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Inflammopharmacology

REVIEW

The regulating effect of curcumin on NF-κB pathway in neurodegenerative diseases: a review of the underlying mechanisms

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Abstract

Neurodegenerative diseases are part of the central nervous system (CNS) disorders that indicate their presence with neuronal loss, neuroinflammation, and increased oxidative stress. Several pathophysiological factors and biomarkers are involved in this inflammatory process causing these neurological disorders. The nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is an inflammation element, which induced transcription and appears to be one of the important players in physiological procedures, especially nervous disorders. NF-κB can impact upon series of intracellular actions and induce or inhibit many inflammation-related pathways. Multiple reports have focused on the modification of NF-κB activity, controlling its expression, translocation, and signaling pathway in neurodegenerative disorders and injuries like Alzheimer's disease (AD), spinal cord injuries (SCI), and Parkinson's disease (PD). Curcumin has been noted to be a popular anti-oxidant and anti-inflammatory substance and is the foremost natural compound produced by turmeric. According to various studies, when playing an anti-inflammatory role, it interacts with several modulating proteins of long-standing disease signaling pathways and has an unprovocative consequence on pro-inflammatory cytokines. This review article determined to figure out curcumin's role in limiting the promotion of neurodegenerative disease via influencing the NF-κB signaling route. Preclinical studies were gathered from plenty of scientific platforms including PubMed, Scopus, Cochrane, and Google Scholar to evaluate this hypothesis. Extracted findings from the literature review explained the repressing impact of Curcumin on the NF-κB signaling pathway and, occasionally down-regulating the cytokine expression. Yet, there is an essential need for further analysis and specific clinical experiments to fully understand this subject.

Keywords Alzheimer's disease · Parkinson's disease · Neuroinflammation · Herbal medicine · Phytopharmacology

Abbreviations

MPP+	1-Methyl-4-phenylpyridinium ion
SNCA	A-Synuclein
AD	Alzheimer disease
ALS	Amyotrophic lateral sclerosis
ApoE4-Tg	ApoE4 transgenic
APOE4	Apolipoprotein E4
BMS	Basso mouse scale
BACE1	Beta-Secretase 1
BDNF	Brain-derived neurotrophic factor
CAMKII	Calcium–calmodulin (CaM)-dependent protein kinase II

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CREB	CAMP response element-binding protein
CAT	Catalase
CNS	Central nervous system
ChAT	Choline acetyltransferase
CSPG	Chondroitin sulfate proteoglycan
Co-Q10	Coenzyme Q10
CRP	C-reactive protein
CXCL10	C-X-C motif chemokine ligand 10
COX-2	Cyclooxygenase 2
DAMP	Damage-associated molecular patterns
DCM	Diabetic cardiomyopathy
DR	Diabetic retinopathy
DMSO	Dimethyl sulfoxide
EMSA	Electrophoretic mobility shift assay
ER	Endoplasmic reticulum
ELISA	Enzyme-linked immunosorbent assay
GI	Gastrointestinal
GFAP	Glial fibrillary acidic protein
GSH	Glutathione
GPx	Glutathione peroxidase
HO-1	Heme oxygenase 1
HTT	Huntingtin protein
HD	Huntington's disease
iNOS	Inducible nitric oxide synthase
IRF3	Interferon regulatory factor 3
IL	Interleukin
i.p.	Intraperitoneal
IP	Intra-peritoneal
IV	Intravenous
Iba1	Ionized calcium-binding adapter molecule 1
IKKβ	IκB Kinase β
KM	Kun-Ming
LRRK2	Leucine-rich repeat kinase 2
LBD	Lewy body dementia
LTP	Like long-term potentiation
LUBAC	Linear ubiquitin chain assembly complex
LPO	Lipid peroxidation
LPS	Lipopolysaccharides
LOX	Lipoxygenase
LTD	Long-term depression
LUBAC	Linear ubiquitin chain assembly complex
MIP-1α	Macrophage inflammatory protein-1alpha
mTOR	Mammalian target of rapamycin
MnSOD	Manganese superoxide dismutase
MEM	Memantine
MCAO	Middle cerebral artery occlusion
mEPSCs	Miniature excitatory post-synaptic currents
MAPK	Mitogen-activated protein kinase
MKK6	Mitogen-activated protein kinase kinase 6
MCP-1	Monocyte chemoattractant protein 1
MS	Multiple sclerosis
MyD88	Myeloid differentiation primary response 88
NGF	Nerve growth factor
ND	Neurodegenerative disease
NO	Nitric oxide
Nrf2	Nuclear factor erythroid 2-related factor 2/ antioxidant responsive element
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
OPTN	Optineurin
p38MAPK	P38 mitogen-activated protein kinases
PAMP	Pathogen-associated molecular patterns
PO	*Per os*
Prdx6	Peroxiredoxin6
PPARγ	Peroxisome proliferator-activated receptor γ
PBS	Phosphate-buffered saline
PI3K	Phosphoinositide-3-kinase
PSD-95	Postsynaptic density protein 95
PFC	Prefrontal cortex
PSEN	Presenilin
PGE2	Prostaglandin E2
Akt	Protein kinase B
AP-1	Activator protein 1
PKC-δ	Protein kinase C-delta
PINK1	PTEN-induced putative kinase 1
ROS	Reactive oxygen species
RANTES	Regulated upon Activation Normal T Cell Expressed, and Secreted
RT-PCR	Reverse transcription polymerase chain reaction
SCO	Scopolamine hydrobromide
SNP	Single-nucleotide polymorphisms
SCI	Spinal cord injury
SPAR	Spine-associated Rap GTPase-activating protein
SOX9	SRY-Box Transcription Factor 9
SN	Substantia nigra
SOD	Superoxide dismutase
TDP-43	TAR DNA-binding protein 43
TAK1	TGF-b-activated kinase 1
TJ	Tight junction protein
TLR4	Toll-like receptor 4
TGF	Transforming growth factor
TIRF	Transmucosal immediate-release fentanyl
TBI	Traumatic brain injury
TREM2	Triggering receptor expressed on myeloid cells 2
Tau	Tubulin-associated unit
TRAF6	Tumor necrosis factor receptor (TNFR)-associated factor 6
TNF-α	Tumor necrosis factor-α
T2DM	Type 2 diabetes mellitus

VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
ZO-1	Zonula occludens 1
α-SMA	α-Smooth muscle actin
Aβ	β-Amyloid peptides
APACHE	Acute physiology and chronic health evaluation
ADAS-Cog	Alzheimer's disease Assessment Scale–cognitive subscale
ADCS-ADL	Alzheimer's disease Cooperative society Study-Activities of Daily Living

Introduction

Neurodegenerative diseases (ND), or continuous loss of neurons' function or structure, are a set of features that gradually lead to neural dysfunction or neural loss. Huntington's disease (HD), spinal cord injury (SCI), Parkinson's disease (PD), and Alzheimer's disease (AD) are among the prevalent central nervous system (CNS) diseases. Neuro-inflammation is considered a common driver of several neurological impairments, which may be induced by trauma, toxic metabolites, and infections, for instance (Kumar et al. 2015b). Furthermore, reports have shown that inflammation cascades affect CNS-exerted functions, i.e., movement, memory and learning, judgment, cognition, and coordination, as well as neuron vitality and structures. In this regard, selective neurons have undergone experiments to obtain more information about the molecular pathogenesis of neurodegenerative diseases (Ransohoff 2016). Multiple studies have demonstrated the capacity of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) production in the development of ND, such as amyotrophic lateral sclerosis (ALS), Huntington's, ischemia, and AD (Fridmacher et al. 2003).

NF-κB is one of the pathways that is involved in neurodegeneration processes. NF-κB is an inflammatory transcription element that is composed of five family members entitled RelA (p65), RelB, c-Rel, NF-κB1 (p105/p50), and NF-κB2 (p100/p52). Stimulation of NF-κB pathway results in the nuclear translocation of the NF-κB p52/RelB or p50/p65 dimers, as well as anti-apoptotic gene expression regulation via these dimers (Sun et al. 2022). NF-κB can be actuated by three distinct pathways: atypical, canonical, and non-canonical. The apparent contradictory effects of these pathways are due to factors for instance the pathway provocations, the cellular position, and the cell sort. During the canonical pathway, pro-inflammatory genes undergo temporary and immediate transcription. In contrast, non-canonical pathway involves protein synthesis through tumor necrosis factor receptors (TNFR) in response to activated stimuli (Mincheva-Tasheva and Soler 2013). RelA/p50 heterodimers Observation in astrocytes, Schwann cells, microglia, also neurons in many portions of promoting and mature nervous system elucidated the participation of NF-κB, hence examining the role of NF-κB in ND was initiated (Mincheva et al. 2011). According to these analysis, cytokines and chemokines from microglia are released by NF-κB expression, contributing to neural inflammations (Thawkar and Kaur 2019). According to NF-κB's broad presence in reacting to cellular inflammation, it has turned to an appealing intention to study (Chiarini et al. 2020). Various research endeavors have been accomplished to fully understand the underlying procedures by which NF-κB plays a part in development of NDs. Moreover, multiple chemical and phytochemicals have been tested for their possible impact regulation of NF-κB pathways. One of the phytochemicals that has been vastly investigated due to its anti-inflammatory features is curcumin. The effect of curcumin in the reduction of undesired activation of NF-κB pathway during inflammation has been demonstrated via many evaluations. Curcumin is known as an active component of a plant called *Curcuma longa* L. This plant, also recognized as turmeric, is an eternal herb from the *Zingiberaceae* family with more than 100 discovered species around the world. Upon the investigation of the rhizomes of turmeric, a yellow pigment known as curcumin was isolated. Curcumin is not only a food-coloring agent, spice, or dietary supplement, but also has been categorized as an herbal medicament (Aggarwal and Sung 2009). Curcumin has a polyphenolic structure and has given the IUPAC ID of (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione)11 by chemical (Fig. 1) (Priyadarsini 2014).

The antimicrobial, antineoplastic, anti-inflammatory, and antioxidant features of curcumin in different organs have made it a considerable option for the prohibition

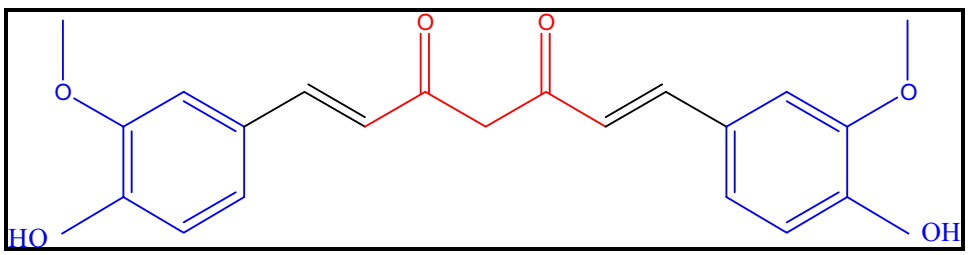

Fig. 1 Curcumin chemical structure and active functional groups (blue: methoxy phenolic groups, red: β-diketone)

or deferment of neurodegenerative diseases (Bhat et al. 2019). However, the low bioavailability and the absorption rate of oral intake of curcumin, along with its high biotransformation and elimination rate, have been of great concern (Rachmawati et al. 2013). Therefore, a wide range of surveys have focused on improving the pharmacokinetics (PK) and delivery systems of curcumin (Anand et al. 2008b).

