords: "Curcuminoids", "antioxidant effects", "Parkinson's Disease", "Alzheimer's Disease", "Amyotrophic Lateral Sclerosis". We considered articles published between 2015 and 2021 demonstrating a neuroprotective role of curcuminoids. In this search, 65 articles were found, as shown in the Prisma flow diagram (Figure 2). In the "Records screened" section, 20 articles were excluded; among them, 12 were not considered because they were different from the focus of our review. Two other articles were excluded because they focused on the antioxidant role of other compounds. Moreover, since we focused on the curcuminoids, we also excluded six articles that evaluated the effects of curcumin combined with other compounds. As this review is intended to provide an overview of experimental studies, in the "Full-text articles assessed for eligibility" section, 13 articles were excluded because they are reviews. Finally, in this manuscript, were considered 27 studies that evaluate the biochemical and molecular mechanisms

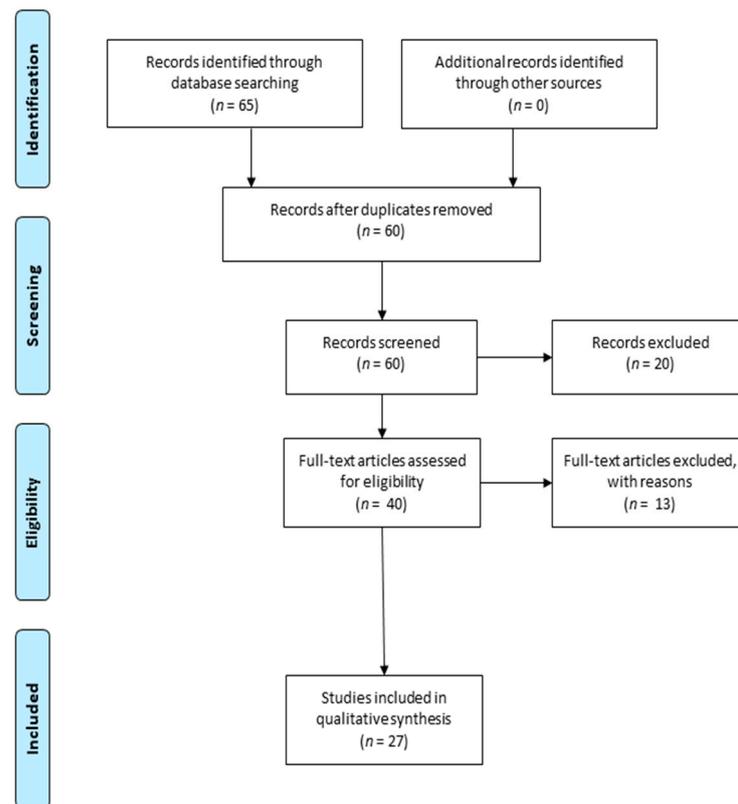underlying the antioxidant effects of curcuminoids and their therapeutic application in neurological diseases.

Figure 2. Prisma flow diagram illustrating the selection methodology of the preclinical studies used for the writing of the review. Duplicate articles were excluded from the total of the studies recorded. Instead, they were considered articles that evaluate the antioxidant effects of curcuminoid in neurological disease. The PRISMA Statement was published in [65].

In order to support the findings of pre-clinical studies, we also provide a summary of current clinical trials recorded on ClinicalTrial.gov (https://clinicaltrials.gov/ accessed on 12 February 2021), using the following keywords: "Curcumin", "Parkinson's Disease" or "Alzheimer's Disease" or "Amyotrophic Lateral Sclerosis".

4. Parkinson's Disease

PD is a progressive and neurodegenerative disease induced by the progressive loss of neurons in the substantia nigra, followed by a decrease in dopamine levels in the striatum [66]. These events lead to a dysfunction of the nigrostriatal pathway which consequent movement disorders [67]. The oxidative stress and inflammation response play a key role in contributing to or exacerbating the nigrostriatal degeneration [68]. The distinctive clinical features of PD are tremor, bradykinesia, rigidity, and balance disturbances. Additionally, in patients with PD also occurs non-motor deficits such as anxiety, dementia, depression, sleep disturbances, and psychosis that negatively condition the quality of life [69]. Moreover, the hallmark of PD is the formation of Lewy bodies, which are cytoplasmic inclusions of alpha-synuclein (α-syn) [70]. However, oxidative stress and inflammation play a key role in PD. In 90% of cases, PD occurs in a sporadic form; only 10% of cases present as a familial form. Familial forms of PD involve α-synuclein gene mutations (*SNCA*), ubiquitin C-terminal hydrolase L1 (*UCHL-1*), phosphatase and tensin homolog-induced putative kinase 1 (*PINK1*), Parkin (*PRKN*), protein deglycase (*DJ-1*), and leucine-rich repeat kinase 2 (*LRRK2*) [71].

To date, treatments for PD include drugs such as 1,3,4-dihydroxyphenylalanine (L-DOPA) or anticholinergic, which help relieve symptoms, but are not effective. In addition, many of these drugs have side effects that limit their use [72]. Therefore, effective and safe therapeutic interventions are necessary. In this context, interest is growing in the use of curcuminoids, which own antioxidant and anti-inflammatory properties, as alternative therapies.

4.1. Anti-Oxidant Effects of Curcuminoids In Vitro Models of PD

Several in vitro evidence has shown that curcumin has antiparkinsonian effects due to its antioxidant [73], anti-inflammatory [74], and anti-apoptotic properties [75], as well as its protective effects against mitochondrial damage [76].

Yu et al. evaluated the effects of curcumin through an in vitro experiment in primary mesencephalic astrocytes treated with 1-methyl-4-phenylpyridinium ion (MPP$^+$) to induce a PD model. The cells were pre-treated with increasing curcumin concentrations (0–16 μM) for 48 h. Through the vitality assay, concentrations greater than 8 μM were found to induce a reduction in cell viability; therefore, 8 μM was chosen as the suitable concentration. Immunofluorescence analysis revealed that pre-treatment with curcumin did not cause significant morphological changes in the astrocytes but reduced their MPP$^+$-induced activation. Furthermore, oxidative stress conditions were assessed through the measurement of ROS and GSH levels in astrocytes, which are determinants in parkinsonian conditions. Curcumin substantially caused a reduction of ROS and an increase of GSH, compared to the primary astrocytes treated with MPP$^+$.

The anti-inflammatory property of curcumin was also evaluated in the present study, focusing in particular on Toll-like receptor 4 (TLR4), which appears to play a key role in PD neurophysiopathology. Pre-treatment with curcumin reduced the MPP$^+$ induced toxicity by reducing the expression of MyD88 and TRIF, inhibiting the TLR4 pathway, a common MyD88-dependent signaling pathway. Curcumin significantly inhibited the NF-κB and IRF3 activation and reduced the TLR4 levels. In this way, the curcumin exerted its anti-inflammatory effects through inhibition of TLR4 and its downstream signaling pathway.

In conclusion, the findings of this experiment highlighted both the antioxidants and the anti-inflammatory properties exerted from curcumin, in MPP$^+$-treated mesencephalic astrocytes [77]. Uğuz A.C. et al. studied the molecular effects of curcumin on several intracellular signaling pathways in the cellular model of oxidative stress. Specifically, the researchers evaluated the effect of curcumin on Ca^{2+} signaling, measurement of ROS, mitochondrial depolarization levels and caspase-3 and -9 activities in SH-SY5Y neuronal cells treated with H$_2$O$_2$. Curcumin protected the cells from H$_2$O$_2$-induced apoptosis. It reduced lipid peroxidation and intracellular Ca^{2+} concentrations compared to the H$_2$O$_2$-treated group of cells. Conversely, curcumin treatment increased GSH and GSH-Px levels. Furthermore, the increased H$_2$O$_2$-induced caspase-3 and caspase-9 expression were reduced by curcumin, thus protecting neuronal cells from oxidative damage [78]. Dehghani Z. et al. showed that curcumin (25 and 50 μM), in a dose-dependent manner, reduced the growth of α-syn fibrils in rat brain mitochondria. It has been observed that curcumin reduced the cytotoxicity of α-syn aggregates by reducing the release of mitochondrial Type 1 Hexokinase and ROS formation induced by α-syn fibrillation products [79].

Instead, Ramkumar et al. evaluated the demethoxycurcumin (DMC), a derivative of curcumin in an in vitro model of PD induced by rotenone (ROT), a phytoactive compound that causes toxicity in neuronal cells. Two hours prior to ROT (100 nM) treatment, SH-SY5Y neuroblastoma cells were pre-treated with DMC (5 nM, 10 nM, 20 nM, 50 nM, 100 nM, 200 nM, 500 nM, and 1 μM). The treatment showed that DMC doses higher than 50 nM were toxic to SH-SY5Y cells; thus, the dose of 50 nM of DMC was chosen for further investigation. The results showed that DMC increased cell viability and its induced a decrease in both MMP and apoptotic process. In this regard, immunoblotting analysis was performed to evaluate the expression of apoptotic proteins in the mitochondria and in the cytosol, detecting that, DMC increased the Bcl-2, Bcl-xL level in the mitochondria. Moreover, the

analysis found that pre-treatment with DMC restored the expression of increased pro-apoptotic proteins following exposure to ROT. DMC improved the ROT-induced oxidative stress through a significantly reduced ROS level in SH-SY5Y cells. In conclusion, these data highlighted that pre-treatment with DMC inhibited the apoptosis process reducing pro-apoptotic proteins, increasing anti-apoptotic proteins, and ameliorating oxidative stress [80].

The in vitro study conducted by Buratta et al. proves the therapeutic and antioxidant properties of curcumin. PC12 cells were treated simultaneously with ROT (0.1–1 μM) and curcumin (10 μM) for 24 h. PC12 treated curcumin increased cell viability and reduced oxidative stress induced by ROT treatment. Furthermore, the authors investigated the effect of curcumin in carbonylation and nitrosation of proteins and the activity of the proteasome. Immunoblot investigations showed that curcumin significantly reduced carbonylation and protein tyrosine nitration. PC12 treated with ROT reduced the activity of the proteasome, which is reflected in a concomitant increase in oxidized proteins. Conversely, treatment with curcumin in PC12 counteracted inhibition of proteasomal activity ROT-induced, restoring the oxidized protein levels. The prevent proteasome activity could be another beneficial effect used from curcumin for exerting its antioxidant properties [81].

4.2. Anti-Oxidant Effects of Curcuminoids in In Vivo Models of PD

In an in vivo study performed on adult male Sprague-Dawley rats injured unilaterally with 6-hydroxydopamine (6-OHDA) in the left striatum to induce the PD model, curcumin increased the levels of the dopamine transporter (DAT) and tyrosine hydroxylase (TH). Contrarily, it reduced the levels of the glial fibrillar acid protein (GFAP). In this way, curcumin could reduce the local tissue damage induced by 6-OHDA. Furthermore, curcumin-treated rats showed a significant increase in Wnt3a and β-catenin mRNA expression. Wnt/β-catenin signaling is involved in neuronal survival, differentiation, axonal extension, promotes neurogenesis, synapse formation, and plasticity, and induces neuroprotection. Therefore, by activating the Wnt/β-catenin signaling pathway curcumin could improve the vitality and survival of neuronal cells.

Furthermore, it was shown that activation of the Wnt/β-catenin pathway also increased the levels of endogenous antioxidant molecules such as GSH-Px, SOD, and reduced the concentration levels of malondialdehyde (MDA). Therefore, curcumin showed antioxidant effects against 6-OHDA injury in PD rats through activation of the Wnt/β-catenin signaling pathway [82].

Despite its beneficial effects, curcumin is a dietary polyphenol with poor bioavailability. In this regard, Hirata et al. evaluated the potential antioxidant effect of GIF-2165X-G1, a hybrid molecule containing an oxindole skeleton of GIF-0726-r and a polyphenol the skeleton of curcumin. The results of in vitro study showed that GIF2165X-G1 (10 μM) increased cell viability, compared to alone oxindole derivative GIF-0726-r or curcumin. Conversely, GIF-2165X-G1 showed lower antioxidant effects compared to curcumin. However, GIF-2165X-G1 has been seen to increase the transcriptional activity of ARE, consequently, the production of antioxidant enzymes such as heme oxygenase-1 (HO-1) is enhanced. In order to confirm the neuroprotective effects demonstrated in vitro study, further investigations were performed on rats injured unilaterally with 6-OHDA in the striatum. GIF-2165X-G1 (1.5 μg) was administered in PD mice. The results showed that these compounds, besides their antioxidant activity, increased TH and DAT levels. Therefore, compound GIF-2165X-G1 shows promise in preserving the functionality of dopaminergic neurons and reducing ROS levels [83].