Recently, extensive surveys have been carried out to discover the pharmacological aim of curcumin to define the molecular processes stimulated through this composite (Basnet and Skalko-Basnet 2011). Evidence shows that curcumin can interact with various factors involved in the inflammation process, including p38 mitogen-activated protein kinase (MAPK), vascular endothelial growth factor (VEGF), glutathione (GSH), p-Tau (p-τ), reactive oxygen species (ROS), cyclin D1, cyclooxygenase-2 (COX-2), tumor necrosis factor- (TNF-) α, inducible nitric oxide synthase (iNOS), NF-κB, DNA (cytosine-5)-methyltransferase-1, nuclear factor E2-related factor 2 (Nrf2), β-catenin, cytosolic PLA2, FOXO3,5-lipoxygenase (5-LOX), and prostaglandin E2 (PGE2), which can activate signaling pathways relevant to chronic diseases (Anand et al. 2008a). Curcumin diminishes the expression of many proinflammatory intracellular inflammatory systems like hypoxia-inducible factor-1 (HIF-1), proinflammatory cytokines in particular TNF-α, interleukin-(IL-)6, and IL-1β, iNOS, and NF-κB, at the molecular level. It also exerts an antiapoptotic impression via a decrease of the bax/Bcl-2 ratio and overexpressing B cell lymphoma 2 (Bcl-2). As an antioxidant, curcumin provokes the nuclear factor erythroid 2-related factor 2/antioxidant responsive element (Nrf2/ARE) pathway, suppresses ROS and mitochondrial cell death pathway, elevates Cu–Zn superoxide dismutase (SOD), and reinstates deficiency of the Glutathione (GSH) levels (Fu et al. 2015).

Unlike the known interaction with functional proteins, the benefits of curcumin at the system levels are still unclear (Grynkiewicz and Ślifirski 2012). Several investigations have declared a lower occurrence of neurological disorders in people consuming curcumin (Sharma et al. 2017). Considering this information, curcumin could be assumed as a prospective candidate for precluding neurodegenerative disease (Garcia-Alloza et al. 2007).

To explicate the defensive influence of curcumin signaling pathways in neurodegenerative diseases, multiple studies have been designed. Recently, curcumin has been exhibited to impede the NF-κB ways as it was a trigger for neuro-inflammation occurrence (Schmidt-Ullrich et al. 1996; Aggarwal and Harikumar 2009). Therefore, this review aims at discovering the mechanisms by which curcumin prevents different kinds of NDs by NF-κB pathway modulation.

Search strategy

Research findings were assembled from scientific databases involving Google Scholar, PubMed, Scopus, and Cochrane Library for, in vitro and in vivo research disclosed in English language from 1997 to 2023 Search words of titles include "Curcumin longa" OR "Curcuma" AND "Neurodegenerative diseases" AND "NF-κB pathway" in order to collect related articles. In the next step, the full-text of each publication was read as well as investigated to find the proper information, which resulted in the elimination of some articles in this stage. Finally, based on available papers, the process of data extraction started.

Results

Curcumin: an overview of the pharmacological actions

Curcumin, with a diferuloylmethane structure, is a natural compound with a variety of functional groups including ketone, phenol, enone, and aromatic ether. It has been proved that methoxy phenolic groups and β-diketone are the active functional groups of this phytochemical that may engage in oxidation (Fig. 1). It is also a diarylheptanoid isolated from *C. longa*, which is native to South Asia (Kumar et al. 2015a).

Curcumin is a well-known spice for coloring and flavoring foods. It is also used in the cosmetic industry. Numerous studies have evaluated curcumin's therapeutic and biological activities. Results have shown that curcumin can ameliorate liver ailments, cardiovascular diseases, urinary tract infections, rheumatoid arthritis, eye diseases namely, conjunctivitis and chronic anterior uveitis, different malignancies including lung, skin, breast, prostate, gastrointestinal, and many neurological diseases including PD, epilepsy, AD, Multiple sclerosis (MS). It also has wound-healing properties (Sharifi-Rad et al. 2020).

The common routes of administration of curcumin for many in vivo and clinical studies are gavage, intra-peritoneal (i.p.), and intravenous (Pivari et al.). However, it has been declared that curcumin's serum level was higher when it was utilized IV or IP. This may be due to its hydrophobicity which is one of the reasons for its low bioavailability. Curcumin is poorly absorbed in the gastrointestinal (GI) tract, rapidly metabolized in the liver and intestine by sulfation and glucuronidation, and is mainly defecated when it is administrated orally (Anand et al. 2007). Different tactics have been assessed to ameliorate curcumin's bioavailability, from installing curcumin in nanoparticles, phospholipid complexes, liposomes, and micelles, to searching for analogs with higher bioavailability i.e., curcuminoids. For example, nanoparticle formulations of curcumin can enhance water

solubility and secure intracellular delivery. Micelles can increase GI absorption, and conjugation with piperine, an alkaloid from black pepper, can slow down its metabolism by suppressing of glucuronidation in the intestine and liver (Nocito et al. 2021).

Most of the curative impacts of curcumin are due to its activity against inflammation and oxidative stress. It is also beneficial in autoimmune diseases, such as MS, regulating cytokines like interleukin-12 (IL-12) and IL-6. Curcumin can affect oxidative stress via scavenging ROS, suppressing enzymes that can generate ROS, such as COX, lipoxygenase (LOX), and xanthine oxidase, up-regulating antioxidant enzymes like SOD, glutathione peroxidase (GPx), catalase (CAT), and heme oxygenase 1 (HO-1), which consequently reduce lipid peroxidation (LPO) (23). These activities can be related to the Nrf2 pathway excitement that can increase antioxidant enzymes and decrease oxidative stress (Ashrafizadeh et al. 2020; Khayatan et al. 2022). Moreover, curcumin can down-regulate the COX pathway which is involved in oncogenesis and inflammation. It can also inhibit the NF-κB pathway so that pro-inflammatory cytokines including IL-8, IL-1β, IL-6, IL-2, TNF-α, PGE2, macrophage inflammatory protein-1alpha (MIP-1α), monocyte chemoattractant protein 1 (MCP-1) and C-reactive protein (CRP) decrease (Sharifi-Rad et al. 2020; Menon and Sudheer 2007). Furthermore, curcumin can down-regulate toll-like receptor 4 (TLR4)/tumor necrosis factor receptor (TNFR)-associated factor 6 (TRAF6)/MAPK pathway, which causes the reduction of pro-inflammatory mediators (Yang et al. 2017).

Several experiments manifested that curcumin ameliorates inflammation and oxidative stress in type 2 diabetes mellitus (T2DM) and it can inhibit the NF-κB signaling pathway that is one of the pathways involved in inflammation. Also, it can regulate lipid metabolism. Additionally, curcumin attenuates T2DM-related diseases including diabetic neuropathy and retinopathy (Pivari et al. 2019).

Various studies on several kinds of cancers like lung, liver, and breast declared that curcumin can suppress the NF-κB pathway. In cancers, curcumin reduces vascular endothelial growth factor receptor (VEGFR) by down-regulation of the phosphoinositide-3-kinase (PI3K)/protein kinase B (Akt) pathway. Thus, angiogenesis is suppressed. Therefore, by the management of NF-κB and activator protein 1 (AP-1), the VEGF level declines (Shanmugam et al. 2015).

Curcumin can act as a neuroprotective compound by scavenging ROS, inducing the Nrf2 pathway, suppressing the NF-κB pathway, decreasing inflammatory cytokines, and affecting other related pathways in the CNS. For instance, an in vivo experiment by Huang et al. in 2018 on Sprague Dawley (SD) male rats with middle cerebral artery occlusion (MCAO) elucidated that curcumin can regulate TLR4/p38/MAPK pathway and inhibit inflammation. They also declared that curcumin can modulate the PI3K/Akt/mammalian target of the rapamycin (mTOR) pathway and lower autophagy in cerebral ischemia–reperfusion (Huang et al. 2018). Another experiment on AD revealed that curcumin decreases microglia and astrocyte activation, suppresses the NF-κB pathway, and elevates peroxisome proliferators-activated receptor γ (PPARγ) expression. These data suggest that curcumin is a potential bioactive molecule against neurodegenerative disorders (Sharifi-Rad et al. 2020).

NF-κB signaling pathways in neurodegenerative disorders

The NF-κB family and its activation pathways

NF-κB contains a group of five transcription factors engaged in different cellular processes, with a notable function in inflammation. This family includes NF-κB1 (p105/p50), NF-κB2 (p100/p52), RelA (p65), RelB, and c-Rel. NF-κB stimulation prompts the transcription of specific genes the majority of which are pro-inflammatory genes. The canonical pathway is well-studied and crucial in inflammatory reactions, a key feature in the development of AD. Initially inert, the p65/p50 dimers in the canonical pathway are confined in the cytoplasm by IκB. Just after encountering pro-inflammatory signals like cytokines, danger-associated molecular patterns, and pathogens, the p65/p50 dimers are liberated from IκB owing to a phosphorylation process that leads to IκB's degradation. Following this, p65/p50 translocates to the nucleus, binding to its target motif (κB motif), and activating NF-κB target genes. Conversely, the noncanonical pathway is induced by certain tumor necrosis factor Receptor (TNFR) superfamily members, triggering NF-κB-inducing kinase (NIK). NIK phosphorylates IκB kinase alpha (IKKα), which then phosphorylates p100's C-terminal, generating p52. During the post-phosphorylation cascade, p52/RelB moves to the nucleus, initiating NF-κB target gene expression that influences immune cell development (Sun 2011). In the nervous system, several methods can trigger stimulation of the NF-κB pathway. The well-known IKK-dependent processes encompass both non-canonical and canonical pathways. However, a novel IKK-independent mechanism, the atypical pathway, has also been identified (Bender et al. 1998). Typically, the non-canonical and the canonical pathways exhibit two key distinctions: the NF-κB dimer translocation to the nucleus (RelA/p50 for canonical, RelB/p52 for non-canonical) and the involvement of IκB in their activation (IκB-dependent for canonical, IκB-independent for non-canonical). NF-κB activation in the cells through the canonical pathway is the most common pathway of its activation (Heissmeyer et al. 1999).

The "atypical pathway" operates independently of IKK but relies on IκBα for its functioning, leading to the

movement of RelA/p50 dimers to the nucleus. In the nervous system, the initiation of this pathway has been linked to stimuli like neurotrophic factors, erythropoietin, and hydrogen peroxide, the non-canonical pathway is also referred to as the IκB-independent pathway (Bonizzi et al. 2004).

NF-κB in neurodegenerative disorders

There are numerous kinds of neurons in the mammalian CNS, which can be classified as sensory, motor, and interneuron or excitatory and inhibitory neurons. NF-κB function has been studied in diverse types of neurons, such as excitatory (glutamatergic) and inhibitory (GABAergic) neurons, as well as at the synapse where neuron connections are formed. Neuronal NF-κB can be activated by several stimuli, like inflammatory mediators and growth factors like nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and excitatory neurotransmitters including glutamate, epinephrine, and norepinephrine (Snow and Albensi 2016). In addition to distinct pathways for activation, there are multiple specific ways to measure NF-κB activation at both behavioral and cellular levels. Within the NF-κB family, members like c-Rel, p50, and p65/RelA as well as IKK, have been associated with the regulation of memory and learning in mice (Dresselhaus and Meffert 2019). However, many studies investigating the specific effects of NF-κB subunits on behavior have not considered cell type specificity. Instead, they have used mouse models lacking certain subunits throughout the body, which result in effects beyond the nervous system. By disrupting NF-κB signaling pathway, especially in specific types of neurons, such as forebrain excitatory neurons or GABAergic interneurons (O'Mahony et al. 2006), researchers have confirmed NF-κB's importance in synaptic plasticity and cognitive behavior. Still, this manipulation does not offer precise subunit-specific insights. Multiple reviews have covered the cognitive impacts of NF-κB signaling (Kaltschmidt and Kaltschmidt 2015). Impairments in NF-κB signaling can to lead to deficits in evaluations of long-term plasticity, long-term potentiation (LTP) (Kyrargyri et al. 2015), and long-term depression (LTD) (O'Riordan et al. 2006). Activating the NF-κB pathway in the excitatory glutamatergic neurons of murine stimulates dendritic spines and excitatory synapse development, whereas reduced NF-κB activity (due to loss of RelA/p65) diminishes dendritic spine size, density, and miniature excitatory post-synaptic currents (mEPSCs). This occurs during the developmental stages of synapse formation and in mature neurons that respond to greater synaptic demand (Boersma et al. 2011). Research from various laboratories suggests that in normal physiological conditions, neuronal NF-κB serves to enhance synapse growth, boost the activity of synapses, and support lasting forms of plasticity. Beyond the gene targets studied before in cancer and immune, NF-κB has also been found to modulate specific downstream targets that significantly contribute to synaptic plasticity. These include Postsynaptic density protein 95 (PSD-95), Spine-associated Rap GTPase-activating protein (SPAR), Protein kinase A (PKA), neuronal Nitric Oxide synthase (nNOS), and growth factors like insulin-like growth factor 2 (IGF-2) and BDNF. The functions related to neuronal plasticity might explain why NF-κB is necessary for the assessment of behavioral indicators of cognition, as observed in numerous investigations. However, it is worth noting that certain behavioral experiments have not exclusively manipulated the NF-κB pathway in neurons, potentially allowing NF-κB in other cell types to contribute to the observed effects. The presence of NF-κB at stimulatory synapses and its triggering via excitatory synaptic activity are also pivotal factors in defining the distinct functions of the NF-κB pathway in mammalian neurons (38). Studies reveal that astrocytes, macrophages, and microglia release radicals, proinflammatory cytokines, and excitotoxins upon activation of NF-κB triggered by TNF-α, promoting neuronal death. Furthermore, inhibiting the NF-κB pathway, only in astrocytes, protects neurons from cell death (Green et al. 1997). Comparable outcomes were seen in hippocampal neurons affected by kainic acid excitotoxicity, where microglial IKKβ gene deletion yielded similar outcomes (Cho et al. 2008). Thus, inhibitors targeting the NF-κB pathway specifically in glial cells are suggested for prospective treatment in neurodegenerative disorders like ALS and AD (Fig. 2) (Mattson and Camandola 2001).

The role of curcumin in regulation of NF-κB in Alzheimer's disease

Alzheimer's disease, a neurodegenerative condition linked to aging, leads to gradual memory loss, cognitive decline, behavior changes, and difficulties with daily tasks. It is characterized by amyloid-β (Ab) plaques, neurofibrillary tangles, inflammation, and vascular changes in the brain. The precise connection between these plaques and tangles and the disease process remains uncertain but is being actively studied. The decline in cognitive function along with nerve cell degeneration is closely tied to abnormal activity within neural networks, synaptic dysfunction, and loss of synapses. Yet, the exact molecular mechanisms driving these effects aren't fully comprehended, with some being challenging to reproduce in mouse models of the disease (De Strooper and Karran 2016). Numerous genes have been linked to the progression of AD through genetic investigations. These genes include amyloid precursor protein (APP), Presenilin1 (PSEN1), Presenilin2 (PSEN2), apolipoprotein E (ApoE), Triggering Receptor Expression on Myeloid cells 2 (TREM2), and others (Kumar and Thakur 2016). Analyzing promoters and conducting examinations have revealed that the expression of each of these genes is regulated by

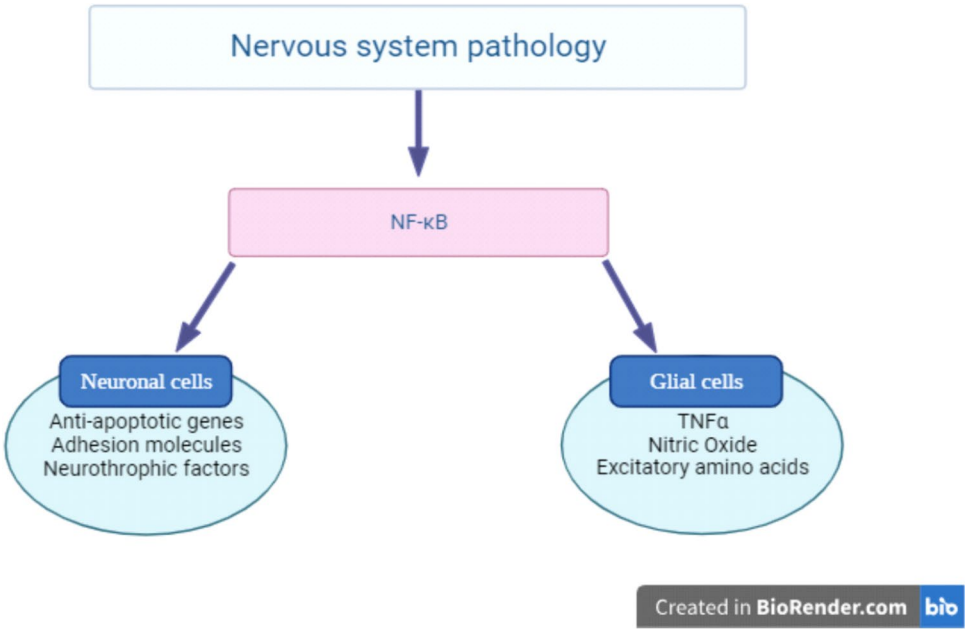

Fig. 2 Divergent impacts of NF-κB activation on neurons and glial cells in pathological contexts. The same trigger that activates NF-κB can yield opposing outcomes in neurons

NF-κB (Chami et al. 2012). In certain instances, products originating from genes linked to AD, such as presenilin1, have demonstrated the ability to reciprocally activate NF-κB, specifically, the RelA/p65 containing dimers, within potential pro-inflammatory cascades (Tanaka et al. 2018).

The TREM family of proteins plays a pivotal role in neuroinflammatory cascades, and emerging evidence points to NF-κB as a primary regulator influencing the expression of both TREM1 and TREM2 (Owens et al. 2017). Within microglia, TREM2 acts as a receptor on the surface essential for activation-related responses, such as survival, proliferation, and phagocytosis. Variants causing reduced TREM2 function have been related to elevated AD with late-onset risk in humans, and the absence of TREM2, as well as TREM2 deficiency in mice, lead to AD-related pathological changes (Guerreiro et al. 2013). It's also suggested that NF-κB's control over microglial TREM2 expression might extend to unexplored effects on synaptic plasticity, which is integral to memory and learning. The comprehensive role of NF-κB in AD is extensively addressed in a specialized review (Snow and Albensi 2016), discussing its regulation by Ab and presenting a broad spectrum of potential NF-κB targets implicated in AD progression or cognitive symptoms, encompassing cAMP response element-binding protein (CREB), manganese superoxide dismutase (MnSOD), Postsynaptic density protein 95 (PSD95), and Calcium–calmodulin (CaM)-dependent protein kinase II (CAMKII). Moreover, NF-κB has been related to the control of ApoE (Fig. 3), wherein the ApoE4 variant is a significant genetic risk factor for AD with late-onset. Analysis of gene promoters has recognized NF-κB-binding sites upstream of the ApoE transcription initiation start site, and functional control of ApoE4 expression through NF-κB signaling has been confirmed through experiments using glial cells (Lahiri 2004). Given NF-κB's multifaceted engagement in cognitive functions and inflammatory processes, it has garnered attention as a potential treatment focus for early intervention in AD. Notably, it's not just genetic factors but additionally, environmental factors contributing to AD risk, along with protective elements like dietary habits, exercise, and anti-inflammatory medications, exhibit correlations with NF-κB. Furthermore, since aging, the primary AD risk factor is linked to heightened brain activation of NF-κB and inflammation specific to certain tissues, there are implications for AD and other neurodegenerative conditions (Jones and Kounatidis 2017). Figure 3 illustrates the pivotal role of NF-κB in AD. Notably, NF-κB activates Beta-Secretase 1 (BACE1), a factor that encourages the establishment of Aβ fibrils. This, in turn, triggers a feedback loop where Aβ fibrils initiate a loop where they directly activate NF-κB, causing the expression of APOE4 and mGluR5. In microglia and astrocytes, Aβ42 also activates NF-κB, leading to the expression of inflammatory molecules that contribute to myelin injury. Moreover, NF-κB's activation initiates the production of microRNAs that suppress the production of diverse neuroprotective substances. Likewise, the accumulation of hyperphosphorylated tau in the AD brain is heightened through NF-κB-driven initiation of SET Nuclear Proto-Oncogene (SET), which inhibits the dephosphorylation of tubulin-associated unit (tau). Conversely, the presence of glycated tau triggers the production of reactive oxygen species (ROS), consequently activating NF-κB. The intricate network of pathways that collectively lead to neurodegeneration in AD demonstrates a strong interconnection, perpetuated by continuous

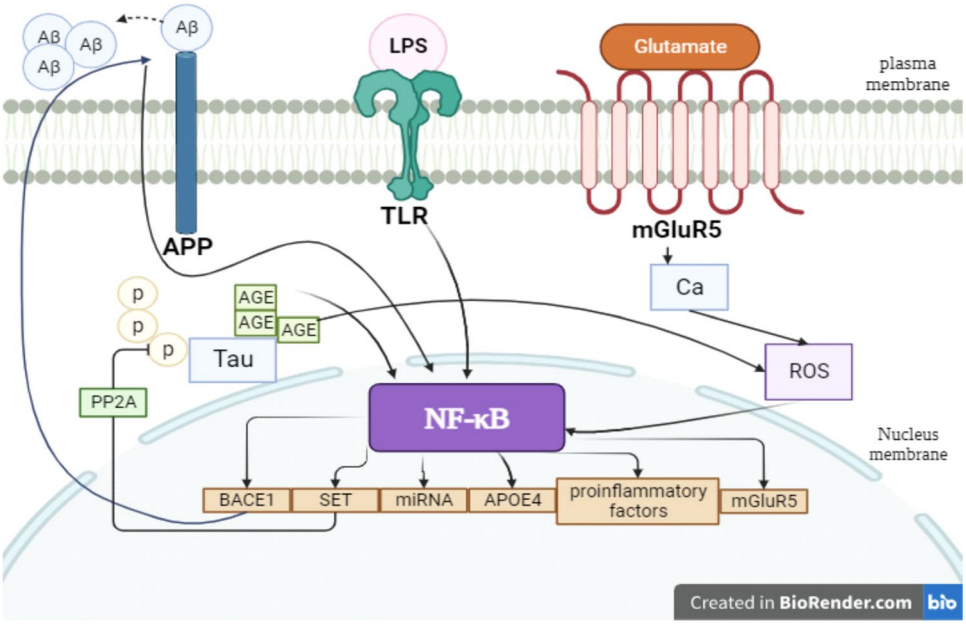

Fig. 3 NF-κB plays a central role in initiating a cascade of factors that are involved in Alzheimer disease-related changes