Instead, M. D. Pandareesh et al. evaluated the neuroprotective effects of curcumin monoglucoside (CMG), bioconjugated curcumin, against ROT-induced toxicity in N27 dopaminergic neuronal cells and *Drosophila* models. Pre-treatment of cells with CMG exerted antioxidant effects by increasing cell GSH levels and decreased ROS. Furthermore, quantitative PCR analysis demonstrated that GMC reduces the upregulation of nitric oxide synthase 2 (NOS2) genes and induced upregulation of NAD(P)H: quinone oxidoreductase

1 (NQO1). Moreover, pretreatment with the synthetic conjugate of curcumin enhanced the activity of the mitochondrial complex I and IV inhibited by ROT. CMG also demonstrated anti-apoptotic effects mediated by a decrease in phosphorylation of JNK3 and c-jun, which induce a reduction of pro-caspase 3. Also in vivo, in the *Drosophila* ROT model, CMG enhanced intracellular antioxidant activity, decreased ROS levels, and prevented dopamine depletion [84]. In line with these results, the antioxidant effects of curcumin have also been demonstrated by Dharmendra K. Khatri et al. In this study, in mice treated with ROT after 21 days of treatment, curcumin reduced MDA and nitrite levels. All three doses of curcumin (50, 100 and 200 mg/kg) used also resulted in a significant reduction in acetylcholinesterase (AChE) activity compared with ROT-treated mice. Conversely, after 21 days, treatment with curcumin at all doses increased the activity of antioxidant enzymes such as SOD and GSH. Furthermore, it reduced oxidative stress also by restoring the activity of the mitochondrial enzyme complex compromised by the ROT. In this way, curcumin improved cognitive function, thus demonstrating its neuroprotective role against PD [85].

Cui Q. et al. demonstrated that pre-treatment with curcumin improved rotational behavior in ROT-treated rats. As shown by Western blot analysis, pretreatment with curcumin decreased ROT-induced loss of TH protein and reduced ROS and MDA production in the substantia nigra pars compacta. Conversely, pre-treatment with curcumin-induced an increase of GSH levels reduced by ROT. Curcumin was shown to exert its antioxidant effects by activating the Akt/Nrf2 signaling pathway in dopaminergic neurons. Indeed, curcumin induced an increase in the expression of the HO-1 and NQO1 proteins and promoted Akt/Nrf2 phosphorylation. In order to confirm this result, rats were infused with an shNrf2 lentivirus or phosphoinositide 3-kinase inhibitor LY294002 prior to treatment with ROT or curcumin. Treatment with shNrf2 or LY294002 inhibited the effects of curcumin, demonstrating that the protective role of curcumin was associated with the Akt/Nrf2 signaling pathway [86].

Nguyen et al. conducted an in vivo experiment using *Drosophila*, which presents ubiquitin carboxyl-terminal hydrolase (dUCH), which is homologous to the human enzyme *UCH-L1* and is useful for reproducing PD. Therefore, targeted studies were carried out on dUCH knockdown flies, in which the oxidative stress condition was highlighted. The authors evaluated the antioxidant properties of curcumin (1 mM). The study was performed both in the larval stage and adult stage; the flies revealed a decrease in ROS in the adult brain and also in the imaginal discs of the eyes. Of considerable interest is that the results found that curcumin improved the motor deficits caused by the knockdown of dUCH. Curcumin has been shown to be relevant in preserving the structure and functionality of dopaminergic neurons by increasing dopamine levels. Notably, a 13% decrease in dopamine was found in curcumin-treated dUCH knockdown flies compared to the control. Instead, 52% of dopamine loss was found in untreated curcumin dUCH knockdown flies compared to the control. Therefore, curcumin confirms its beneficial effects on dopaminergic neurons [87].

The results of these in vivo and in vitro studies have demonstrated that curcuminoids can exert neuroprotective effects both in PD models induced by several environmental factors (such as 6-OHDA, MPTP and ROT), and in PD models induced by genetic factors including α-syn and UCH-L1 (Table 1). Preclinical studies demonstrated that pre-treatment with curcuminoids attenuate the level of oxidative stress and mitochondrial dysfunction. Additionally, curcuminoids prevent α-syn aggregation and fibrillation, consequently, improving the impaired cognitive and motor functions symptoms. To date, there are no available clinical studies that supported the pre-clinical data. Therefore, clinical studies would be necessary to evaluate the efficacy of curcuminoids in patients with PD.

Table 1. Antioxidant effects of Curcuminoids in PD.

Models	Curcuminoids	Curcuminoids Dose	Treatments	Mechanism of Action	Ref.
			In vitro experimental models		
MPP^+ Stimulated primary mesencephalic astrocytes	Curcumin	8 μM	28 h of treatment	Pre-treatment with curcumin reduced the oxidative stress in primary mesencephalic astrocytes induced by MPP^+ -treatment. Therefore, curcumin decreased ROS and increased GSH compared to primary astrocytes treated with MPP^+.	[77]
Model of oxidative stress in SH-SY5Y neuronal cells induced by the H_2O_2	Curcumin	5 μM	24 h of treatment	Curcumin reduced lipid peroxidation and intracellular Ca^{2+} concentrations; conversely enhanced GSH and GSH-Px levels compared to the H_2O_2-treated group of cells. In cells treated with curcumin caspase-3 and caspase-9 expression were reduced.	[78]
Mouse brain mitochondria treated with α-syn and hen egg white lysozyme	Curcumin	25 and 50 μM	Mitochondrial homogenates were pre-incubated with curcumin for 30 min at 30 °C, prior to adding α-syn fibrillation products	Curcumin, in a dose-dependent manner, reduced the growth of α-syn fibrils in rat brain mitochondria, by preventing mitochondrial Type 1 Hexokinase release and ROS formation.	[79]
SH-SY5Y ROT-treated	DMC	50 nM	2 h of pre-treatment	DMC inhibited the apoptosis process reducing pro-apoptotic proteins, increasing anti-apoptotic proteins, and ameliorating oxidative stress.	[80]
PC12 ROT-treated	Curcumin	10 μM	24 h of co-treatment	Curcumin increased cell viability and reduced oxidative stress. Treatment also decreased carbonylation and protein tyrosine nitration. Curcumin, prevent proteasome degradative system ROT-induced.	[81]
			In vivo experimental models		
Adult male Sprague-Dawley rats injured unilaterally with 6-OHDA in the left striatum	Curcumin	10 μmol/L	Intragastrically administration once each day for 3 consecutive weeks	Curcumin induced a significant increase in Wnt3a and β-catenin mRNA expression. It increased levels of GSH-Px, SOD, and reduced MDA. Curcumin reduced the local tissue damage induced by 6-OHDA, increasing the levels of the DAT, TH, and reducing GFAP.	[82]

Table 1. *Cont.*

Models	Curcuminoids	Curcuminoids Dose	Treatments	Mechanism of Action	Ref.
			In vivo experimental models		
HT-22 cells glutamate-induced and adult C57Bl/6 mice injured unilaterally with 6-OHDA in the right striatum	GIF-2165X-G1	10 μM (in vitro); 1.5 μg (in vivo)	HT-22 cells pre-treated with GIF-2165X-G1 for 24 h; mice were co-treated with injections of GIF-2165X-G1 and 6-OHDA in the right striatum	GIF-2165X-G1 in HT-22 neuronal cells increases cell viability. GIF-2165X-G1 increased the transcriptional activity of ARE, consequently, enhanced antioxidant enzymes such as HO-1. Instead, in mice, besides its antioxidant activity, GIF-2165X-G1 increased TH and DAT levels, improving the functionality of dopamine neurons.	[83]
N27 cell and *Drosophila* ROT-induced PD models	CMG	0.25−5 μM (in vitro); 500 μM (in vivo)	N27 cells pre-treated with CMG for 24 h; flies were pre-treated with CMG via diet for 5 days	CMG increased glutathione levels and decreased ROS. CMG upregulated the expression of NOS2 and downregulated the NQO1. CMG reduced the phosphorylation of JNK3 and c-jun, with a consequent decrease of pro-caspase 3. The same results were also obtained in the *Drosophila* ROT model.	[84]
ROT-treated Swiss albino male mice	Curcumin	50, 100 and 200 mg/kg	Orally administration for 21 days 1 h before ROT treatment	Curcumin (50, 100 and 200 mg/kg) increased SOD and GSH; instead, it reduced MDA, nitrite levels and the AchE activity. Curcumin improved the activity of the mitochondrial enzyme complex and ameliorated cognitive function.	[85]
ROT-treated male Lewis rats	Curcumin	100 mg/kg	Intragastrically administration twice a day for 50 days, before to ROT administration	Pretreatment with curcumin decreased ROT-induced loss of TH protein, ROS and MDA production and increased GSH levels through activation of the Akt/Nrf2 signaling pathway in dopaminergic neurons.	[86]
Drosophila model with dUCH Knockdown	Curcumin	1 mM	-	Curcumin lowered ROS levels in the brain and imaginal discs of the eyes. It also has beneficial effects on dopaminergic neurons, preserving their structure and functionality	[87]

MPP$^+$, 1-methyl-4-phenylpyridinium ion; ROS, reactive oxygen species; GSH, glutathione; H_2O_2, hydrogen peroxide; GSH-Px, glutathione peroxidase; α-syn, α-synuclein; ROT, rotenone; PD, Parkinson's disease; DMC, demethoxycurcumin; 6-OHDA, 6-hydroxydopamine; SOD, superoxide dismutase; MDA, malondialdehyde; DAT, dopamine transporter; TH, tyrosine hydroxylase; GFAP, glial fibrillar acid protein; CMG, curcumin monoglucoside; NOS2, nitric oxide synthase 2; NQO1, NAD(P)H: quinone oxidoreductase 1; JNK3, c-Jun N-terminal kinase; AChE, acetylcholinesterase; dUCH, ubiquitin carboxyl-terminal hydrolase.

5. Alzheimer's Disease

AD is a neurodegenerative disease that occurs with aging and the cause can be determined by several and concomitant risk factors [88]. Most AD cases occur sporadically. Alone in 10% of cases, AD is caused by genetic mutations in genes such as amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*) [89]. AD is characterized by the deposition of extracellular deposits of amyloid-β (Aβ) peptides and neurofibrillary tangles (NFTs) in brain tissue. Under physiological conditions, APP follows the non-amyloidogenic pathway, and is cleaved by α- and γ-secretases [90]. Conversely, in pathological conditions, APP follows the amyloidogenic pathway, which involves the cleavage by two enzymes, β- and γ-secretase, involved in the formation of Aβ. Specifically, $A\beta_{1-40}$ is the most abundant peptide in the brain. In patients with AD, $A\beta_{1-42}$ represents the most abundant and most toxic form due to its predisposition to aggregate and form oligomers [91]. Instead, NFTs are composed of hyperphosphorylated Tau protein, which destabilizes the microtubules inducing tangles formation. The deposition of amyloid plaques and NFTs are the events responsible for the loss of neurons and synapses with consequent impairment of neurotransmission [92,93]. Several studies demonstrate the relationship between oxidative stress and AD development. Indeed, an oxidative imbalance, especially at the mitochondrial level, can cause an increase in ROS, which in turn implies neuronal damage [88,94]. Moreover, it was shown the activation of the N-methyl-D-aspartate receptor (NMDAR) to be involved in oxidative stress, and in particular, in the development and progression of AD. NMDA activation induces an increase in intracellular Ca^{2+}, which leads mitochondrial dysfunctions with a consequent increase of oxidative stress [95].

For these reasons, antioxidant therapy in AD patients could be useful. In this context, several studies have been performed on natural compounds such as curcumin, whose antioxidant properties are widely known [96]. Curcumin appears able to inhibit Aβ formation, attenuates the hyperphosphorylation of tau, thus reducing the progression of neuronal damage [97].

5.1. Antioxidant Effects of Curcumin in In Vitro AD Model

The efficacy of curcumin was evaluated by Qian et al., in an in vitro experiment on PC12 cells treated with $A\beta_{25-35}$ to reproduce the AD model. The PC12 cells $A\beta_{25-35}$ treated with different doses of curcumin (5, 10, 20, 30 μM/L) showed an increase of cell viability in a dose-dependent manner. Furthermore, the 24 h of pre-treatment with curcumin in a dose-dependent manner has allowed a considerable reduction of apoptosis, through a reduction of caspase 3 expression and increase of Akt phosphorylation. In order to evaluate the antioxidant effects of curcumin, lactate dehydrogenase (LDH) and MDA levels were measured. The curcumin treatment, in a dose-dependent manner, has reduced LDH and MDA levels. Finally, the authors also evaluated that increasing doses of curcumin promoted the expression of NR2A, a subunit of NMDAR, which is important for the functionality of neuronal cells. The authors in this study highlighted the potential neuroprotective and antioxidant role of curcumin in AD [98].

In compliance with these results, Jaroonwitchawan et al. evaluated the ability of curcumin to reduce Aβ production and oxidative stress in SH-SY5Y cells exposed to paraquat. SH-SY5Y cells were treated with paraquat (0.5 mM) for 24 h, evaluating the effects on the expression of genes involved in AD progression. In detail, the paraquat treatment showed an increase in the mRNA transcription of *APP* and *PSEN1* genes. Following 2 h of pre-treatment with curcumin (5 and 10 μM), it was observed a significant reduction of *APP* expression and APP proteins. Additionally, a significant reduction in the Bax/Bcl-2 ratio induced by curcumin would evidence the antiapoptotic effects of this compound. Furthermore, the pre-treatment with curcumin highlighted the antioxidant potential through an increase of SOD and GSH-Px levels. Noteworthy, curcumin enhanced autophagy activity by upregulating LC3I/II. As it is known that the impairment of the autophagic process

could play a key role in the processing of APP, the improvement of this process could be a mechanism of action used by curcumin to protect against neurodegeneration [99].