NF-κB activity in both glial cells and neurons (Sun et al. 2022). An in vivo study by Zhanget al. on Apolipoprotein E4 transgenic mice (ApoE4-Tg) revealed that delivery of curcumin, 40 mg/kg, i.p., impeded the translocation of the NF-κB subunit p65. This study elucidated that the incidence of Endoplasmic reticulum (ER) stress occurrence and the NF-κB signaling pathway activation is evident in ApoE4- Tg mice was inhibited by curcumin (40 mg/kg, i.p.) therapy. Therefore, neuroinflammation and subsequently leading and memory capability in ApoE4-Tg mice got better (Kou et al. 2021). In a study performed in 2023 by Kumar et al., the effect of different treatments against Alzheimer's disease was measured. The treatments included Scopolamine hydrobromide (2.5 mg/kg i.p.), Curcumin (100, 200 mg/kg p.o.), Coenzyme Q10 (Co-Q10) (200 mg/kg p.o.), Memantine (MEM) (10 mg/kg i.p.), and their combination. The results showed that administering a high dose of curcumin for 4 weeks, either alone or in combination with Co-Q10, significantly enhanced the function of mature female Wistar rats with Alzheimer's disease and reduced the expression of NF-κB (Kumar et al. 2023). An in vitro study on SH-SY5Y cells elucidated that curcumin (10 μM) upregulates PPARγ expression, which regulates inflammation in transcription level and inhibits NF-κB signaling pathway in APOE4-induced neurological damage. It was also manifested that this agent could decrease neuro-inflammation by reducing TNF-α, IL-1β, and NO creation while simultaneously reducing COX-2 and iNOS protein production (Wang et al. 2020). Another in vitro study exerted by Wang et al. confirmed that upregulation of PPARγ by curcumin (0–30 μmol/l) can inhibit NF-κB signaling in SH-SY5Y cells, which led to alleviation of injuries induced by ApoE4 (Wang et al. 2020). In addition, Song Yu et al. attempted to evaluate the beneficial impact of curcumin on the pathophysiology of PD in an in vitro rat pups' astrocyte cell. An administration of 1, 2, 4, and 8 Mμ of curcumin reported a reduction in quantities of TLR4 and its subsequent components including NF-κB, MyD88, interferon regulatory factor 3 (IRF3), and transmucosal immediate-release fentanyl (TIRF), which are stimulated by 1-methyl-4-phenylpyridinium ion (MPP+). Additionally, curcumin can inactivate the immune response of morphological and TLR4 stimulation in MPP+-induced astrocytes (Yu et al. 2016). Curcumin's efficacy in 2 μM concertation has been assessed in oxidative stress and hypoxia in hippocampal cells by Chhunchha et al. in 2013. Results have shown that curcumin can reduce ROS, inhibit NF-κB stimulation, decrease Bax and caspases, and prevent apoptosis via peroxiredoxin6 (Prdx6) up-regulation after hypoxia (Chhunchha et al. 2013). To investigate their claim, Wang et al. experimented in vitro study on MES23.5 cells. The result showed, 2×104 μmol per L curcumin in dimethyl sulfoxide (DMSO) for 24 h reduced ROS generation, which led to inhibition and regulation of 6-OHDA-inudced NF-κB nuclear translocation (42). Alzheimer's pathology is related to toxic plaque accumulation that is composed of Aβ. Rate-limiting protease in Aβ generation is BACE1 accordingly. BACE1 inhibitors are a potent treatment for AD. In 2020, Huang et al. study demonstrated enhanced BACE1 promotor activity and Aβ production correlated to NF-κB activation and indicated that curcumin's role in inhibiting NF-κB activity is at promotor level (Huang et al. 2020). Due to the possible impacts of high levels of PGs on neurodegeneration, Kang et al. performed a study that indicated the therapeutic consequences of curcumin on BV2 microglial

cells stimulated by LPS in a concentration-dependent manner, 16 μM curcumin reduced more than 50% of NF-κB and AP-1 DNA bindings and also had a great impact on reduction of COX-2 mRNA, protein, and enzyme activity (Kang et al. 2004).

The role of curcumin in the regulation of NF-κB in Parkinson's disease

Parkinson's disease (PD) is a significant neurodegenerative condition that influences around 1% of individuals over 60 years old. It causes unintended or uncontrollable movements, such as tremors, rigidity, and bradykinesia (DeMaagd and Philip 2015). Oxidative stress is thought to prompt the apoptosis of the substantia nigra's dopaminergic neurons, leading to the observed neurodegenerative symptoms in PD patients, PD was initially reported by James Parkinson in 1817 (Parkinson 2002). Like AD, PD entails alterations in the neuronal cytoskeleton, albeit affecting specific nerve cell types that are particularly susceptible. Cases are mostly sporadic and many genes have been identified to relate to several gene's mutations. The main genes implicated in PD are a-synuclein (SNCA), parkin, PTEN-induced putative kinase 1 (PINK1), leucine-rich repeat kinase 2 (LRRK2), and DJ-1 (Wood-Kaczmar et al. 2006). SNCA is a protein pivotal in synaptic dopamine release process. It can accumulate in Lewy bodies in Lewy body dementia (LBD), which can be an infection associated with abnormal accumulation of SNCA in the brain. These deposits, called Lewy bodies, affect chemicals in the brain, changes in which can lead to problems with development, considering, temperament, and behavior (Prasad et al. 2023). This SNCA accumulation in Lewy bodies is in a similar manner to prions, and is considered a key component of PD (Steiner et al. 2018). PD biological staging system describes PD according to neuronal pathologic SNCA and dopaminergic neuron dysfunction/degeneration (Chahine et al. 2023). It is also believed that the characteristic SNCA pathology in PD can expand from the gut to the brain through the vagus nerve (Braak et al. 2003). Furthermore, evidence has showed transmission of gut-to-brain pathology and dopaminergic neuron loss after injecting prion-like alpha-synuclein fibrils into gut muscles in mice (Braak et al. 2003).

The low function of the PARKIN E3 ubiquitin ligase has long been genetically linked to PD (Panicker et al. 2021). Recent in vitro analysis demonstrated that overexpressing PARKIN enhances TNF-α-mediated NF-κB activation, suggesting a function for this E3 ubiquitin ligase in TNFα-mediated NF-κB signaling by stabilizing linear ubiquitin chain assembly complex (LUBAC) (Meschede et al. 2020). TNFα activated NF-κB and caused neuroprotection of cell death from oxidative stress-induced in both sexes. The gene expression behind this neuroprotection is sexually dimorphic, with females upregulating superoxide dismutase 2 (SOD2) and IGF2 and males showing elevated protein kinase A (PKA) cat alpha expression. Inhibition of cRel, a key regulator of neuronal expansion from neural crest cells, shifts the fate of these stem cells from neuronal to oligodendrocytic lineage (Ruiz-Perera et al. 2018). From neurons, it is recognized as damage-associated molecular patterns (DAMP) or pathogen-associated molecular patterns (PAMP) by microglial toll-like receptor2 (TLR2). Following TLR2 stimulation, myeloid differentiation factor 88 (MyD88) and NF-κB pathways are activated, leading to the production of IL-1β and TNF-α (Fig. 4) (Béraud and Maguire-Zeiss 2012). Accordingly, it has been revealed that stromal cell-derived factor (CXCL12)/CXCR4/Focal adhesion kinase (FAK)/Sarcoma (Src)/Rac1 signaling pathway leads to SNCA-induced accumulation of microglia and thereby promoting neuroinflammation (Li et al. 2019). Figure 4 shows aggregated SNCA binds to CD36 on microglia, leading to the recruitment of Fyn kinase, which in turn triggers protein kinase C-delta (PKC-δ) activation. This sequence facilitates the migration of the p65 subunit of NF-κB to the nucleus (Panicker et al. 2019). Within the nucleus, the p65 subunit enhances the expression of IL-1β and the NLR family pyrin domain containing 3 (NLRP3) inflamed (Dolatshahi et al. 2021). According to another in vivo study on APP/PS1 double-transgenic mice-induced AD, improvement of memory deficits could be through inhibition of NF-κB and stimulation of PPARγ pathway, which can occur by curcumin (150 mg/kg, i.p.) administration. The valuable impacts of curcumin on AD were because of neuroinflammation inhibition, as exhibited by the declined cytokine expression and stimulation of glia, as much as suppression of the NF-κB pathway (Liu et al. 2016). In a 2017 study on 10- to 12-week-old male Sprague Dawley rats as shown in reverse transcription polymerase chain reaction (RT-PCR) and electrophoretic mobility shift assay (EMSA), 40 mg/kg of birthweight of Curcumin, i.p., impeded NF-κB, microglia, and astrocytes activation. The activity of brain's DNA-binding to NF-κB lessened in EMSA assay and NF-κB expression down-regulated, reducing pro-inflammatory cytokines TNF-α and IL-1β. This process caused dopaminergic neuron protection in opposition to LPS-induced PD and inflammatory action (Sharma et al. 2017). Zhang et al. in 2019 evaluated the effects of curcumin, 5 and 10 μM, on BV2 microglial cell lines after LPS-induced neurotoxicity. It was manifested that curcumin could suppress pro-inflammatory pathways like NF-κB/ TLR4 and decrease IL-6, IL-1β, iNOS, and CD16/32 expression. Moreover, it was declared that curcumin could exert its beneficial effects by regulating the triggering receptor expressed on the TREM2 pathway and increasing IL-10, IL-4, arginase 1, and CD206 (Zhang et al. 2019). Yang et al. investigated curcumin as a microglia-dependent neuroprotector that affects midbrain