Also, the neuroprotective effects of curcumin were evaluated by Shi et al. in a study conducted on mouse hippocampal HT-22 neuronal cells treated with acrolein to reproduce the AD model. The pre-treatment with curcumin (5 μg/mL) for 30 min showed an increase in cell viability and a decrease in the apoptotic process, reducing the neurotoxic effects of acrolein. Furthermore, pre-treatment with curcumin induced an increase in SOD, GSH levels and showed a reduction in MDA levels in acrolein-treated HT-22 cells. On the other hand, curcumin is able to counteract BDNF/TrkB signaling inhibition induced by acrolein toxicity. The results confirmed curcumin as a neuroprotective agent against AD. In particular, an increase in α-secretase (ADAM-10) was observed, which facilitates the breakdown of APP. Simultaneously, beta-amyloid converting enzyme 1 (BACE1) increased by acrolein exposure was restored [100].

Morales et al. carried out a study to evaluate the antioxidant properties of curcumin in N2a neuroblastoma cells after exposure to cytotoxic compounds. N2a cells were treated separately with ferric nitrilotriacetate and H_2O_2, and subsequently treated with curcumin (5–15 μM). Curcumin treatment showed an increase in cell viability, thus confirming cytoprotective effect in neuronal cells. In addition, the researchers incubated human tau (htau40) in N2a cells to reproduce the AD model. N2a cells were incubated for 8 days with monomeric htau40 and heparin to form Tau aggregates. The experimental results were visualized by means of thioflavin-S fluorescence analysis, directly proportional to the aggregated Tau concentration. Simultaneous treatment of curcumin and heparin after one day of incubation showed a reduction in fluorescence, thus a reduction in Tau aggregates. However, the administration of curcumin three days after heparin treatment alone showed a drastic reduction in fluorescence, demonstrating an incisive action against already formed Tau aggregates [101].

In consideration of these findings, Buccarello et al. evaluated the antioxidants properties of curcumin in H_2O_2-treated SH-SY5Y cells. The cells were pre-treatment with curcumin (1, 2.5, 5, 10 and 15 μM) for 24, followed by treatment with 0.5 mM of H_2O_2 for 30 min. The LDH dosage and cell viability showed that curcumin protected cells against oxidative stress induced by H_2O_2. Pre-treatment with curcumin-induced a decrease of caspase-3 level (at the high doses) and LC3B II/I ratio (at each dose tested). Conversely, cells treated with 10 μM of curcumin showed increased ubiquitin levels. Moreover, it was observed that curcumin caused a significant decrease of SUMO-1ylation, the phosphorylation of c-JNK and ERK. Additionally, among the doses of curcumin, only 5 μM induced a significant decrease of Tau phosphorylation compared to control, demonstrating the role of curcumin in the prevention of Tau phosphorylation. Interestingly, immunofluorescence analysis showed that pre-treatment with curcumin (5 μM) reduced the co-localization of SUMO-1-p-JNK-Tau proteins in nuclear bodies induced by H_2O_2 treatment [102].

The efficacy of curcumin treatment against oxidative stress was evaluated in macrophages of patients with AD. Jairani et al. conducted an experiment in human monocytic THP-1 cells derived from acute monocytic leukemia, subsequently differentiated into macrophages. Macrophages were treated with H_2O_2 (500 μM) to reproduce the AD model. The findings showed less efficient phagocytosis in H_2O_2 treated macrophages. Subsequently, macrophages were incubated overnight with HiLyte Flour 488-labeled $A\beta_{1-42}$ (1 μg/mL) to evaluate $A\beta_{1-42}$ internalization. Additionally, the lysosomal marker was used to evaluate $A\beta_{1-42}$ internalization into lysosomes. Therefore, the authors treated the macrophages with curcumin (10 μM). Curcumin improved $A\beta_{1-42}$ internalization in macrophages and lysosomal localization. The investigation also evaluated the presence of Apolipoprotein E (APOE) polymorphisms in AD patients. APOEε3 patient macrophages treated with curcumin internalize more $A\beta_{1-42}$ than APOEε4 patients. Therefore, curcumin ameliorated phagocytic activity in macrophages by preventing neurodegeneration [103].

A recent study illustrated the protective effect of curcumin in the SH-SY5Y cells transfected with the *APPswe* gene, a Swedish mutation, which causes an accumulation of

Aβ peptides. The cells were treated with curcumin (0.625–5 µM) for 4 h and subsequently exposed with H_2O_2 (250 µM) for 24 h to induce oxidative stress. Curcumin treatment enhanced cell proliferation and reduced LDH release, showing that it decreased H_2O_2-induced cell damage. Curcumin reduced the structural changes of neuronal cells, causing less condensation of chromatin with a consequent reduction in the apoptotic process. In order to evaluate the damage induced from oxidative stress to mitochondrial function, it was observed that curcumin was able to decrease the damaging activity of the electron transport chain and reduced the H_2O_2–induced mitochondrial membrane depolarization. Oxidative stress has been shown to influence the expression of the *APP* and *BACE1* genes which, conversely, was restored by curcumin. Moreover, curcumin prevented the APP β-cleavage, and intracellular Aβ generation stimulated from H_2O_2. Therefore, the antioxidant effects of curcumin, also able to reduce intracellular Aβ, strengthen the hypothesis that it can be used to treat AD [104].

In compliance with the previous study, Yan et al. also showed that curcumin (6.25–25 µM) reduced H_2O_2-induced oxidative stress in neuronal PC12 cells. However, curcumin, in addition to reducing ROS levels, is also capable of chelating several metal ions. Indeed, it has been shown that curcumin complexes with metallic ions work in a similar way to SOD. In this context, the authors investigated the protective effects of curcumin-Cu^{2+} or -Zn^{2+} complexes against injury in PC12 cells induced from H_2O_2. It was found that the curcumin-Cu^{2+} complex increased cell viability compared to the curcumin or curcumin-Zn^{2+} complex. Furthermore, the curcumin-Cu^{2+} complex showed a rapid increase in the levels of antioxidant enzymes such as SOD, CAT, GSH-Px and it decreased the level of MDA, caspase-3, and caspase-9. On the other hand, curcumin and curcumin-Cu^{2+} or -Zn^{2+} complexes increased the Bcl-2/Bax ratio, and reduced the level of NF-κB p65, demonstrating that curcumin suppresses apoptosis. Therefore, these results highlight the potential therapeutic value of curcumin complexed with metal ions in AD [105].

However, curcumin is known to have low bioavailability, which makes it difficult to clearly understand its pharmacological effects. Djiokeng Paka et al., in order to increase the bioavailability of this compound, carried out an in vitro experiment through the encapsulation of curcumin inside poly (lactide-co-glycolide) (PLGA) nanoparticles (NPs) with a ratio of 50% lactic acid (LA) and 50% glycolic acid (GA) (NPs-Curcumin 50:50) or with a ratio of 65% LA and 35% GA (NPs-Curcumin 65:35). SKN-SH cells were treated with free curcumin (0.5 µM), NPs-Curcumin 50:50 and NPs-Curcumin 65:35 for 1 h. The findings showed good absorption of NPs-Curcumin 50:50 in neuronal cells. In order to evaluate the antioxidant effects of curcumin, the cells were exposed to H_2O_2. NPs-Curcumin 50:50 significantly reduced ROS levels. Therefore, the authors focused their attention on the Nrf2/Keap1 pathway showing that the treatment with free curcumin (0.5 µM) and NPs-Curcumin 50:50 in SK-N-SH H_2O_2-treated cells reduced the activation of Keap1 and consequently of Nrf2 activation.

Oxidative stress plays a key role also in Akt and Tau phosphorylation. In this case, NPs-Curcumin 50:50 have been shown to be effective in reducing their phosphorylation. It was also evaluated the change expression of genes that play an important role in antioxidant and neuroprotective processes. In particular, NPs-Curcumin increased transcripts of glutaredoxine (*GLRX*), thioredoxine (*TRX*), and a decrease in apolipoprotein J (*APOJ*). Both NPs-Curcumin 50:50 and NPs-Curcumin 65:35 appear more effective than free curcumin in modulating these genes. In conclusion, the use of curcumin encapsulated in PLGA nanoparticles could be a valid therapeutic strategy to overcome the problems of the clinical application of curcumin related to its poor bioavailability [106].

The poor stability and low bioavailability of curcumin are due to β-diketone moiety that induces rapid degradation. In this context, two mono-carbonyl analogues of curcumin, (1E, 4E)-1,5-bis(4-hydroxy-3-methoxyphenyl)penta-1,4-dien-3-one (CB) and (1E, 4E)-1-(3,4-dimethoxyphenyl)-5-(4-hydroxy-3, 5-dimethoxyphenyl) Penta-1, 4-dien-3-one (FE) were synthesized. PC12 cells were treated with Aβ$_{25–35}$ (10 µM) before, concurrently, or after treatment with curcumin, CB, and FE at different concentrations (0.1–20 µM).

Treatment with CB and FE showed improvements in cell viability and counteracted the increase in ROS following $A\beta_{25-35}$ induced toxicity. Additionally, CB and FE have been shown to be effective in restoring levels of antioxidant enzymes such as CAT and SOD. Significant reductions in MDA and LDH dosages were also found following treatment with curcumin and analogues. CB and FE also resulted in an increase in the Bcl2/BAX ratio and a reduction in cytochrome c release as a result of inhibition of apoptosis. However, proteins of the Keap1/Nrf2/HO-1 signaling pathway were evaluated in PC12 cells, a key pathway to protect the cells from oxidative stress and apoptosis. Curcumin, CB, and FE reduced Keap1 expression and simultaneously increased Nrf2 and HO-1 expression. This study highlighted that the mono-carbonyl analogues of curcumin showed great efficacy at lower doses compared to curcumin. This demonstrated that the CB and FE used a similar mechanism of curcumin, and they showed major stability. Thus, the modification of mono-ketone moiety could improve the stability bioavailability of curcumin. In conclusion, the results of this study demonstrated mono-carbonyl analogues of curcumin might be implicated in the treatment of AD [107].

Instead, Pinkaew et al. evaluated the neuroprotective effects di-O-demethylcurcumin, a modified analog of curcumin. In this study, SK-N-SH cells were pre-treated with di-O-demethylcurcumin (1–8 μM) for 2 h and then incubated with $A\beta_{25-35}$ (10 μM) overnight. The di-O-demethylcurcumin pre-treatment showed a reduction in cell toxicity and in ROS and NO levels compared to $A\beta_{25-35}$ group. The pretreatment with di-O-demethylcurcumin downregulated iNOS expression, thereby reducing NO production. Further, di-O-demethylcurcumin exposure increased Nrf2 protein expression in the nucleus with a consequent increase of pathway-related proteins such as HO-1, NQO1, and SOD. Additionally, di-O-demethylcurcumin showed anti-inflammatory properties avoiding the translocation of NF-kB p65 into the nucleus. Therefore, di-O-demethylcurcumin could be a valid candidate against $A\beta_{25-35}$-induced neurotoxicity [108].

The curcumin derivatives behavior was also explored by Orteca et al. in hippocampal HT-22 mouse cells. In order to improve bioavailability and curcumin stability, the researchers modified the molecule of curcumin through the removal of the keto-enol fraction, the addition of pyrazole ring, or insertion of the phthalimide-functionalized chain. To induce neurotoxicity, HT-22 cells were treated with glutamate (2 μM) and subsequently were co-treated with curcumin and curcumin derivatives (1 μM) for 24 h. The curcumin derivatives compared to curcumin showed a greater reduction in the cytotoxic effects and the apoptotic process induced by the treatment with glutamate. Additionally, curcumin derivatives downregulated iNOS and decreased the ratio of Bax/Bcl2 transcripts, thus confirming their cytoprotective and antiapoptotic actions against oxidative stress. Further, fluorescence analysis was done to study the interaction between curcumin derivatives and amyloid fibrils. In this regard, HT-22 cells were treated with $A\beta_{1-40}$ (10 μM) to induce the AD model. The treatment with curcumin derivative (10 μM) for 24 h, displayed that these compounds own higher binding affinity and depolymerization of fibrillar aggregates compared to curcumin. Therefore the curcumin-derived compounds exhibited a high bioavailability compared to curcumin, and they reveal satisfactory ability to counteract oxidative stress and depolymerize fibrillar aggregates [109].

5.2. Antioxidant Effects in In Vivo AD Model

The effects of curcumin on behaviors and biochemical markers related to AD-like symptoms were investigated in vivo experimental model AD. The AD model was induced by bilateral hippocampal injection of streptozotocin (3.0 mg/kg), associated with subcutaneous administration of D-galactose (125 mg/kg) for 7 weeks, which served to promote neurodegeneration and increase oxidative stress. Rats were treated with curcumin (10 mg/kg) via intraperitoneal injection for 7 weeks. After treatment, an increase in GSH-Px enzymatic activity was observed in the blood samples of the curcumin-treatment group compared to the AD groups. Curcumin reduced oxidative stress damage induced by the combination of streptozotocin and D-galactose. The histochemical investigations allowed

it to visualize the effects of curcumin-mediated treatment in the cortex and hippocampus regions CA1 and CA3. The curcumin-mediated treatment avoided a substantial loss of neurons in the hippocampal tissue. Moreover, curcumin reduced the APP β-cleavage and formation of amyloid-like and reduced the $A\beta_{1-42}$ in the hippocampal compared to the AD group. Also, in the curcumin group, it was observed the reduction of PSEN1 and BACE1 expression. Therefore, curcumin prevented neurodegeneration and preserved the integrity of hippocampal tissue [110].

Although curcumin has excellent therapeutic potential against AD, its poor bioavailability and biodistribution could reduce its effectiveness. In this context, Fidelis et al. evaluated antioxidant and antidepressant effects using curcumin-loaded lipid core capsules (NLC C) in Swiss male mice reproducing AD models. In order to induce the AD model, aggregated acetyl $A\beta_{25-35}$ (3 nmol/3μL) was administered intracerebroventricularly. Curcumin was administrated via intragastrical, in order to overcome its low bioavailability. The mice were pre-treated with NLC C (10 mg/kg) every 48 h for 12 days. The results of the present study showed that NLC C reduced the levels of ROS and regularized the levels of antioxidant enzymes such as SOD and CAT raised by treatment with $A\beta_{25-35}$ in the prefrontal cortex. However, studies carried out on the hippocampus did not reveal significant differences, but NCL C resulted in an increase in the SOD/CAT ratio. Therefore, NLC C proved to be an effective treatment against oxidative stress induced by $A\beta_{25-35}$ in the prefrontal cortex, and also proved effective in attenuating the depressive behavior induced by $A\beta_{25-35}$ infusion [97].

Also, Malvajerd et al. evaluated the effects of NLC C in male Sprague-Dawley rats $A\beta_{1-42}$-treated to induce a model of AD. The treatment of NLC C (4 mg/kg) administered intracerebroventricularly showed an overall reduction in the oxidative stress induced by the $A\beta_{1-42}$ treatment in the hippocampal tissue of rats. Specifically, the results showed a decrease in MDA, ROS levels, and lipid peroxidation in the hippocampal tissue, demonstrating that curcumin counteracts oxidative stress. Moreover, the researchers found an increase of thiols, peculiar for their antioxidant properties. A significant finding, the ADP/ATP ratio was also assessed, it was decreased in NLC C treatment compared to the sham group. The efficacy of NLC C for brain delivery of curcumin was also confirmed by the improvement of spatial memory in rats. This evidence confirmed the antioxidant properties of curcumin and proved that NLC C to be a good vector for reaching optimal concentrations in the brain [111].

5.3. Antioxidant Effects of Curcumin in Clinical Trial

Some clinical studies were conducted in order to investigate the potential effects of the efficacy of CBD in the management of AD.

A group of Chinese researchers performed a phase 1/2 trial (NCT00164749), to evaluate the efficacy of curcumin in slowing the progression of AD. In this study, 36 patients (50 years and older) with a progressive decline in cognitive function and memory for at least six months were enrolled. Patients were treated with a placebo or with 1 or 4 g of curcumin per day. Additionally, all patients were treated with 120 mg of ginkgo extract per day. All participants were monitored at baseline, 1, 3, and 6 months after treatment. The primary outcome of the study was to assess the safety of curcumin in order to be able to design a larger study to test curcumin against AD. The secondary objective of the study was to establish the biochemical mechanism used from curcumin and explain which of the two doses was more effective. Therefore, to assess whether curcumin could reduce levels of Aβ and oxidative stress-related proteins, blood samples were analyzed to measure levels of isoprostane, Aβ protein, metals, and cholesterol. Cognitive tests were performed to evaluate the effects of curcumin on cognitive impairments typical of AD. In conclusion, the results of this study will help us understand whether curcumin can be used as a treatment to delay the progression of AD.

The complete phase 2 study (NCT00099710), double-blind, aimed to evaluate the safety and tolerability of two doses of Curcumin C3 Complex ® in patients with mild or

moderate AD. The study enrolled 33 patients (50 years and older) randomized to receive one of two doses of oral curcumin (2 or 4 mg), or a placebo, for the first six months of the study. After six months, patients in the placebo group received one of two doses of curcumin, thereby extending the study to another six months. Participants achieved seven visits during the 12-month study. Physical and neurological examinations, routine laboratory tests, and neuropsychological assessments were performed during these visits. Specifically, Alzheimer's Disease Assessment Scale, cognitive sub-portion (ADAS-Cog), the Neuropsychiatric Inventory (NPI) tool, and Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) were used to assess the clinical outcomes of the treatment. Blood and cerebrospinal fluid tests were also done to assess how curcumin is absorbed by the body and its possible antioxidant and anti-inflammatory effects.

Part of the study results was published in the study conducted by Ringman J. M. et al. In this study, the authors reported only efficacy data at 6 months post-treatment and tolerability measures of curcumin up to 12 months. After one year of treatment, curcumin was well tolerated; of the 33 patients enrolled, only three subjects withdrew from the study due to severe gastrointestinal symptoms. However, the study results did not report clinical data on the efficacy of curcumin against AD. Indeed, there were no significant differences between the treatment groups in ADAS-Cog, NPI, and ADCS-ADL scores. There were also no significant changes in plasma and cerebrospinal fluid levels of $A\beta_{1-40}$, $A\beta_{1-42}$, tau, and p-tau. Additionally, curcumin appears to have shown low bioavailability. In conclusion, the poor bioavailability, the lack of clinical data demonstrating the efficacy of curcumin in AD, and the partial publication of the data, do not allow definitive conclusions to be drawn from this study, further observations and long-term clinical studies will be necessary to understand the mechanisms used by curcumin to exert its beneficial effects.

Due to the poor bioavailability of curcumin, which does not allow for positive results in clinical studies, a phase 2 clinical trial (NCT01001637) was designed to determine the efficacy and safety of the highly bioavailable curcumin, solid-lipid curcumin particle (SLCP or Longvida). The study enrolled 26 participants (50 to 80 Years) with moderate or severe AD. The patients were randomly divided into a group that received a placebo and a group treated with oral curcumin formulation at a dose of 2000 mg or 3000 mg daily. The primary outcome of the study was to evaluate the efficacy of curcumin formulation on the mental abilities of AD patients 2 months after treatment. The trial also aimed to evaluate changes in serum $A\beta$ concentrations. The results of the study have not yet been published, however, they will help to understand the oral dosing of curcumin solid-lipid particles, and to evaluate its safety. Furthermore, data will be helpful to understand whether formulated curcumin induces improvements in memory deficits and influences biomarkers of AD better than non-formulated curcumin.

In conclusion, preclinical findings demonstrated that curcuminoids during pre-treatment inhibit the $A\beta$ aggregation, attenuate the tau hyperphosphorylation and, consequently, improve cognitive function and prevent the development of dementia (Table 2). However, clinical studies that reveal the efficacy of curcuminoids treatment in AD patients with mild or moderate stages of the disease are few. Thus, further studies will be needed to encourage the use of curcuminoids as valid therapeutic tools in the management of AD.

Table 2. Antioxidant effects of curcuminoids in AD.

Models	Curcuminoids	Curcuminoids Dose	Treatments	Mechanism of Action	Ref.
In vitro experimental models					
PC12 cells treated with $A\beta_{25-35}$	Curcumin	5, 10, 20, 30 μM/L	24 h of pre-treatment	Curcumin increased the cell viability in a dose-dependent manner and reduced apoptosis, through caspase 3 expression reduction and Akt phosphorylation increase. The treatment, in a dose-dependent manner, has reduced LDH and MDA levels. Conversely, treatment enhanced the expression of NR2A, a subunit of NMDAR, highlighting the antioxidant properties of curcumin in AD.	[98]
SH-SY5Y paraquat-treated	Curcumin	5 and 10 μM	2 h of pre-treatment	Curcumin reduced APP expression and APP proteins. This compound also reduced the ratio Bax/Bcl-2 induce by curcumin, evidencing the antiapoptotic effects. While the antioxidants effects were highlighted from increased SOD and GSH-Px levels. Curcumin enhanced autophagy activity by upregulating LC3I/II.	[99]
HT-22 treated with acrolein	Curcumin	5 μg/mL	0.5 h of pre-treatment	Curcumin induced an increase in the levels of SOD, GSH and a reduction in the levels of MDA. Furthermore, curcumin is able to counteract BDNF/TrkB pathway inhibition.	[100]
N2a cells treated with ferric nitrilotriacetate or H_2O_2 or htau40	Curcumin	5–15 μM	24 h or 1 and 3 days after htau40 treatment.	Curcumin showed increased cell viability induced by ferric nitrilotriacetate or H_2O_2. Furthermore, the curcumin treatment reduced Tau aggregates.	[101]
SH-SY5Y cells treated with H_2O_2	Curcumin	1, 2.5, 5, 10 and 15 μM	24 h of pre-treatment	Curcumin increased cell viability after H_2O_2 treatment. in addition, it decreased caspase 3 levels and the LC3B II/I ratio. Moreover, curcumin (5 μM) reduces Tau phosphorylation and co-localization of SUMO-1-p-JNK-Tau proteins in nuclear bodies, demonstrating neuroprotective effects.	[102]

Table 2. *Cont.*

Models	Curcuminoids	Curcuminoids Dose	Treatments	Mechanism of Action	Ref.
			In vitro experimental models		
Macrophages treated with H_2O_2 or $A\beta_{1-42}$	Curcumin	10 μM	24 h of treatment	Curcumin enhanced the phagocytic activity of macrophages through the internalization of $A\beta_{1-42}$ into lysosomes. Therefore, curcumin prevents neurodegeneration.	[103]
SH-SY5Y cells transfected with the APPswe gene and exposed to H_2O_2	Curcumin	0.625–5 μM	4 h of pre-treatment	Curcumin ameliorated cell proliferation and decreased LDH release. Treatment reduced the structural changes, preventing the apoptotic process. Curcumin inhibited oxidative stress-induced damage to impaired mitochondrial function. It restored the expression of the APP and BACE1 genes and avoided the APP β-cleavage and intracellular Aβ generation.	[104]
Model of oxidative stress in PC12 cells induced by the H_2O_2	Curcumin, curcumin-Cu^{2+} complexes and curcumin-Zn^{2+} complexes	0.5 μM	0.5 h of pre-treatment	Curcumin-Cu^{2+} or -Zn^{2+} complexes enhanced the levels of antioxidant enzymes such as SOD, CAT, GSH-Px and decreased the MDA levels. Both complexes suppressed apoptosis through reduced caspase-3, caspase-9, and NF-κB p65 levels; conversely, it increased the Bcl-2/Bax ratio. Compared to the curcumin or curcumin-Zn^{2+} complex, curcumin-Cu^{2+} appeared most efficacy also in the increase of cell viability.	[105]
Model of oxidative stress in SK-N-SH cells induced by the H_2O_2	NPs-Curcumin formulations	0.5 μM	1 h of treatment	NPs-curcumin 50:50 significantly reduced ROS levels inhibiting the Keap1 and Nrf2 activation and reducing the phosphorylation of Akt and Tau. NPs-curcumin appears more effective than free curcumin in modulating the expression of genes that play an important role in antioxidant and neuroprotective processes, such as *GLRX*, *TRX*, and *APOJ*.	[106]

Table 2. *Cont.*

Models	Curcuminoids	Curcuminoids Dose	Treatments	Mechanism of Action	Ref.
			In vitro experimental models		
PC12 Aβ_{25-35}-treated	Curcumin, CB And FE	0.1–20 µM	-	Treatment with CB and FE improved cell viability and counteracted the increase in ROS. Both mono-carbonyl analogues of curcumin restored levels of antioxidant enzymes (such as CAT and SOD) and reduced MDA and LDH. CB and FE also increased the Bcl2/BAX ratio and reduced cytochrome c release as a result of inhibition of apoptosis. Curcumin, CB, and FE reduced Keap1 expression and simultaneously increased Nrf2 and HO-1 expression. The mono-carbonyl analogues of curcumin showed great efficacy at lower doses compared to curcumin.	[107]
SK-N-SH Aβ_{25-35}-treated	Di-O-demethylcurcumin	1–8 µM	2 h of pre-treatment	The di-O-demethylcurcumin reduced ROS and iNOS expression, thus decreasing NO production. The di-O-demethylcurcumin exposure increased Nrf2 protein expression in the nucleus with a consequent increase of pathway-related proteins such as HO-1, NQO1, and SOD.	[108]
HT-22 cells glutamate-treated or Aβ_{1-40}-treated	Curcumin and curcumin derivatives	1 µM and 10 µM	24 h of co-treatment	Curcumin derivatives showed reduced cytotoxic effects and apoptotic processes. Indeed, curcumin derivatives downregulated iNOS and reduced the ratio of Bax/Bcl2 transcripts. Moreover, curcumin derivatives exhibited higher binding affinity and depolymerization of fibrillar aggregates, thus they showed neuroprotective effects.	[109]