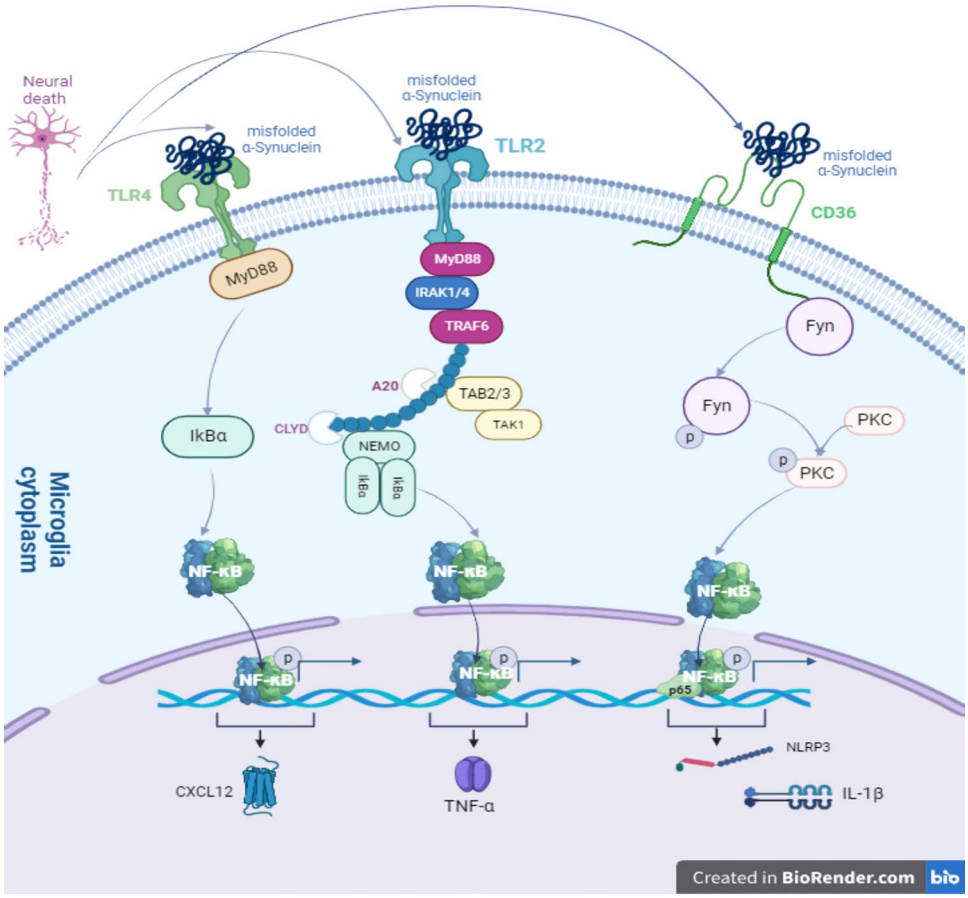

Fig. 4 Clumped α-synuclein, when it attaches to CD36 on microglia and enlists Fyn kinase, prompts the activation of protein kinase C-delta (PKC-δ)

dopaminergic (DA) neurons against LPS-induced neurotoxicity. The administration of curcumin (10 μM) along with LPS-induced neurotoxicity in mesencephalic neuron-glia cultures showed a considerable decrease in NF-κB DNA binding ability, and expression of NO, iNOS mRNA, IL-1β, and its mRNA, and COX-2 mRNA, TNF-α and its mRNA, as well as, decreased neurotoxic factors and inhibited NF-κB and AP-1 (Yang et al. 2008). Scientists have declared that the NF-κB signaling pathway may be effective in curcumin's impact on PD. Xu et al. induced PD by 3 mg/kg/day rotenone subcutaneous injection in mice's substantia nigra and concluded that treatment with intraperitoneal injection of 50 mg/kg/day curcumin resulted in NF-κB signaling pathway inhibition. To analyze in detail, they performed western blots to examine NF-κB and p-NF-κB levels, which were down-regulated in the curcumin-treated group (Xu et al. 2023).

The role of curcumin in the regulation of NF-κB in Huntington's disease

Huntington's disease (HD) is an inheritable dominant autosomal neurodegenerative disease characterized by mood changes, decreased neuromuscular coordination, and cognitive decline, ultimately leading to fatality (Gatto et al. 2020). The disease is caused by mutations that expand the repeating region of the nucleobase cytosine–adenine–guanine (CAG) triplet of the Huntington gene, which encodes a polyglutamine tract (polyQ) within the amino terminus of the Huntingtin protein (HTT). A normal HTT has less than 26 repetitions, while in the disease-associated mutant version, typically more than 35 repeats exist. A higher count is associated with a greater severity and an earlier onset, the expansion of polyglutamine in HTT appears to alter its conformation (Bates et al. 2015). Although HTT is expressed in every part of the body, the precise role of normal HTT and why the mutated form disrupts neurons to a greater extent remains unclear. Notably, normal HTT interacts with various neuronal proteins, such as NF-κB subunits p50 and p65 (Takano and Gusella 2002). HTT is notably concentrated at the post-synaptic density of neuronal synapses alongside these NF-κB subunits. Notably, HTT tends to bind selectively to activated NF-κB, facilitating the movement of p65-containing NF-κB dimers away from dendritic spines. However, the polyQ expansion found in HD-associated HTT disrupts this localization at the post-synaptic density, hindering its movement out of dendritic spines and the subsequent nuclear aggregation of NF-κB

(Marcora and Kennedy 2010). This indicates that the atypical transport of NF-κB from synapses to the nucleus in neurons could potentially play a role in the development of HD. Although most experiments have focused on the links among NF-κB and HD within types of neuronal cells, mutant HTT seems to influence neuroinflammation, potentially indicating its role in glial cells. In HD patients and an HD mouse model, astrocytes from the caudate nucleus brain region and the cortex display heightened NF-κB activation (Hsiao et al. 2013). This increase in activation primarily occurs in astrocytes rather than neurons or microglia. Elevated astrocyte IKK activity seems to drive this NF-κB activation, consistent with a study showing excessive IKK activities in an HD mouse model's brain (Khoshnan et al. 2004). HD astrocytes ameliorate HD symptoms and block IKK, which mitigates neurotoxicity (Hsiao et al. 2013). NF-κB also regulates HTT at the transcription level. An NF-κB-binding site and a single-nucleotide polymorphism (SNP) within it were identified as the HTT promoter. This SNP impairs NF-κB binding and reduces HTT transcription. Notably, this SNP's influence on the HTT mutant allele delays HD onset, while its existence on the wild-type HTT allele is related to early onset. Though primarily studied at the genomic level, the effects of the NF-κB-binding site and SNP in the HTT promoter were verified in ST14A cells, derived from the striatal brain region that coordinates several facets of cognition, including both motor and action planning, decision-making, motivation, reward perception, and reinforcement and also displaying medium spiny neuron features (Bečanović et al. 2015). In conclusion, the NF-κB pathway and its role in regulating HTT gene expression are in the advancement and progression of HD (Fig. 5).

The role of curcumin in modulation of NF-κB in ALS and other neuronal injuries

Amyotrophic lateral sclerosis (ALS) involves the degradation in motor neurons, which leads to increasing loss of voluntary muscle control, speech difficulties, and breathing problems. Despite almost all ALS patients are periodical, about 10% have a hereditary basis (Masrori and Van Damme 2020). Several genes are associated with familial ALS, and NF-κB's involvement in their regulation or interaction is notable (Mead et al. 2023). The human SOD1 promoter's NF-κB-binding site responds to phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) pathway, leading to increased SOD1 levels (Rojo et al. 2004). The NF-κB's p65 subunit links with TAR DNA-binding protein 43 (TDP-43), a connection heightened in ALS. TDP-43 is believed to act as NF-κB's co-activator. Mutations of Optineurin (OPTN) have shown its relation to ALS (Ouali Alami et al. 2018). Optineurin is one of the four genes linked to glaucoma that interacts with proteins including myosin VI, Rab8, TANK-binding kinase 1, huntingtin, and transferrin receptor. It also

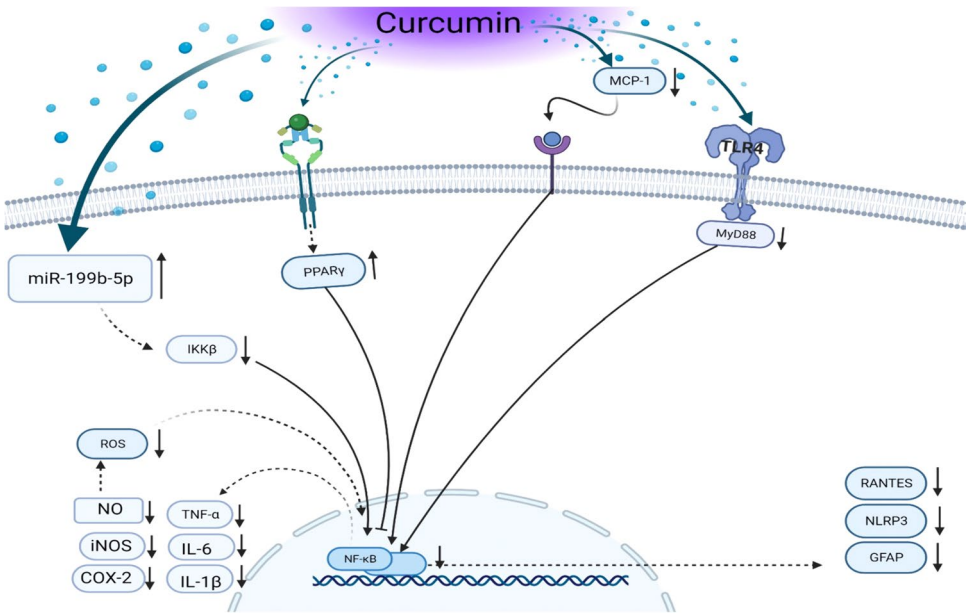

Fig. 5 Effect of curcumin on NF-κB signaling pathway. Inducible nitric oxide synthase (iNOS), Cyclooxygenase 2 (COX2), Nitric oxide (NO), Tumor necrosis factor alpha (TNF-α), Interleukin 6 (IL-6), Interleukin 1 Beta (IL1B), Inhibitor of nuclear factor kappa-B kinase subunit beta (IKK-β), hypoxamiR (miR-199a-5p), Reactive oxygen species (ROS), Peroxisome proliferators–activated receptor γ (PPARγ), Monocyte chemoattractant protein 1 (MCP-1), Toll-like receptor 4 (TLR 4), Myeloid differentiation primary response 88 (MYD88), Nucleotide-binding domain, leucine-rich containing family, pyrin domain containing 3 (NLRP3), Glial fibrillary acidic protein (GFAP)

involves in intracellular processes, such as transportation of proteins, Golgi's apparatus maintenance, as well as NF-κB pathway's antiviral, and antibacterial signaling (Ying and Yue 2012). While normal OPTN inhibits TNF-α-induced NF-κB activation, ALS-associated OPTN mutations abolish this inhibitory effect. Neuroinflammation and activated microglia are distinct features of ALS (Swarup et al. 2011). Both inherited and sporadic ALS forms exhibit activation of NF-κB located in glial cells. Recent research indicates that astrocyte NF-κB activation might contribute to ALS by influencing microglial proliferation and immune responses (Ouali Alami et al. 2018).

To wrap up the whole evidence, besides its effects on motor neurons, NF-κB operation in non-neuronal cells significantly participates in the development of ALS (Dresselhaus and Meffert 2019).