Table 2. *Cont.*

Models	Curcuminoids	Curcuminoids Dose	Treatments	Mechanism of Action	Ref.
			In vivo experimental models		
Sprague-Dawley rats streptozotocin and D-galactose co-treated	Curcumin	10 mg/kg	Intraperitoneal injection for 7 weeks	Curcumin increased the GSH-Px reducing oxidative stress damage induced by the combination of STZ and D-galactose. The treatment ameliorated the loss of neurons in the hippocampal tissue. Curcumin reduced the AβPP β-cleavage, formation of amyloid-like, and reduced the Aβ$_{1-42}$ in the hippocampal. It also decreased the PSEN1 and BACE1 expression.	[110]
Swiss male mice-treated Aβ$_{25-35}$	NLC C	10 mg/kg	Intragastrically administration once every 48 h for 12 days	NLC C restored SOD and CAT concentrations in the prefrontal cortex. In the hippocampus it was observed that NCL C increased the SOD/CAT ratio.	[97]
Sprague-Dawley male rats-treated Aβ$_{1-42}$	NLC C	4 mg/kg	Intracerebro-ventricular administration for 4 days after Aβ$_{1-42}$ injection	NLC C reduced ROS and MDA levels and increased the concentration of thiol groups, indicating a contrasting action in oxidative stress. It also preserved mitochondrial functionality. NLC C promoted the restoration of cognitive functions.	[111]

Aβ, amyloid-β; LDH, lactate dehydrogenase; MDA, malondialdehyde; NMDAR, N-methyl-D-aspartate receptor; APP, amyloid precursor protein; BACE1, beta-amyloid converting enzyme 1; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; H$_2$O$_2$, hydrogen peroxide; JNK, Jun N-terminal kinase; Cu^{2+}, copper; Zn^{2+}, zinc; CAT, catalase; NF-κB, nuclear factor κB; NPs, nanoparticles; GLRX, glutaredoxine; TRX, thioredoxine; APOJ, apolipoprotein J; PSEN1, presenilin 1; NLC C, curcumin-loaded lipid core capsules; CB, (1E, 4E) -1, 5-bis (4-hydroxy-3-methoxyphenyl) penta-1, 4-dien-3-one; FE, (1E, 4E)-1-(3,4-dimethoxyphenyl)-5-(4-hydroxy-3,5-dimethoxyphenyl) Penta-1, 4-dien-3-one; HO-1, heme oxygenase-1; NQO1, NAD(P)H quinone oxidoreductase 1.

6. Amyotrophic Lateral Sclerosis

ALS is a neurodegenerative disease characterized by progressive degeneration of both upper and lower motor neurons, resulting in muscle atrophy, gradual paralysis that generally results in respiratory failure [112]. Respiratory failure usually occurs within 2–5 years of diagnosis due to respiratory muscle involvement. Furthermore, about 50% of ALS patients show evidence of frontal and temporal lobe dysfunction, while about 15% of patients with ALS, show some degree of motor involvement [113]. About 10% of patients with ALS follow a family pattern, mostly autosomal dominant (familial ALS), while 90% show a genetic basis (sporadic ALS). Several gene mutations linked to ALS have been associated to date, including superoxide dismutase 1 (SOD1), TAR DNA-binding protein 43 (TDP43), and fused in sarcoma/translocated in sarcoma (FUS) genes. The etiology of ALS still remains completely misunderstood, however like other neurodegenerative diseases it is a multifactorial pathology [114]. Certainly, glutamate-induced excitotoxicity, microglia activation, apoptosis, neuroinflammation, oxidative stress and mitochondrial dysfunction are all factors that play a key role in the pathogenesis of this disease [115,116].

Several studies have demonstrated the important role that oxidative stress plays a key role in the development and progression of ALS. Indeed, oxidative damage due to ROS accumulation has been confirmed in NSC-34 cells expressing mutant or wild-type TDP-43 genes [117]. Oxidative stress is responsible for alterations in redox signaling that exacerbate other pathophysiological processes such as excitotoxicity [118], mitochondrial damage [119], alterations in astrocyte and microglia signaling [120,121], responsible for damage to motor neurons. Treatment with antioxidants compounds may slow the progression of the disease in animal models of ALS [122,123]. Curcumin, in motor neuron cell lines transfected with the TDP-43 mutant, reduces oxidative stress and protects cells from mitochondrial damage [124,125]. Furthermore, curcumin activates Nrf2 target genes in primary astrocytes of the spinal cord. Since Nrf2 is a regulator of antioxidant genes, the activation of this antioxidant pathway may be a valid therapeutic strategy used by curcumin to prevent the loss of motor neurons in the spinal cord [126].

In this regard, Chico L. et al. evaluated the effects of curcumin in patients with ALS. Patients were randomized into two groups, one group received a placebo for three months and subsequently received oral curcumin (600 mg/day, Brainoil), for three months. While a second group was treated with curcumin for six months (600 mg/day, Brainoil). Evaluations were performed at baseline after three months and after six months. Clinical evaluations were performed and biomarkers of oxidative stress were measured, including oxidative protein products (AOPP), ferric reducing capacity (FRAP), total thiols (T-SH), and lactate which were compared with a control group. Throughout the entire study, the group that received curcumin from the outset showed a stable Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) score. Furthermore, this group always showed a reduction in AOPP ($p < 0.01$), which was not observed in group A. Curcumin administered for six months also maintained stable FRAP and decreased lactate. Furthermore, the patients with ALS recruited in the study showed an increase in oxidative stress compared to healthy subjects. However, treatment with curcumin reduced oxidative stress. Thus oral supplementation of curcumin revealed encouraging data indicating a slight slowdown in disease progression, ameliorating aerobic metabolism, and reducing oxidative damage [127].

The effects of curcumin are also being evaluated in another clinical trial still under study. The ongoing trial registered in ClinicalTrials.gov (accessed on 12 February 2021) (NCT04654689), intends to evaluate the effects of curcumin used in combination with another polyphenol, resveratrol. The study was recruited 100 ALS patients (over 18 years of age) for at least 6 months that were randomized into two groups. One group will receive a single daily dose of the combination of resveratrol (75 mg) and curcumin (200 mg) liposomed with dutasteride for 6 months. The second group will receive placebo at the same dose and for the same time frame. The placebo will consist of sucrose as a replacement for liposomal polyphenols, and a soft capsule of microcrystalline methylcellulose, instead

of Dutasteride. During the study, assessments will be performed at baseline, three months, and six months after treatment. Patients will undergo clinical evaluations using functional, cognitive, and behavioral tests through ALSFRS-R, electromyography, and measurement of forced vital capacity evaluations.

Furthermore, to evaluate the possible antioxidant and anti-inflammatory effects induced by the treatment, quantitative plasma measurements of inflammatory cytokines such as plasma IL-6 and TNF-α and of oxidative stress markers such as Trolox Equivalent Antioxidant Capacity (TEAC), 8-oxoguanine and MDA. The choice of using these compounds in liposomes or nanoparticles increases their stability, bioavailability, and absorption of the antioxidant. Indeed, the use of nanobiotechnology with curcumin (80 mg/day) in the treatment of patients with ALS has obtained positive outcomes demonstrating that nanocurcumin is safe and could improve the course of the disease, as well as proving to be a valid therapeutic strategy to use as an adjunct treatment in patients with ALS [128]. Therefore, the results of this clinical study will be useful in understanding the mechanisms by which these compounds exert their protective effects. Additionally, they will also be necessary to assess if natural compounds such as curcumin could be a valid therapeutic strategy to use in patients with ALS.

These results suggest that curcuminoids, through their antioxidant effects, are able to prevent the loss of motor neurons. Interestingly, the treatment of ALS patients with curcumin is safe and useful in improving and preventing the progression of the disease. Therefore, these data encourage the use of curcuminoids as a therapeutic strategy in the treatment of ALS.

7. Conclusions

This review summarized the studies that evaluate the antioxidant properties of curcuminoids related to their potential neuroprotective effects. Specifically, curcuminoids highlight powerful antioxidant actions through the activation of Akt/Nrf2 pathway (Figure 3). Several preclinical studies have shown that curcuminoids possess therapeutic efficacy against AD, PD and ALS. However, there are not available clinical studies for PD. Instead, few clinical trials are recorded concerning AD and ALS that limited results reported efficacy and safety of curcuminoids. Therefore, clinical studies are needed in order to include curcuminoids in clinical practice.
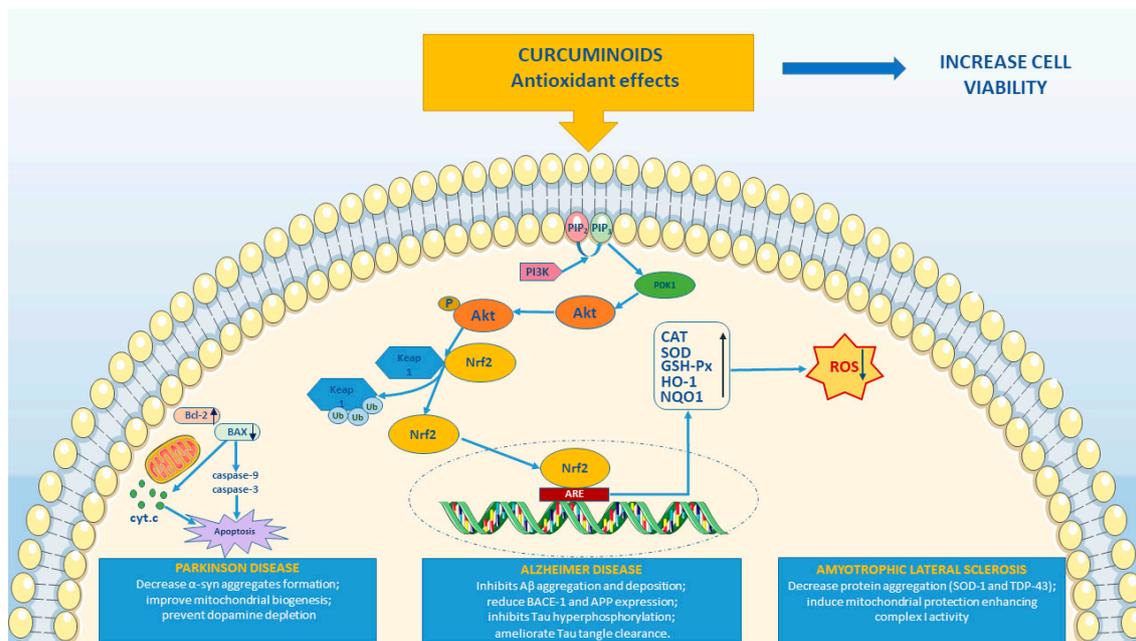
Figure 3. Graphical representation illustrates the principal antioxidant effects of curcuminoids in Parkinson's disease (PD), Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS). The figure was made taking the images from Servier Medical Art (available at http://smart.servier.com/ accessed on 12 February 2021), licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/ accessed on 12 February 2021). PIP$_2$, Phosphatidylinositol 4,5-bisphosphate; PIP$_3$, Phosphatidylinositol (3,4,5)-trisphosphate; PDK1, Phosphoinositide-dependent kinase-1; PI3K, Phosphoinositide 3-kinase; Akt, Protein kinase B; Keap1, Kelch-like ECH-associated protein 1; Ub, Ubiquitin; P, phosphate; Nrf2, Nuclear factor erythroid 2-related factor 2; ARE Antioxidant response element; CAT, catalase; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; HO-1, heme oxygenase-1; NQO1, NAD(P)H quinone oxidoreductase 1; ROS, Reactive oxygen species; Bcl-2, B-cell lymphoma 2; BAX, bcl-2-like protein 4; cyt. c, cytochrome complex; α-syn, alpha-synuclein; Aβ amyloid-β; BACE1, beta-amyloid converting enzyme 1; Tau, Tau protein; APP, Amyloid precursor protein; SOD1, superoxide dismutase 1; TDP43, TAR DNA-binding protein 43.

References

1. WHO. *WHO Methods and Data Sources for Global Burden of Disease Estimates 2000–2011*; Department of Health Statistics and Information Systems: Geneva, Switzerland, 2013; Available online: http://www.who.int/healthinfo/statistics/GlobalDALYmethods_2000_2011.pdf?ua=1 (accessed on 6 November 2020).
2. Olofsson, P.S.; Rosas-Ballina, M.; Levine, Y.A.; Tracey, K.J. Rethinking inflammation: Neural circuits in the regulation of immunity. *Immunol. Rev.* **2012**, *248*, 188–204. [CrossRef] [PubMed]
3. Barnham, K.J.; Masters, C.L.; Bush, A.I. Neurodegenerative diseases and oxidative stress. *Nat. Rev. Drug Discov.* **2004**, *3*, 205–214. [CrossRef]
4. Hsieh, H.L.; Yang, C.M. Role of Redox Signaling in Neuroinflammation and Neurodegenerative Diseases. *Biomed. Res. Int.* **2013**, *2013*, 484613. [CrossRef] [PubMed]

5. Schieber, M.; Chandel, N.S. ROS Function in Redox Signaling and Oxidative Stress. *Curr. Biol.* **2014**, *24*, R453–R462. [CrossRef]
6. Guzman-Martinez, L.; Maccioni, R.B.; Andrade, V.; Navarrete, L.P.; Pastor, M.G.; Ramos-Escobar, N. Neuroinflammation as a Common Feature of Neurodegenerative Disorders. *Front. Pharm.* **2019**, *10*, 1008. [CrossRef] [PubMed]
7. Chen, X.P.; Guo, C.Y.; Kong, J.M. Oxidative stress in neurodegenerative diseases. *Neural Regen. Res.* **2012**, *7*, 376–385.
8. Dadhania, V.P.; Trivedi, P.P.; Vikram, A.; Tripathi, D.N. Nutraceuticals against Neurodegeneration: A Mechanistic Insight. *Curr. Neuropharmacol.* **2016**, *14*, 627–640. [CrossRef]
9. Rehman, M.U.; Wali, A.F.; Ahmad, A.; Shakeel, S.; Rasool, S.; Ali, R.; Rashid, S.M.; Madkhali, H.; Ganaie, M.A.; Khan, R. Neuroprotective Strategies for Neurological Disorders by Natural Products: An update. *Curr. Neuropharmacol.* **2019**, *17*, 247–267. [CrossRef]
10. Chainani-Wu, N. Safety and anti-inflammatory activity of curcumin: A component of tumeric (Curcuma longa). *J. Altern. Complement. Med.* **2003**, *9*, 161–168. [CrossRef]
11. Sharma, R.; Gescher, A.; Steward, W. Curcumin: The story so far. *Eur. J. Cancer* **2005**, *41*, 1955–1968. [CrossRef]
12. Cousins, M.; Adelberg, J.; Chen, F.; Rieck, J. Antioxidant capacity of fresh and dried rhizomes from four clones of turmeric (Curcuma longa L.) grown in vitro. *Ind. Crop. Prod.* **2007**, *25*, 129–135. [CrossRef]
13. Sahebkar, A. Molecular mechanisms for curcumin benefits against ischemic injury. *Fertil. Steril.* **2010**, *94*, e75–e76. [CrossRef]
14. Gupta, S.C.; Patchva, S.; Aggarwal, B.B. Therapeutic roles of curcumin: Lessons learned from clinical trials. *AAPS J.* **2013**, *15*, 195–218. [CrossRef] [PubMed]
15. Iranshahi, M.; Sahebkar, A.; Hosseini, S.; Takasaki, M.; Konoshima, T.; Tokuda, H. Cancer chemopreventive activity of diversin from Ferula diversivittata in vitro and in vivo. *Phytomedicine* **2010**, *17*, 269–273. [CrossRef]
16. Aggarwal, B.B.; Gupta, S.C.; Sung, B. Curcumin: An orally bioavailable blocker of TNF and other pro-inflammatory biomarkers. *Br. J. Pharmacol.* **2013**, *169*, 1672–1692. [CrossRef] [PubMed]
17. Shehzad, A.; Rehman, G.; Lee, Y.S. Curcumin in inflammatory diseases. *Biofactors* **2013**, *39*, 69–77. [CrossRef] [PubMed]
18. Sahebkar, A.; Mohammadi, A.; Atabati, A.; Rahiman, S.; Tavallaie, S.; Iranshahi, M.; Akhlaghi, S.; Ferns, G.A.; Ghayour-Mobarhan, M. Curcuminoids modulate pro-oxidant–antioxidant balance but not the immune response to heat shock protein 27 and oxidized LDL in obese individuals. *Phytother. Res.* **2013**, *27*, 1883–1888. [CrossRef]
19. Panahi, Y.; Saadat, A.; Beiraghdar, F.; Nouzari, S.M.H.; Jalalian, H.R.; Sahebkar, A. Antioxidant effects of bioavailability-enhanced curcuminoids in patients with solid tumors: A randomized double-blind placebo-controlled trial. *J. Funct. Foods* **2014**, *6*, 615–622. [CrossRef]
20. Darvesh, A.S.; Carroll, R.T.; Bishayee, A.; Novotny, N.A.; Geldenhuys, W.J.; Van der Schyf, C.J. Curcumin and neurodegenerative diseases: A perspective. *Expert Opin. Investig. Drugs* **2012**, *21*, 1123–1140. [CrossRef]
21. Motterlini, R.; Foresti, R.; Bassi, R.; Green, C.J. Curcumin, an antioxidant and anti-inflammatory agent, induces heme oxygenase-1 and protects endothelial cells against oxidative stress. *Free Radic. Biol. Med.* **2000**, *28*, 1303–1312. [CrossRef]
22. Aggarwal, B.B. Targeting inflammation-induced obesity and metabolic diseases by curcumin and other nutraceuticals. *Annu. Rev. Nutr.* **2010**, *30*, 173–199. [CrossRef] [PubMed]
23. Kalpana, C.; Rajasekharan, K.; Menon, V.P. Modulatory effects of curcumin and curcumin analog on circulatory lipid profiles during nicotine-induced toxicity in Wistar rats. *J. Med. Food* **2005**, *8*, 246–250. [CrossRef]
24. Zbarsky, V.; Datla, K.P.; Parkar, S.; Rai, D.K.; Aruoma, O.I.; Dexter, D.T. Neuroprotective properties of the natural phenolic antioxidants curcumin and naringenin but not quercetin and fisetin in a 6-OHDA model of Parkinson's disease. *Free Radic. Res.* **2005**, *39*, 1119–1125. [CrossRef] [PubMed]
25. Lim, G.P.; Chu, T.; Yang, F.; Beech, W.; Frautschy, S.A.; Cole, G.M. The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse. *J. Neurosci.* **2001**, *21*, 8370–8377. [CrossRef] [PubMed]
26. Bhatia, N.K.; Srivastava, A.; Katyal, N.; Jain, N.; Khan, M.A.; Kundu, B.; Deep, S. Curcumin binds to the pre-fibrillar aggregates of Cu/Zn superoxide dismutase (SOD1) and alters its amyloidogenic pathway resulting in reduced cytotoxicity. *Biochim. Biophys. Acta* **2015**, *1854*, 426–436. [CrossRef]
27. Murakami, Y.; Ishii, H.; Takada, N.; Tanaka, S.; Machino, M.; Ito, S.; Fujisawa, S. Comparative anti-inflammatory activities of curcumin and tetrahydrocurcumin based on the phenolic O-H bond dissociation enthalpy, ionization potential and quantum chemical descriptor. *Anticancer Res.* **2008**, *28*, 699–707.
28. Ak, T.; Gulcin, I. Antioxidant and radical scavenging properties of curcumin. *Chem. Biol. Interact.* **2008**, *174*, 27–37. [CrossRef] [PubMed]
29. Ruby, A.J.; Kuttan, G.; Babu, K.D.; Rajasekharan, K.N.; Kuttan, R. Anti-tumour and antioxidant activity of natural curcuminoids. *Cancer Lett.* **1995**, *94*, 79–83. [CrossRef]
30. Reddy, A.C.; Lokesh, B.R. Studies on the inhibitory effects of curcumin and eugenol on the formation of reactive oxygen species and the oxidation of ferrous iron. *Mol. Cell. Biochem.* **1994**, *137*, 1–8. [CrossRef]
31. Khopde, S.M.; Priyadarsini, K.I.; Guha, S.N.; Satav, J.G.; Venkatesan, P.; Rao, M.N. Inhibition of radiation-induced lipid peroxidation by tetrahydrocurcumin: Possible mechanisms by pulse radiolysis. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 503–509. [CrossRef]
32. Lao, C.D.; Ruffin, M.T.; Normolle, D.; Heath, D.D.; Murray, S.I.; Bailey, J.M.; Boggs, M.E.; Crowell, J.; Rock, C.L.; Brenner, D.E. Dose escalation of a curcuminoid formulation. *BMC Complement. Altern. Med.* **2006**, *6*, 1–4. [CrossRef]

33. Priyadarsini, K.I.; Maity, D.K.; Naik, G.; Kumar, M.S.; Unnikrishnan, M.; Satav, J.; Mohan, H. Role of phenolic OH and methylene hydrogen on the free radical reactions and antioxidant activity of curcumin. *Free Radic. Biol. Med.* **2003**, *35*, 475–484. [CrossRef]

34. Scapagnini, G.; Colombrita, C.; Amadio, M.; D'Agata, V.; Arcelli, E.; Sapienza, M.; Quattrone, A.; Calabrese, V. Curcumin activates defensive genes and protects neurons against oxidative stress. *Antioxid. Redox Signal.* **2006**, *8*, 395–403. [CrossRef] [PubMed]

35. Stridh, M.H.; Correa, F.; Nodin, C.; Weber, S.G.; Blomstrand, F.; Nilsson, M.; Sandberg, M. Enhanced glutathione efflux from astrocytes in culture by low extracellular Ca 2+ and curcumin. *Neurochem. Res.* **2010**, *35*, 1231–1238. [CrossRef]

36. Shukla, P.K.; Khanna, V.K.; Khan, M.Y.; Srimal, R.C. Protective effect of curcumin against lead neurotoxicity in rat. *Hum. Exp. Toxicol.* **2003**, *22*, 653–658. [CrossRef] [PubMed]

37. Zhu, Y.-G.; Chen, X.-C.; Chen, Z.-Z.; Zeng, Y.-Q.; Shi, G.-B.; Su, Y.-H.; Peng, X. Curcumin protects mitochondria from oxidative damage and attenuates apoptosis in cortical neurons. *Acta Pharmacol. Sin.* **2004**, *25*, 1606–1612. [PubMed]

38. Shin, H.K.; Kim, J.; Lee, E.J.; Kim, S.H. Inhibitory effect of curcumin on motility of human oral squamous carcinoma YD-10B cells via suppression of ERK and NF-kappaB activations. *Phytother. Res. PTR* **2010**, *24*, 577–582. [CrossRef]

39. Dhandapani, K.M.; Mahesh, V.B.; Brann, D.W. Curcumin suppresses growth and chemoresistance of human glioblastoma cells via AP-1 and NFkappaB transcription factors. *J. Neurochem.* **2007**, *102*, 522–538. [CrossRef] [PubMed]

40. Wang, Z.W.; Zhang, Y.X.; Banerjee, S.; Li, Y.W.; Sarkar, F.H. Notch-1 down-regulation by curcumin is associated with the inhibition of cell growth and the induction of apoptosis in pancreatic cancer cells. *Cancer Am. Cancer Soc.* **2006**, *106*, 2503–2513. [CrossRef]

41. Prasad, C.P.; Rath, G.; Mathur, S.; Bhatnagar, D.; Ralhan, R. Potent growth suppressive activity of curcumin in human breast cancer cells: Modulation of Wnt/beta-catenin signaling. *Chem. Biol. Interact.* **2009**, *181*, 263–271. [CrossRef]

42. Chen, A.; Xu, J. Activation of PPAR{gamma} by curcumin inhibits Moser cell growth and mediates suppression of gene expression of cyclin D1 and EGFR. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2005**, *288*, G447–G456. [CrossRef]

43. Hayden, M.S.; Ghosh, S. Shared principles in NF-kappaB signaling. *Cell* **2008**, *132*, 344–362. [CrossRef]

44. Cui, J.G.; Li, Y.Y.; Zhao, Y.; Bhattacharjee, S.; Lukiw, W.J. Differential regulation of interleukin-1 receptor-associated kinase-1 (IRAK-1) and IRAK-2 by microRNA-146a and NF-kappaB in stressed human astroglial cells and in Alzheimer disease. *J. Biol. Chem.* **2010**, *285*, 38951–38960. [CrossRef]

45. Singh, S.; Aggarwal, B.B. Activation of Transcription Factor Nf-Kappa-B Is Suppressed by Curcumin (Diferulolylmethane). *J. Biol. Chem.* **1995**, *270*, 24995–25000. [CrossRef]

46. Aggarwal, S.; Takada, Y.; Singh, S.; Myers, J.N.; Aggarwal, B.B. Inhibition of growth and survival of human head and neck squamous cell carcinoma cells by curcumin via modulation of nuclear factor-kappaB signaling. *Int. J. Cancer* **2004**, *111*, 679–692. [CrossRef]

47. Reddy, S.; Aggarwal, B.B. Curcumin is a non-competitive and selective inhibitor of phosphorylase kinase. *FEBS Lett.* **1994**, *341*, 19–22. [CrossRef]

48. Hasmeda, M.; Polya, G.M. Inhibition of cyclic AMP-dependent protein kinase by curcumin. *Phytochemistry* **1996**, *42*, 599–605. [CrossRef]

49. Rajasingh, J.; Raikwar, H.P.; Muthian, G.; Johnson, C.; Bright, J.J. Curcumin induces growth-arrest and apoptosis in association with the inhibition of constitutively active JAK-STAT pathway in T cell leukemia. *Biochem. Biophys. Res. Commun.* **2006**, *340*, 359–368. [CrossRef] [PubMed]

50. Kim, G.Y.; Kim, K.H.; Lee, S.H.; Yoon, M.S.; Lee, H.J.; Moon, D.O.; Lee, C.M.; Ahn, S.C.; Park, Y.C.; Park, Y.M. Curcumin inhibits immunostimulatory function of dendritic cells: MAPKs and translocation of NF-kappa B as potential targets. *J. Immunol.* **2005**, *174*, 8116–8124. [CrossRef] [PubMed]

51. Rafiee, P.; Nelson, V.M.; Manley, S.; Wellner, M.; Floer, M.; Binion, D.G.; Shaker, R. Effect of curcumin on acidic pH-induced expression of IL-6 and IL-8 in human esophageal epithelial cells (HET-1A): Role of PKC, MAPKs, and NF-kappaB. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2009**, *296*, G388–G398. [CrossRef] [PubMed]

52. Johnson, S.M.; Gulhati, P.; Arrieta, I.; Wang, X.; Uchida, T.; Gao, T.; Evers, B.M. Curcumin inhibits proliferation of colorectal carcinoma by modulating Akt/mTOR signaling. *Anticancer Res.* **2009**, *29*, 3185–3190.