NF-κB activation, triggered by traumatic as well as ischemic circumstances of brain and spinal cord, has emerged as a pivotal player in modulating neuronal responses. Experimental stroke and injury models have indicated that the NF-κB path exerts diverse effects on neuronal degeneration and protection (Kaltschmidt et al. 1999). Opposing outcomes are obtained according to the findings that mice with p50 subunit deficiency exhibit reduced infarct size (Nurmi et al. 2004), while IKK/NF-κB signaling has been exposed in ischemic brain damage (Schwaninger et al. 2006). Conversely, in the hippocampus and the striatum, NF-κB contributes to survival signaling post-temporary focal ischemia (Duckworth et al. 2006). Recent research even suggests that inhibiting glial's NF-κB can mitigate discomfort and inflammation responses in chronic sciatic nerve constriction (Fu et al. 2010). Collectively, these findings underscore the contentious position of the NF-κB pathway in neuron's related harm and illnesses. In order to address these seeming contradictions, two conjectures have been suggested. The more recent one, proposed by Kaltschmidt et al. (2005), is the NF-κB homeostasis model (Kaltschmidt et al. 2005). This model states that sustained different stages of NF-κB operation over long-term periods may induce neuronal loss, in physiological situations, nuclear RelA activates replications of apoptosis-inhibitor genes, contingent upon IκB protein's role in localizing RelA to the cytoplasm. Pathological conditions can disrupt this balance, leading to NF-κB shifting from a critical promoter to a supreme blocker of apoptosis-inhibitor genes, thereby triggering neuronal cell death. An alternate hypothesis, advocated by Mattson and Camandola (2001), suggests that NF-κB operation in neuronal cells stimulates anti-apoptotic genes promoting their survival. Conversely, NF-κB operation in glial cells stimulates the creation of proinflammatory cytokines, culminating in neuronal loss. This divergence in responses to the same stimulus results from NF-κB activation in distinct cell units. TNF-α, which glial cells produce, exemplifies this duality. TNF-α and TNFR1 connection in glial cells incites NO production and may cause loss of neurons, while TNFR2 neuronal activation prompts anti-apoptotic gene expression. This theory gains support from studies revealing that neuronal toxicity of TNF-α hinges on the presence of glial cells (Reich and Hölscher 2022). Notably, microglia, macrophages, and astrocytes release proinflammatory cytokines, excitotoxins, as well as free radicals due to TNF-α-stimulated activation of NF-κB, driving neuronal loss, in the models of neuron harm, inhibiting the route exclusively in astrocytes which indicated neuroprotection (Meunier et al. 2007). Consequently, glial-specific NF-κB pathway inhibition emerges as a potential therapy perspective for neurodegenerative circumstances such as AD, as well as ALS (Thomsen et al. 2009). An in vivo study on SD rats with SCI conducted by Yu et al. showed that curcumin injection in the dose of 150 mg/kg i.p. can reduce NF-κB and TNF-α expression. It also can amend motor dysfunction caused by SCI. Moreover, they manifested that curcumin increases heme oxygenase 1 (HO-1), tight junction protein (TJ), zonula occludens 1 (ZO-1), and occludin (Yu et al. 2014). Besides, another study on SD rats with TBI conducted by Sun et al., demonstrated that the use of Curcumin, 30 mg/kg i.p., can improve neurogenesis, as well as reduce pro-inflammatory regulators like TNF-α, IL-18, IL-6, as well as IL-1β expression. It was presented that blockage of TLR4-MAPK/NF-κB route might represent a possible mechanism involved in the reduction of these pro-inflammatory mediators (Sun et al. 2020). Yuan et al. in 2015 evaluated the curcumin's impacts (300, 100, and 30 mg per kg, i.p.) on the Female SD rat model of SCI. By assessing behavior, western blotting, immunohistochemistry, real-time polymerase chain reaction, and enzyme-linked immunosorbent assay, it has been observed that curcumin given to rats showed an anti-inflammatory property through NF-κB signaling pathway, decreased glial scar, improved functional recovery, and impeded proinflammatory cytokines expression like TNF-α, interleukin-1β (IL-1β), as well as NF-κB (Yuan et al. 2015). According to an in vivo study, SCI was induced by the method of Allen's and western blot. Enzyme-linked immunosorbent assay (ELISA), Basso mouse scale (BMS), immunohistochemical, and Griess assay are other methods of experiment. 100 adult female Kun-Ming (KM) mice conducted by Zhang et al. in 2017, curcumin administration (50,100, or 200 mg per kg) can inhibit the TGF-b-activated kinase 1 (TAK1)/mitogen-activated protein kinase kinase 6(MKK6)/p38 mitogen-activated protein kinases (p38MAPK) via the TAK1 and NF-κB routes and inflammation. Curcumin decreased the phosphorylation levels of IκB Kinase β (IKKβ) and IkB. IKKβ and IkB are the main upstream regulators for NF-κB activity. The overall protein transcription of IKKβ and IkB was reduced too. It has been discovered that curcumin reacts as inhibitor of

SCI-stimulated IKK and IkB (Zhang et al. 2017). In a study on adult KunMing mice (male), it has been examined the effects of curcumin (50 mg/kg, i.p.) on attenuated lipopolysaccharide (LPS)-stimulated microglial activity, as well as overproduction of proinflammatory cytokine IL-1, TNF-α, the levels of iNOS and COX2 mRNA in the hippocampus and prefrontal cortex (PFC). Furthermore, curcumin reduced LPS-induced NF-κB activity in the hippocampus and PFC. Curcumin showed antidepressant-like effects that might be regulated by decreasing the levels of stress-stimulated proinflammatory cytokines, iNOS and COX-2 mRNA by NF-κB signaling mechanism. There have been observed alterations in the stages of IL-1β, TNF-α, iNOS, and COX-2, as well as alterations of NF-κB activities in special brain sectors like the PFC and hippocampus (Wang et al. 2014). According to an in vivo experiment on female SD rats (curcumin 100 mg per kg, i.p.) and an in vitro experiment on cortical astrocytes (curcumin 1 μmol/l) in SCI by Yuan et al. in 2017, curcumin can reduce monocyte chemoattractant protein 1 (MCP-1), Regulated upon Activation, Normal T Cell Expressed, and Secreted (RANTES), C-X-C motif chemokine ligand 10 (CXCL10) and T cell infiltration by blockage of NF-κB pathway, as well as astrocyte activity. In addition, curcumin can down-regulate SRY-Box Transcription Factor 9 (SOX9) pathway, reduce α-smooth muscle actin (α-SMA) and glial fibrillary acidic protein (GFAP) expression and decrease chondroitin sulfate proteoglycan (CSPG) deposition (Yuan et al. 2017). In another study conducted in 2015, density depletion of NF-κB-positive nuclei and lessened NF-κB activity occurred in SCI rats when they were on i.p. injection containing 6 mg/ kg/ day curcumin diluted in olive oil during and after 28 days of treatment duration (Machova Urdzikova et al. 2015). According to a 2013 investigation on the inflammatory impacts of curcumin in experimental white matter harms in rats, administration of 100 mg per kg curcumin in phosphate-buffered saline (PBS), which contains 1% dimethyl sulfoxide (DMSO) by i.p. injection, led to reduced binding activity of NF-κB (Ni et al. 2015). Daverey & colleagues performed an in vitro trial on male Wistar rats' spinal cord dorsal columns. In their model, they observed 50 μM curcumin in 95% N2 & 5% CO_2 lessened NF-κB expression induced by hypoxia in the cytosol, which secured curcumin-mediated protection of neuron cells. This group also tried NF-κB-specific inhibition experiment that resulted in a noticeable regulatory weight of the NF-κB signaling route in preventing pro-inflammatory cytokines (Daverey and Agrawal 2020). Curcumin, as a NF-κB/TLR inhibitor, was administrated in the Giacomeli et al. study in which lipid core nanocapsules (LNC) were used to overcome the low bioavailability of curcumin. Three drugs containing curcumin were investigated and all three caused a reduction of mRNA expression of NF-κB. Meanwhile, lipid nanocapsules of curcumin 10 mg per kg (LNC10) treatment presented a noticeable reduction in mRNA transcription of NF-κB in comparison with the two following drugs: lipid nanocapsules of curcumin 1, and 10 mg/kg (Giacomeli et al. 2019). Ni H et al. investigation examined the influence of curcumin on the expression of TLR4 and NF-κB inflammatory signaling pathway in SCI rats. The effect of curcumin (100 mg/kg, i.p) on suppressing the growth of TLR4 levels was proved. Moreover, curcumin down-regulated NF-κB DNA-binding activity and reduced TNF-α, IL-1β, and IL-6 along with BBB locomotion score, spinal cord edema, and apoptotic index in contrast to those in the sham group (Ni et al. 2015). In 2019, Gao et al. conducted an in vitro study on BV2 microglial cells. The study results suggested that curcumin at a concentration of 8 μM can down-regulate the IKKβ/NF-κB pathway by up-regulating miR-199b-5p. Additionally, curcumin at this concentration can also inhibit the replication of TNF-α, IL-1β, iNOS, and phosphorylated-p65 (Gao et al. 2019). Xie et al. researched the role of Curcumin (2, 4, & 8 μM) impact in LPS-influenced inflammatory injury on BV2 cells. In this process, they found out the preventive position of Curcumin on NF-κB signaling using miR3623p/TLR4 axis (Xie et al. 2020).

Curcumin's beneficial impacts on neurodegenerative diseases based on clinical evidence

There are no clinical studies about the effects of curcumin and its derivatives on ND via regulating NF-kB; however, there are a few clinical studies about the beneficial effects of curcumin on ND improvement, which could be due to inflammation reduction that can be mediated via NF-kB signaling pathway regulation. In a clinical study published in 2008, curcumin at the dose of 1 and 4 g/day was given orally to 34 patients who have been involved in the experiment. There were no significant changes in MMSE scores between placebo and curcumin groups. Moreover, there was a rise in amyloid-beta 40 levels in the blood that could be due to the curcumin disaggregation effect of amyloid-beta 40 in the brain (Baum et al. 2008). In another clinical study by Ringman et al. (2012), the effects and adverse effects of curcumin in AD patients were evaluated. Curcumin was given to 36 persons in a 24- to 48-week period at a dose of 2 and 4 g/day orally. There were no significant changes in amyloid-beta 40 and 42 levels in blood or CSF between the two groups. Furthermore, curcumin did not affect Alzheimer's Disease Assessment Scale–cognitive subscale (ADAS-Cog) and Alzheimer's Disease Cooperative Society Study-Activities of Daily Living (ADCS-ADL) scale. Positively, curcumin showed no important adverse effect and it was well tolerated in patients (Ringman et al. 2012).