53. Shinojima, N.; Yokoyama, T.; Kondo, Y.; Kondo, S. Roles of the Akt/mTOR/p70S6K and ERK1/2 signaling pathways in curcumin-induced autophagy. *Autophagy* **2007**, *3*, 635–637. [CrossRef]

54. Kizhakkayil, J.; Thayyullathil, F.; Chathoth, S.; Hago, A.; Patel, M.; Galadari, S. Modulation of curcumin-induced Akt phosphorylation and apoptosis by PI3K inhibitor in MCF-7 cells. *Biochem. Biophys. Res. Commun.* **2010**, *394*, 476–481. [CrossRef] [PubMed]

55. Camacho-Barquero, L.; Villegas, I.; Sanchez-Calvo, J.M.; Talero, E.; Sanchez-Fidalgo, S.; Motilva, V.; Alarcon de la Lastra, C. Curcumin, a Curcuma longa constituent, acts on MAPK p38 pathway modulating COX-2 and iNOS expression in chronic experimental colitis. *Int. Immunopharmacol.* **2007**, *7*, 333–342. [CrossRef]

56. Cho, J.W.; Lee, K.S.; Kim, C.W. Curcumin attenuates the expression of IL-1beta, IL-6, and TNF-alpha as well as cyclin E in TNF-alpha-treated HaCaT cells; NF-kappaB and MAPKs as potential upstream targets. *Int. J. Mol. Med.* **2007**, *19*, 469–474. [PubMed]

57. Ranjan, D.; Chen, C.; Johnston, T.D.; Jeon, H.; Nagabhushan, M. Curcumin inhibits mitogen stimulated lymphocyte proliferation, NFkappaB activation, and IL-2 signaling. *J. Surg. Res.* **2004**, *121*, 171–177. [CrossRef]

58. Kobayashi, T.; Hashimoto, S.; Horie, T. Curcumin inhibition of Dermatophagoides farinea-induced interleukin-5 (IL-5) and granulocyte macrophage-colony stimulating factor (GM-CSF) production by lymphocytes from bronchial asthmatics. *Biochem. Pharmacol.* **1997**, *54*, 819–824. [CrossRef]

59. Cohen, A.N.; Veena, M.S.; Srivatsan, E.S.; Wang, M.B. Suppression of interleukin 6 and 8 production in head and neck cancer cells with curcumin via inhibition of Ikappa beta kinase. *Arch. Otolaryngol. Head Neck Surg.* **2009**, *135*, 190–197. [CrossRef]

60. Fahey, A.J.; Adrian Robins, R.; Constantinescu, C.S. Curcumin modulation of IFN-beta and IL-12 signalling and cytokine induction in human T cells. *J. Cell. Mol. Med.* **2007**, *11*, 1129–1137. [CrossRef] [PubMed]

61. Grandjean-Laquerriere, A.; Antonicelli, F.; Gangloff, S.C.; Guenounou, M.; Le Naour, R. UVB-induced IL-18 production in human keratinocyte cell line NCTC 2544 through NF-kappaB activation. *Cytokine* **2007**, *37*, 76–83. [CrossRef]

62. Tak, P.P.; Firestein, G.S. NF-kappaB: A key role in inflammatory diseases. *J. Clin. Investig.* **2001**, *107*, 7–11. [CrossRef]

63. Ganguli, M.; Chandra, V.; Kamboh, M.I.; Johnston, J.M.; Dodge, H.H.; Thelma, B.K.; Juyal, R.C.; Pandav, R.; Belle, S.H.; DeKosky, S.T. Apolipoprotein E polymorphism and Alzheimer disease—The Indo-US cross-national dementia study. *Arch. Neurol-Chic.* **2000**, *57*, 824–830. [CrossRef]

64. Alladi, P.A.; Mahadevan, A.; Yasha, T.C.; Raju, T.R.; Shankar, S.K.; Muthane, U. Absence of Age-Related Changes in Nigral Dopaminergic Neurons of Asian Indians: Relevance to Lower Incidence of Parkinson's Disease. *Neuroscience* **2009**, *159*, 236–245. [CrossRef] [PubMed]

65. Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G.; Group, P. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med.* **2009**, *6*, e1000097. [CrossRef]

66. Beitz, J.M. Parkinson's disease: A review. *Front. Biosci.* **2014**, *6*, 65–74. [CrossRef] [PubMed]

67. Dauer, W.; Przedborski, S. Parkinson's disease: Mechanisms and models. *Neuron* **2003**, *39*, 889–909. [CrossRef]

68. Sharma, N.; Nehru, B. Characterization of the lipopolysaccharide induced model of Parkinson's disease: Role of oxidative stress and neuroinflammation. *Neurochem. Int.* **2015**, *87*, 92–105. [CrossRef]

69. Schneider, R.B.; Iourinets, J.; Richard, I.H. Parkinson's disease psychosis: Presentation, diagnosis and management. *Neurodegener. Dis. Manag.* **2017**, *7*, 365–376. [CrossRef] [PubMed]

70. Olanow, C.W.; Wakeman, D.R.; Kordower, J.H. Peripheral alpha-synuclein and Parkinson's disease. *Mov. Disord. Off. J. Mov. Disord. Soc.* **2014**, *29*, 963–966. [CrossRef]

71. Cannon, J.R.; Greenamyre, J.T. Gene-environment interactions in Parkinson's disease: Specific evidence in humans and mammalian models. *Neurobiol. Dis.* **2013**, *57*, 38–46. [CrossRef]

72. Brichta, L.; Greengard, P.; Flajolet, M. Advances in the pharmacological treatment of Parkinson's disease: Targeting neurotransmitter systems. *Trends Neurosci.* **2013**, *36*, 543–554. [CrossRef] [PubMed]

73. Joe, B.; Vijaykumar, M.; Lokesh, B.R. Biological properties of curcumin-cellular and molecular mechanisms of action. *Crit. Rev. Food Sci. Nutr.* **2004**, *44*, 97–111. [CrossRef] [PubMed]

74. Fetoni, A.R.; Paciello, F.; Mezzogori, D.; Rolesi, R.; Eramo, S.L.; Paludetti, G.; Troiani, D. Molecular targets for anticancer redox chemotherapy and cisplatin-induced ototoxicity: The role of curcumin on pSTAT3 and Nrf-2 signalling. *Br. J. Cancer* **2015**, *113*, 1434–1444. [CrossRef]

75. Abe, Y.; Hashimoto, S.; Horie, T. Curcumin inhibition of inflammatory cytokine production by human peripheral blood monocytes and alveolar macrophages. *Pharmacol. Res.* **1999**, *39*, 41–47. [CrossRef] [PubMed]

76. Fang, X.; Fang, L.; Gou, S.; Cheng, L. Design and synthesis of dimethylaminomethyl-substituted curcumin derivatives/analogues: Potent antitumor and antioxidant activity, improved stability and aqueous solubility compared with curcumin. *Bioorganic Med. Chem. Lett.* **2013**, *23*, 1297–1301. [CrossRef]

77. Yu, S.; Wang, X.; He, X.; Wang, Y.; Gao, S.; Ren, L.; Shi, Y. Curcumin exerts anti-inflammatory and antioxidative properties in 1-methyl-4-phenylpyridinium ion (MPP(+))-stimulated mesencephalic astrocytes by interference with TLR4 and downstream signaling pathway. *Cell Stress Chaperones* **2016**, *21*, 697–705. [CrossRef]

78. Uguz, A.C.; Oz, A.; Naziroglu, M. Curcumin inhibits apoptosis by regulating intracellular calcium release, reactive oxygen species and mitochondrial depolarization levels in SH-SY5Y neuronal cells. *J. Recept. Signal Transduct. Res.* **2016**, *36*, 395–401. [CrossRef]

79. Dehghani, Z.; Meratan, A.A.; Saboury, A.A.; Nemat-Gorgani, M. alpha-Synuclein fibrillation products trigger the release of hexokinase I from mitochondria: Protection by curcumin, and possible role in pathogenesis of Parkinson's disease. *Biochim. Biophys. Acta. Biomembr.* **2020**, *1862*, 183251. [CrossRef] [PubMed]

80. Ramkumar, M.; Rajasankar, S.; Gobi, V.V.; Dhanalakshmi, C.; Manivasagam, T.; Justin Thenmozhi, A.; Essa, M.M.; Kalandar, A.; Chidambaram, R. Neuroprotective effect of Demethoxycurcumin, a natural derivative of Curcumin on rotenone induced neurotoxicity in SH-SY 5Y Neuroblastoma cells. *BMC Complement. Altern. Med.* **2017**, *17*, 217. [CrossRef] [PubMed]

81. Buratta, S.; Chiaradia, E.; Tognoloni, A.; Gambelunghe, A.; Meschini, C.; Palmieri, L.; Muzi, G.; Urbanelli, L.; Emiliani, C.; Tancini, B. Effect of Curcumin on Protein Damage Induced by Rotenone in Dopaminergic PC12 Cells. *Int. J. Mol. Sci.* **2020**, *21*, 2761. [CrossRef] [PubMed]

82. Wang, Y.L.; Ju, B.; Zhang, Y.Z.; Yin, H.L.; Liu, Y.J.; Wang, S.S.; Zeng, Z.L.; Yang, X.P.; Wang, H.T.; Li, J.F. Protective Effect of Curcumin Against Oxidative Stress-Induced Injury in Rats with Parkinson's Disease Through the Wnt/ beta-Catenin Signaling Pathway. *Cell. Physiol. Biochem.* **2017**, *43*, 2226–2241. [CrossRef] [PubMed]

83. Hirata, Y.; Ito, Y.; Takashima, M.; Yagyu, K.; Oh-Hashi, K.; Suzuki, H.; Ono, K.; Furuta, K.; Sawada, M. Novel Oxindole-Curcumin Hybrid Compound for Antioxidative Stress and Neuroprotection. *ACS Chem. Neurosci.* **2020**, *11*, 76–85. [CrossRef]

84. Pandareesh, M.D.; Shrivash, M.K.; Naveen Kumar, H.N.; Misra, K.; Srinivas Bharath, M.M. Curcumin Monoglucoside Shows Improved Bioavailability and Mitigates Rotenone Induced Neurotoxicity in Cell and Drosophila Models of Parkinson's Disease. *Neurochem. Res.* **2016**, *41*, 3113–3128. [CrossRef]

85. Khatri, D.K.; Juvekar, A.R. Neuroprotective effect of curcumin as evinced by abrogation of rotenone-induced motor deficits, oxidative and mitochondrial dysfunctions in mouse model of Parkinson's disease. *Pharmacol. Biochem. Behav.* **2016**, *150–151*, 39–47. [CrossRef]

86. Cui, Q.; Li, X.; Zhu, H. Curcumin ameliorates dopaminergic neuronal oxidative damage via activation of the Akt/Nrf2 pathway. *Mol. Med. Rep.* **2016**, *13*, 1381–1388. [CrossRef]

87. Nguyen, T.T.; Vuu, M.D.; Huynh, M.A.; Yamaguchi, M.; Tran, L.T.; Dang, T.P.T. Curcumin Effectively Rescued Parkinson's Disease-Like Phenotypes in a Novel Drosophila melanogaster Model with dUCH Knockdown. *Oxid. Med. Cell. Longev.* **2018**, *2018*, 2038267. [CrossRef] [PubMed]

88. Tonnies, E.; Trushina, E. Oxidative Stress, Synaptic Dysfunction, and Alzheimer's Disease. *J. Alzheimer's Dis.* **2017**, *57*, 1105–1121. [CrossRef] [PubMed]

89. Giau, V.V.; Bagyinszky, E.; Yang, Y.S.; Youn, Y.C.; An, S.S.A.; Kim, S.Y. Genetic analyses of early-onset Alzheimer's disease using next generation sequencing. *Sci. Rep.* **2019**, *9*, 8368. [CrossRef] [PubMed]

90. Sadigh-Eteghad, S.; Sabermarouf, B.; Majdi, A.; Talebi, M.; Farhoudi, M.; Mahmoudi, J. Amyloid-beta: A crucial factor in Alzheimer's disease. *Med Princ. Pract.* **2015**, *24*, 1–10. [CrossRef] [PubMed]

91. Butterfield, D.A.; Swomley, A.M.; Sultana, R. Amyloid beta-peptide (1-42)-induced oxidative stress in Alzheimer disease: Importance in disease pathogenesis and progression. *Antioxid. Redox Signal.* **2013**, *19*, 823–835. [CrossRef] [PubMed]