Dolati et al. reported that daily 80 mg of nano-curcumin has advantageous impacts on MS patients by affecting Treg cells function and circulation period (Dolati et al. 2019). 7

Table 1 In vivo studies concerning the effects of Curcumin on neurodegenerative disease

Study design	Disease	Intervention		Number of animals	Treatment duration	Results	Adverse effects	Refs.
		case	Control					
Male SD rats	TBI	Curcumin 75, 150, and 300 mg/kg (i.p.)	VEH	$N=5$/Group	28 days	• ↑BDNF/Trkb expression and PI3K/Akt signaling • ↓TNF-α, IL-1β, IL-18, IL-6 and NLRP3 levels • ↑Hippocampal neurogenesis • ↓neuro-inflammation • ↓TLR4/ NF-κB pathway • ↓TNF-α, IL-1β, IL-18, and IL-6 expression	N/A	Sun et al. (2020)
female SD rats	SCI	Curcumin 100 mg/kg (i.p.); DMSO; siRNA	Sham	$N=70$/Group	7 days	• ↓GFAP, CSPG, and cystic cavity volume • ↓NF-κB activity • ↓MCP-1, RANTES and CXCL10 • ↓$CD11b^{+}/CD45^{high}$ macrophages cell, $CD3^{+}$ $CD4^{+}$ T cell and $CD3^{+}$ $CD8^{+}$ T-cells • ↓SOX9 expression • ↓α-SMA expression	N/A	Yuan et al. (2017)
Male SD rats	SCI	Curcumin 75, 150, and 300 mg/kg (i.p.) + Znpp 25 µmol/kg (i.p.)	Sham	$N=6$/Group	21 days	• ↓TNF-α and NF-κB expression • ↓hindlimb motor dysfunction • ↑HO-1 • ↑TJ protein, ZO-1 and occludin	N/A	Yu et al. (2014)

Table 1 (continued)

Study design	Disease	Intervention		Number of animals	Treatment duration	Results	Adverse effects	Refs.
		case	Control					
ApoE4-Tg Mice C57BL/6 J mice (WT)	AD	Curcumin (40 mg/kg, i.p.)	–	*N* = 8/Group	21 days	• ↓ApoE4 in Transgenic Mice • ↓deficiency of spatial learning in ApoE4-Tg Mice • ↓Neuronal Cell Death • ↓Cerebral Inflammation • ↓COX-2 and iNOS • Inhibition ER Stress in ApoE4-Tg Mice • ↑learning and memory • ↓TNF-α and IL-1β • ↓Nuclear translocation of p65 • 10. inhibition of NF-κB expression	N/A	Kou et al. (2021)
Mature female Wistar rats	AD	SCO (2.5 mg/kg i.p.) SCO (2.5 mg/kg i.p.) + CURCUMIN (100 mg/kg p.o.) SCO (2.5 mg/kg i.p.) + CURCUMIN (200 mg/kg p.o.) SCO (2.5 mg/kg i.p.) + CoQ10 (200 mg/kg p.o.) SCO (2.5 mg/kg i.p.) + CURCUMIN (200 mg/kg p.o.) + CoQ10 (200 mg/kg p.o.) SCO (2.5 mg/kg i.p.) + MEM (10 mg/kg i.p.)	VEH	*N* = 6/Group	28 days	• ↑improvement in animal model of Alzheimer's disease • ↓NF-κB expression	N/A	Kumar et al. (2023)
APP/PS1 transgenic mice (Swedish mutant AβPP695)	AD	Curcumin (150 mg/kg, i.p.) + PPARγ inhibitor GW9662 (4 mg/kg, i.p.)	–	*N* = 10/Group	28 days	• ↓escape latency • ↑platform crossing number • ↑time spent in the target quadrant • ↓travel distance • inhibition of the NF-κB signaling pathway	N/A	Liu et al. (2016)

Table 1 (continued)

Study design	Disease	Intervention		Number of animals	Treatment duration	Results	Adverse effects	Refs.
		case	Control					
8-week-old C57BL/6 J mice	Rotenone-induced PD	Rotenone (3 mg/kg/day, s.c.) + Curcumin (50 mg/kg/day, i.p.) Rotenone (3 mg/kg/day, s.c.) + 0.1% DMSO(i.p.)	Sunflower oil	*N* = 5/Group	35 days	• ↓behavioral defects • ↓dopamine neurons reduction • ↓microglial activation • ↓NLPR3 inflammasome activation • ↓cytokines overexpression • ↓NF-κB signaling pathway • ↓excessive mitochondrial fission • ↓IL-18 • ↓IL-1β	N/A	Xu et al. (2023)
10–12-week-old male SD rats	LPS-induced PD	LPS (5 µg/5 µl PBS) LPS (5 µg/5 µl PBS) + Curcumin (40 mg/kg b.wt [i.p.]) 5 µl PBS + Curcumin (40 mg/kg b.wt [i.p.])	5 µl PBS	*N* = 14/Group	21 days	• ↓astrocytic activation • ↓Iba-1 • ↓microglial activation • ↓GFAP mRNA • ↑TH • ↑TH-positive neurons • ↑dopamine • ↑dopamine metabolites (HVA & DOPAC) • ↓transcription factor NF-κB gene expression • ↓TNF-α • ↓IL-1β • ↓NF-κB DNA-binding activity in brain • ↓NADPH oxidase activity • ↓ROS levels • ↓lipid peroxidation • ↓NO • ↓caspase-3 & caspase-9 • ↑total locomotor activity • ↓behavioral deficits	N/A	Boersma et al. (2011)

Table 1 (continued)

Study design	Disease	Intervention		Number of animals	Treatment duration	Results	Adverse effects	Refs.
		case	Control					
Ten-week-old male Wistar rats	SCI	Curcumin (6 mg/kg/day diluted in olive oil [i.p.] & in situ 60 mg/kg/ml/week diluted in olive oil	Olive oil	*N* = 30/Group	28 days	• ↓glial scar formation • ↓MIP1α • ↓IL-2 • ↓RANTES production • ↓NF-κB activity • ↓NF-κB positive nuclei density • ↓p65 translocation into nucleus • ↑IL-4 • ↑IL-6 p70 • ↑IL-12 p70 • ↓GFAP • ↑Irf5 • ↑Gap43	N/A	Cho et al. (2008)
Female SD rats	SCI	Curcumin (300, 100, and 30 mg/kg i.p.)	–	*N* = 8/Group	7 days	• ↓TNF-α, IL-1β • ↓GFAP • ↓intracellular and extracellular expression of cytokines • ↓scar area • ↓TGF-b1, TGF-b2, and SOX-9 • ↓NF-κB • ↓reactive gliosis	N/A	Yuan et al. (2015)
Female KM mice	SCI	Curcumin (50, 100, and 200 mg/kg i.v.)	NaNO2	*N* = 10/Group	7 days	• ↓total protein expression of IKKb and IkB • ↓GFAP • ↓TNF-α, IL-1β, IL-6 • NO phosphorylation levels of TAK1,MKK6 • ↓p38 MAPKs • inhibition of TAK1/MKK6/p38MAPK via the TAK1 • ↓NFkB pathways	N/A	Giacomeli et al. (2019)
Male KM mice	LPS (0.83 mg/kg i.p.)	Curcumin (50 mg/kg i.p.)	DMSO 0.1% + Vehicle	*N* = 10/Group	7 days	• ↓iNOS, COX-2 mRNA via NF-κB • ↓TNF-α • ↓IL-1β • ↓sucrose consumption	N/A	Wang et al. (2014)

Table 1 (continued)

Study design	Disease	Intervention		Number of animals	Treatment duration	Results	Adverse effects	Refs.
		case	Control					
Aged female Swiss Albino mice	$A\beta_{1\text{-}42}$ -induced	Free curcumin 50 mg/kg curcumin-loaded lipid core nanocapsules 10 mg/kg curcumin-loaded lipid core nanocapsules 1 mg/kg	Sham (saline)	$N=8$/Group	14 days	• ↓mRNA expression of NF-κB in	N/A	Giacomeli et al. (2019)
Male Sprague Dawley rats	SCI	SCI SCI + Curcumin (100 mg/kg, i.p.)	Sham (DMSO equal volume)	$N=16$/Group	3 days	• ↓TLR4 • ↓NF-κB DNA-binding activity • ↓TNF-α, IL-1β, and IL-6 • ↓BBB locomotion score • ↓SCI-induced spinal cord edema • ↓AI in the spinal cord	N/A	Ni et al. (2015)

curcumin (Cur), Vehicle (VEH), Sprague Dawley (SD), Traumatic brain injury (TBI), Intraperitoneal (i.p), Tumor necrosis factor-α (TNF-α), Brain-derived neurotrophic factor (BDNF), Tropomyosin receptor kinase B (Trkb), Phosphoinositide-3-kinase (PI3K), Protein kinase B (PKB or Akt), Nucleotide-binding domain, leucine-rich-containing family, pyridine domain containing 3 (NLRP3), Interleukin-1β (IL-1β), Interleukin-18 (IL-18), Interleukin 6 (IL-6), Toll-like receptor 4 (TLR4), Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), glial fibrillary acidic protein (GFAP), chondroitin sulfate proteoglycan (CSPG), monocyte chemoattractant protein 1 (MCP-1), Regulated upon Activation, Normal T cell Expressed, and Secreted (RANTES), C-X-C motif chemokine ligand 10 (CXCL10), SRY-Box Transcription Factor 9 (SOX9), α-smooth muscle actin (α-SMA), dimethyl sulfoxide (DMSO), ApoE4 transgenic (ApoE4-Tg), Coenzyme Q10 (Co-Q10), Endoplasmic Reticulum (ER), Scopolamine hydrobromide (SCO), Memantine (MEM), Proliferator- activated receptor gamma (PPARγ), Glial fibrillary acidic protein (GFAP), Ionized calcium-binding adapter molecule 1 (Iba1), Choline acetyltransferase (ChAT), β-amyloid peptides (Aβ), Alzheimer disease (AD), 1-methyl-4-phenylpyridinium ion (MPP+), Interferon regulatory factor 3 (IRF3), Myeloid differentiation primary response 88 (MyD88), Transmucosal immediate-release fentanyl (TIRF), *per os* (p.o.), Parkinson's disease (PD), subcutaneous (s.c.), milligram (mg), kilogram (kg), Lipopolysaccharide (LPS), phosphate-buffered Saline (PBS), microliter (μl), birthweight (b.wt), messenger ribonucleic acid (*Mrna)*, Tyrosine hydroxylase (TH), homo vanillic acid (HVA), 3,4-Dihydroxyphenylacetic acid (*DOPAC)*, Reactive oxygen species (ROS), Nitric oxide (NO), up-regulation, induction, increase (↑), down-regulation, reduction, inhibition (↓), spinal cord injury (SCI), group (gp), Macrophage inflammatory protein 1 *alpha* (MIP1α), Growth Associated Protein 43 (Gap43), nuclear factor erythroid 2–related factor 2 (*Nrf2)*, spinal cord injury (SCI), Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), Tumor necrosis factor-α (TNF-α), Interleukin-1β (IL-1β), Nitric oxide (NO), Inducible nitric oxide synthase (iNOS), Cyclooxygenase 2 (COX-2), lipopolysac-charide (LPS), IκB Kinase β (IKKβ), TGF-b-activated kinase 1 (TAK1), transforming growth factor (TGF), glial fibrillary acidic protein (GFAP), SRY-Box Transcription Factor 9 (SOX9), mitogen-activated protein kinase kinase 6(MKK6), p38 mitogen-activated protein kinases(p38MAPK), dimethyl sulfoxide (DMSO), Kun-Ming(KM)

Table 2 In vitro studies concerning effects of Curcumin on neurodegenerative disease

Cell type	Model	Intervention		Number of Cells	Treatment Duration	Results	Adverse Effects	Refs.
		Case	Control					
Neuroblastoma SH-SY5Y cells	APOE4-induced neurological damage	Curcumin (10,20 and 30 µmol/l)	–	–	2 days	• ↓TNF-α, IL-1β and NO • ↓iNOS and COX-2 expression • Inhibition of NF-κB p65 translocation • ↓ p65 and p-p65 expression • ↑ PPARγ expression	Toxicity at 20 µM	Wang et al. (2020)
BV2 microglial cell lines	LPS-induced neurotoxicity	Curcumin (1,5, 10, 20, and 40 µM—2 h) LPS (1 µg/mL—24 h)	–	1×10^6 cells/well (2 mL medium/well)	2 days	• ↓ IL-1β, IL-6, iNOS and CD16/32 • ↑ IL-4, IL-10, arginase 1, CD206 and TREM2 • ↓ p-IκB-α, p-NF-κB p65 and TLR4	Cytotoxicity at 20 µM	Zhang et al. (2019)
Hippocampal cells (HT22)	CoCl2- or ROS-based ER stress	Curcumin (1,2 and 5 µM) CoCl2 (100 and 200 µM) or O2 (1%)	Tunicamycin + DMSO + Vehicle	7×10^5 cells	3 days	• ↓ ROS, arrest in S and G2 phase • ↓ LPO • ↑ Prdx6 • ↓ CHOP, Bip, Bax and caspases • ↓ NF-κB and HIF-1 α		Chhunchha et al. (2013)
BV2 microglial cell	LPS-activated neuro-inflammation	Curcumin (2, 4, and 8 µM)	–	–	2 days	• ↓ TNF-α, IL-1β, iNOS and p-p65 • ↓ IKKβ/ NF-κB • ↑ miR-199b-5p		Gao et al. (2019)