92. Mondragon-Rodriguez, S.; Perry, G.; Zhu, X.; Moreira, P.I.; Acevedo-Aquino, M.C.; Williams, S. Phosphorylation of tau protein as the link between oxidative stress, mitochondrial dysfunction, and connectivity failure: Implications for Alzheimer's disease. *Oxid. Med. Cell. Longev.* **2013**, *2013*, 940603. [CrossRef] [PubMed]

93. Oakley, H.; Cole, S.L.; Logan, S.; Maus, E.; Shao, P.; Craft, J.; Guillozet-Bongaarts, A.; Ohno, M.; Disterhoft, J.; Van Eldik, L.; et al. Intraneuronal beta-amyloid aggregates, neurodegeneration, and neuron loss in transgenic mice with five familial Alzheimer's disease mutations: Potential factors in amyloid plaque formation. *J. Neurosci.* **2006**, *26*, 10129–10140. [CrossRef]

94. Wang, X.; Wang, W.; Li, L.; Perry, G.; Lee, H.G.; Zhu, X. Oxidative stress and mitochondrial dysfunction in Alzheimer's disease. *Biochim. Biophys. Acta* **2014**, *1842*, 1240–1247. [CrossRef] [PubMed]

95. De Felice, F.G.; Velasco, P.T.; Lambert, M.P.; Viola, K.; Fernandez, S.J.; Ferreira, S.T.; Klein, W.L. Abeta oligomers induce neuronal oxidative stress through an N-methyl-D-aspartate receptor-dependent mechanism that is blocked by the Alzheimer drug memantine. *J. Biol. Chem.* **2007**, *282*, 11590–11601. [CrossRef] [PubMed]

96. Reddy, P.H.; Manczak, M.; Yin, X.; Grady, M.C.; Mitchell, A.; Tonk, S.; Kuruva, C.S.; Bhatti, J.S.; Kandimalla, R.; Vijayan, M.; et al. Protective Effects of Indian Spice Curcumin Against Amyloid-beta in Alzheimer's Disease. *J. Alzheimer's Dis.* **2018**, *61*, 843–866. [CrossRef]

97. Fidelis, E.M.; Savall, A.S.P.; da Luz Abreu, E.; Carvalho, F.; Teixeira, F.E.G.; Haas, S.E.; Bazanella Sampaio, T.; Pinton, S. Curcumin-Loaded Nanocapsules Reverses the Depressant-Like Behavior and Oxidative Stress Induced by beta-Amyloid in Mice. *Neuroscience* **2019**, *423*, 122–130. [CrossRef]

98. Qian, W.; Li, H.; Pan, N.; Zhang, C. Curcumin Treatment is Associated with Increased Expression of the N-Methyl-D-Aspartate Receptor (NMDAR) Subunit, NR2A, in a Rat PC12 Cell Line Model of Alzheimer's Disease Treated with the Acetyl Amyloid-beta Peptide, Abeta(25–35). *Med. Sci. Monit.* **2018**, *24*, 2693–2699. [CrossRef] [PubMed]

99. Jaroonwitchawan, T.; Chaicharoenaudomrung, N.; Namkaew, J.; Noisa, P. Curcumin attenuates paraquat-induced cell death in human neuroblastoma cells through modulating oxidative stress and autophagy. *Neurosci. Lett.* **2017**, *636*, 40–47. [CrossRef]

100. Shi, L.Y.; Zhang, L.; Li, H.; Liu, T.L.; Lai, J.C.; Wu, Z.B.; Qin, J. Protective effects of curcumin on acrolein-induced neurotoxicity in HT22 mouse hippocampal cells. *Pharmacol. Rep.* **2018**, *70*, 1040–1046. [CrossRef] [PubMed]

101. Morales, I.; Cerda-Troncoso, C.; Andrade, V.; Maccioni, R.B. The Natural Product Curcumin as a Potential Coadjuvant in Alzheimer's Treatment. *J. Alzheimer's Dis.* **2017**, *60*, 451–460. [CrossRef]

102. Buccarello, L.; Dragotto, J.; Iorio, F.; Hassanzadeh, K.; Corbo, M.; Feligioni, M. The pivotal role of SUMO-1-JNK-Tau axis in an in vitro model of oxidative stress counteracted by the protective effect of curcumin. *Biochem. Pharmacol.* **2020**, *178*, 114066. [CrossRef]

103. Jairani, P.S.; Aswathy, P.M.; Krishnan, D.; Menon, R.N.; Verghese, J.; Mathuranath, P.S.; Gopala, S. Apolipoprotein E Polymorphism and Oxidative Stress in Peripheral Blood-Derived Macrophage-Mediated Amyloid-Beta Phagocytosis in Alzheimer's Disease Patients. *Cell. Mol. Neurobiol.* **2019**, *39*, 355–369. [CrossRef] [PubMed]

104. Song, X.J.; Zhou, H.Y.; Sun, Y.X.; Huang, H.C. Inhibitory effects of curcumin on H2O2-induced cell damage and APP expression and processing in SH-SY5Y cells transfected with APP gene with Swedish mutation. *Mol. Biol. Rep.* **2020**, *47*, 2047–2059. [CrossRef] [PubMed]

105. Yan, F.S.; Sun, J.L.; Xie, W.H.; Shen, L.; Ji, H.F. Neuroprotective Effects and Mechanisms of Curcumin-Cu(II) and -Zn(II) Complexes Systems and Their Pharmacological Implications. *Nutrients* **2017**, *10*, 28. [CrossRef]

106. Djiokeng Paka, G.; Doggui, S.; Zaghmi, A.; Safar, R.; Dao, L.; Reisch, A.; Klymchenko, A.; Roullin, V.G.; Joubert, O.; Ramassamy, C. Neuronal Uptake and Neuroprotective Properties of Curcumin-Loaded Nanoparticles on SK-N-SH Cell Line: Role of Poly(lactide-co-glycolide) Polymeric Matrix Composition. *Mol. Pharm.* **2016**, *13*, 391–403. [CrossRef]

107. Xu, J.; Zhou, L.; Weng, Q.; Xiao, L.; Li, Q. Curcumin analogues attenuate Abeta25-35-induced oxidative stress in PC12 cells via Keap1/Nrf2/HO-1 signaling pathways. *Chem. Biol. Interact.* **2019**, *305*, 171–179. [CrossRef] [PubMed]

108. Pinkaew, D.; Changtam, C.; Tocharus, C.; Govitrapong, P.; Jumnongprakhon, P.; Suksamrarn, A.; Tocharus, J. Association of Neuroprotective Effect of Di-O-Demethylcurcumin on Abeta25-35-Induced Neurotoxicity with Suppression of NF-kappaB and Activation of Nrf2. *Neurotox. Res.* **2016**, *29*, 80–91. [CrossRef] [PubMed]

109. Orteca, G.; Tavanti, F.; Bednarikova, Z.; Gazova, Z.; Rigillo, G.; Imbriano, C.; Basile, V.; Asti, M.; Rigamonti, L.; Saladini, M.; et al. Curcumin derivatives and Abeta-fibrillar aggregates: An interactions' study for diagnostic/therapeutic purposes in neurodegenerative diseases. *Bioorganic. Med. Chem.* **2018**, *26*, 4288–4300. [CrossRef]

110. Huang, H.C.; Zheng, B.W.; Guo, Y.; Zhao, J.; Zhao, J.Y.; Ma, X.W.; Jiang, Z.F. Antioxidative and Neuroprotective Effects of Curcumin in an Alzheimer's Disease Rat Model Co-Treated with Intracerebroventricular Streptozotocin and Subcutaneous D-Galactose. *J. Alzheimer's Dis.* **2016**, *52*, 899–911. [CrossRef]

111. Sadegh Malvajerd, S.; Izadi, Z.; Azadi, A.; Kurd, M.; Derakhshankhah, H.; Sharifzadeh, M.; Akbari Javar, H.; Hamidi, M. Neuroprotective Potential of Curcumin-Loaded Nanostructured Lipid Carrier in an Animal Model of Alzheimer's Disease: Behavioral and Biochemical Evidence. *J. Alzheimer's Dis.* **2019**, *69*, 671–686. [CrossRef]

112. Lu, H.; Le, W.D.; Xie, Y.Y.; Wang, X.P. Current Therapy of Drugs in Amyotrophic Lateral Sclerosis. *Curr. Neuropharmacol.* **2016**, *14*, 314–321. [CrossRef]

113. Swinnen, B.; Robberecht, W. The phenotypic variability of amyotrophic lateral sclerosis. *Nat. Rev. Neurol.* **2014**, *10*, 661–670. [CrossRef]

114. Shaw, P.J. Molecular and cellular pathways of neurodegeneration in motor neurone disease. *J. Neurol. Neurosurg. Psychiatry* **2005**, *76*, 1046–1057. [CrossRef] [PubMed]

115. Liu, J.; Wang, F. Role of Neuroinflammation in Amyotrophic Lateral Sclerosis: Cellular Mechanisms and Therapeutic Implications. *Front. Immunol.* **2017**, *8*, 1005. [CrossRef]

116. Thonhoff, J.R.; Simpson, E.P.; Appel, S.H. Neuroinflammatory mechanisms in amyotrophic lateral sclerosis pathogenesis. *Curr. Opin. Neurol.* **2018**, *31*, 635–639. [CrossRef]

117. Hong, K.; Li, Y.; Duan, W.; Guo, Y.; Jiang, H.; Li, W.; Li, C. Full-length TDP-43 and its C-terminal fragments activate mitophagy in NSC34 cell line. *Neurosci. Lett.* **2012**, *530*, 144–149. [CrossRef] [PubMed]

118. Rao, S.D.; Weiss, J.H. Excitotoxic and oxidative cross-talk between motor neurons and glia in ALS pathogenesis. *Trends Neurosci.* **2004**, *27*, 17–23. [CrossRef]

119. Duffy, L.M.; Chapman, A.L.; Shaw, P.J.; Grierson, A.J. The role of mitochondria in the pathogenesis of amyotrophic lateral sclerosis. *Neuropathol. Appl. Neurobiol.* **2011**, *37*, 336–352. [CrossRef]

120. Sargsyan, S.A.; Monk, P.N.; Shaw, P.J. Microglia as potential contributors to motor neuron injury in amyotrophic lateral sclerosis. *Glia* **2005**, *51*, 241–253. [CrossRef] [PubMed]

121. Blackburn, D.; Sargsyan, S.; Monk, P.N.; Shaw, P.J. Astrocyte function and role in motor neuron disease: A future therapeutic target? *Glia* **2009**, *57*, 1251–1264. [CrossRef] [PubMed]

122. Gurney, M.E.; Cutting, F.B.; Zhai, P.; Doble, A.; Taylor, C.P.; Andrus, P.K.; Hall, E.D. Benefit of vitamin E, riluzole, and gabapentin in a transgenic model of familial amyotrophic lateral sclerosis. *Ann. Neurol.* **1996**, *39*, 147–157. [CrossRef] [PubMed]

123. Matthews, R.T.; Yang, L.; Browne, S.; Baik, M.; Beal, M.F. Coenzyme Q10 administration increases brain mitochondrial concentrations and exerts neuroprotective effects. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 8892–8897. [CrossRef]

124. Lu, J.; Duan, W.; Guo, Y.; Jiang, H.; Li, Z.; Huang, J.; Hong, K.; Li, C. Mitochondrial dysfunction in human TDP-43 transfected NSC34 cell lines and the protective effect of dimethoxy curcumin. *Brain Res. Bull.* **2012**, *89*, 185–190. [CrossRef] [PubMed]

125. Duan, W.; Guo, Y.; Xiao, J.; Chen, X.; Li, Z.; Han, H.; Li, C. Neuroprotection by monocarbonyl dimethoxycurcumin C: Ameliorating the toxicity of mutant TDP-43 via HO-1. *Mol. Neurobiol.* **2014**, *49*, 368–379. [CrossRef]

126. Jiang, H.; Tian, X.; Guo, Y.; Duan, W.; Bu, H.; Li, C. Activation of nuclear factor erythroid 2-related factor 2 cytoprotective signaling by curcumin protect primary spinal cord astrocytes against oxidative toxicity. *Biol. Pharm. Bull.* **2011**, *34*, 1194–1197. [CrossRef]

127. Chico, L.; Ienco, E.C.; Bisordi, C.; Lo Gerfo, A.; Petrozzi, L.; Petrucci, A.; Mancuso, M.; Siciliano, G. Amyotrophic Lateral Sclerosis and Oxidative Stress: A Double-Blind Therapeutic Trial After Curcumin Supplementation. *CNS Neurol. Disord. Drug Targets* **2018**, *17*, 767–779. [CrossRef] [PubMed]

128. Ahmadi, M.; Agah, E.; Nafissi, S.; Jaafari, M.R.; Harirchian, M.H.; Sarraf, P.; Faghihi-Kashani, S.; Hosseini, S.J.; Ghoreishi, A.; Aghamollaii, V.; et al. Safety and Efficacy of Nanocurcumin as Add-On Therapy to Riluzole in Patients With Amyotrophic Lateral Sclerosis: A Pilot Randomized Clinical Trial. *Neurotherapeutics* **2018**, *15*, 430–438. [CrossRef]