Table 2 (continued)

Cell type	Model	Intervention		Number of Cells	Treatment Duration	Results	Adverse Effects	Refs.
		Case	Control					
Rat cortical astrocytes	Inflammatory cytokine stimulation	Curcumin (0.1, 0.5, 1, 2, 5, 10, 20 and 40 µmol/l) + TNF-α (20 ng/ml), IL-1β, TGF-β1 and TGF-β2 (10 ng/ml)	–	2×10^5 cells	2 days	• ↓ astrocyte activity and GFAP • ↓ NF-κB activity and p-IKK-α, p-IKK-β, p-IκB- α and p-65 expression • ↓ MCP-1, RANTES and CXCL10 • ↓ SOX9 expression and CSPG • ↓ α-SMA expression		Yuan et al. (2017)
Cell culture (isolated astrocyte from rat pup's brain aged 1–3 days old)	PD	Curcumin (1,2,4,8,16µM)	–	2×10^3 /well	2 days	• inhibition of NF-κB and IRF3 activation in MPP + -aroused astrocytes • ↓ MPP + -stimulated oxidative mediator in astrocytes • ↓ TNF-α and IL-6 production • ↑ IL-10 expression	Cur 16 µM ↓ cell vitality	Yu et al. (2016)
19 days Rats' embryos hippocampus neuronal/glial cultures	AD	Curcumin (10 µM) Aβ1–42 (25 µM) (1 h later) GW9662 (1 µM)	–	–	4 days	• ↓GFAP- and Iba-1-positive cells • ↓ IL-1β level • ↓TNF-α level • ↓COX-2 • ↓NO level • ↑ ChAT levels • Inhibition of NF-κB signaling pathway	N/A	Liu et al. (2016)

Table 2 (continued)

Cell type	Model	Intervention		Number of Cells	Treatment Duration	Results	Adverse Effects	Refs.
		Case	Control					
MES23.5 cells	6-OHDA induced PD	Curcumin in DMSO 2×10^4 μmol/L	DMSO	2×10^4 cells/well	1 days	• ↑ cell viability • ↓ cell death • ↑ mitochondrial membrane potential • Reinstate mitochondria function • ↓ oxidative stress • ↓ ROS generation • ↑ Cu/Zn-SOD • ↓ Nf-κB nuclear translocation	N/A	O'Riordan et al. (2006)
BV2 cells	LPS-induced inflammatory injury	LPS + Curcumin (2, 4, 8 μM)	LPS	–	26 h	• ↓ cell apoptosis & inflammation • ↑ cell viability • ↓ IL-6 • ↓ TNF-α • ↓ IL-1β • ↑ IL-10 • ↑ miR-362-3p • ↓ TLR4 • ↑ cytoprotectivity • ↓ caspase-3 • ↓ p65 • ↓ Nf-κB signaling pathway	N/A	Green et al. (1997)
Mesencephalic neuron-glia cultures	LPS-induced PD	LPS (5 ng/ml) Curcumin (10 μM) Curcumin (10 μM) 0.5 h, 1 h, 3 h and 6 h after LPS (5 ng/ml)	–	–	–	• ↓ NO and iNOS mRNA • ↓ TNF-α and its mRNA • ↓ PGE_2 • ↓ COX_2 mRNA • ↓ IL-1β and its mRNA • ↓ Neurotoxic factors • ↓ NFκB and AP-1	N/A	Yang et al. (2008)

Table 2 (continued)

Cell type	Model	Intervention		Number of Cells	Treatment Duration	Results	Adverse Effects	Refs.
		Case	Control					
HEK293 cells	Transfected with p65 Plasmid AD	pBACE1-NFκB + Curcumin pBACE1-NFκB + Flag-p65 + Curcumin pNFκB + Curcumin pNFκB + Flag-p65 + Curcumin	pBACE1-NFκB pBACE1-NFκB + Flag-p65 pNFκB pNFκB + Flag-p65	—	—	• ↓ BACE1 • ↓ $A\beta_{1-42}$ • ↓ pBACE1-NFκB • ↓ pNFκB	N/A	Huang et al. (2020)
SY5Y cells	Transfected with TNFα AD	TNFα + Curcumin	TNFα	—	—	• ↓ phosphorylation and degradation of IκBα • ↓ ser536 phosphorylation of NFκB p65 subunit • ↓ nucleus translocation of p65 • ↓ NFκB	N/A	Huang et al. (2020)
BV2 microglial cells	LPS-induced neurotoxicity AD	Curcumin (2 μM) + LPS (0.2 ng/ml) Curcumin (4 μM) + LPS (0.2 ng/ml) Curcumin (8 μM) + LPS (0.2 ng/ml) Cur (16 μM) + LPS (0.2 ng/ml)	No treatment LPS (0.2 ng/ml)	—	—	• ↓ AP-1 binding activity • ↓ NF-κB DNA binding • ↓ COX-2 mRNA • ↓ COX-2 protein and enzyme activity (PGE2)	N/A	Kang et al. (2004)

Tumor necrosis factor-α (TNF-α), N-acetyl cysteine (Nac), Apolipoprotein E4 (APOE4), Hippocampal cells (HT22), Curcumin (Cur), Reactive oxygen species (ROS), endoplasmic reticulum (ER), Dimethyl sulfoxide (DMSO), Lipid peroxidation (LPO), Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), Hypoxia-inducible factor-1α (HIF-1 α), C/EBP homologous protein (CHOP), Inducible nitric oxide synthase (iNOS), Lipopolysaccharide (LPS), Nitric oxide (NO), B cell inhibitor (IκB), Peroxiredoxin6 (Prdx6), Cyclooxygenase 2 (COX-2), Toll-like receptor 4 (TLR4), Triggering receptor expressed on myeloid cells 2 (TREM2), Interleukin-1β (IL-1β), Interleukin-10 (IL-10), Interleukin 6 (IL-6), Interleukin-4 (IL-4), phosphorylated p-65 (p-p65), IκB Kinase β (IKKβ), glial fibrillary acidic protein (GFAP), transforming growth factor-β1 (TGF-β1), transforming growth factor-β2 (TGF-β2), monocyte chemoattractant protein 1 (MCP-1), Regulated upon Activation, Normal T cell Expressed, and Secreted (RANTES), C-X-C motif chemokine ligand 10 (CXCL10), SRY-Box Transcription Factor 9 (SOX9), chondroitin sulfate proteoglycan (CSPG), α-smooth muscle actin (α-SMA), Parkinson disease (PD), Alzheimer disease (AD), 6-Hydroxydopamine (6-OHDA), Copper (Cu), Zinc (Zn), up-regulation, induction, increase (↑), down-regulation, reduction, inhibition (↓), spinal cord injury (SCI), hypoxia (Hyp), neurofilament-H (NF-H), nuclear factor erythroid 2–related factor 2 (Nrf2), Bcl-2-associated X-protein (Bax), cytochrome C oxidase IV (COXIV), Heme oxygenase 1 (HO-1)

days of treatment with 500 mg curcuminoids can improve conditions in hospitalized TBI patients compared to placebo. Curcuminoid supplementation attenuated levels of CRP, MCP-1, IL-6, and TNF-α levels while it didn't alter enzymatic activities of SOD and GPx significantly. Moreover, it reduced the mortality risk rate based on the acute physiology and chronic health evaluation (APACHE) II test. It could be possible that curcuminoid exert its anti-inflammatory effects via regulating NF-kB pathway (Zahedi et al. 2021). Moreover, addition of curcuminoids (500 mg), besides 5 mg/day piperine to routine therapeutic approaches compared to placebo for 7 days, diminished levels of leptin, but it didn't change adiponectin in TBI patients (Shadnoush et al. 2020). Curcumin (180 mg/day) prevents development of T2DM and AD. It was observed that curcumin treatment for 12 weeks led to glycogen synthase kinase-3-β and islet amyloid polypeptide levels reduction. It also decreased insulin resistance compared to placebo (Thota et al. 2020). Ahmadi et al. considered the addition of nano-curcumin (containing 80 mg curcuminoids) addition to riluzole in ALS patients. Compared to a placebo, it enhanced the survival rate without exerting any major side effects (Ahmadi et al. 2018).

Discussion, concluding remarks and future perspectives

The development of neurodegenerative diseases is highly dependent on the neuroinflammation and neural cell loss. Hence, regulating these two factors can prevent further progression of the ND. Scientists have tested and analyzed different natural and chemical compounds to manage the sign and symptoms of NDs, i.e., ALS, PD, SCI, HD, and AD. The noteworthy remark is that how inflammatory cascades in cellular levels can directly affect the patients' health-related circumstances. Hence, the ultimate goal is to investigate involved pathophysiologic mechanism and their affected pathways for better understanding the process of the incidents, discover suitable compounds and agent, hinder the progression of the disease, and raise the well-being of the patients.

NF-κB expression and its following signaling pathway have gained noticeable attention due to enormous impact on production of inflammatory proteins. Understanding the NF-κB mechanism and targeting it, seems to be an effective strategy for ameliorating NDs.

Curcumin is approved as a promising anti-oxidant, and anti-inflammatory compound in previous experiments.

Other review articles have pointed out curcumin's therapeutic role in AD, MS, and other neurological disorders due to its antioxidant, anti-inflammatory, and anti-apoptotic properties (Ghanaatian et al. 2019; Farkhondeh et al. 2019; Bland et al. 2023; Bhat et al. 2019). However, our study is the first review highlighting the NF-κB signaling pathway as curcumin's main target in all forms of NDs. Also, different studies have shown the curcumin's helpful anti-inflammatory effect in neurodegenerative diseases, mainly induced by modulation of NF-κB signaling route. The current review highlighted curcumin's remarkable impacts on restricting neuronal cell loss and inflammatory-related conditions by down-regulation of involved chemicals, cytokines, and signaling pathways.

Particularly, results from in vitro, as well as in vivo studies manifest the inhibitory influence of curcumin which happens on NF-κB signaling pathway as a way of reducing neuroinflammation, which is the primary cause of NDs.

The number of clinical trials on this matter is not satisfying yet. Thus, it seems more profound and concentrated experiments are needed to determine curcumin's exact administration dose, pharmacokinetics, pharmacodynamics, safety, and adverse consequences for reducing NF-κB activity in neurodegenerative disorders. Additional studies are required to examine not only the short-term effects but also the long-term outcomes of using curcumin to impede the NF-κB signaling mechanism in the referred disease (Tables 1, 2).

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