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Role of the NF-κB Signalling Pathway in the Pathophysiology in Depression

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Abstract:

- ***Introduction:***

Depression is a multifactorial psychiatric disorder closely associated with chronic inflammation and stress. The nuclear factor kappa-B (NF-κB) signalling pathway, a major regulator of immune and inflammatory responses, has emerged as a key molecular link between these factors and depression. Under chronic stress, NF-κB becomes over activated in neurons and glial cells, promoting the release of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. This heightened inflammatory response contributes to oxidative stress, neuronal dysfunction, and reduced neuroplasticity—central features of depressive disorders.

- ***Methods:***

This study employed a comprehensive literature review approach to investigate the role of the NF-κB signaling pathway in the pathophysiology of depression. The search used keywords such as "NF-κB," "depression," "inflammation," "cytokines," and "BDNF." Both experimental (animal and cellular) and clinical studies were included to evaluate molecular mechanisms linking NF-κB activation with depressive symptoms.

- ***Results:***

This review shows that NF-κB overactivation increases cytokines and oxidative stress, causing neuronal dysfunction. The Notch2/NF-κB pathway increases stress susceptibility, while NF-κB inhibition reduces depressive behaviours, suggesting therapeutic potential.

- ***Conclusion:***

NF-κB overactivation links inflammation and depression by impairing neuroplasticity and hormonal balance. Targeting this pathway may help reduce neuroinflammation and improve depressive symptoms. Further research should explore NF-κB inhibitors in clinical settings.

Keywords: *NF-κB, Depression, Inflammation, BDNF, Cytokines.*

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I. INTRODUCTION

Neurodegenerative diseases (NDDs) including Alzheimer's disease (AD), Parkinson's disease (PD), and related dementias are among the fastest-growing causes of disability and dependency worldwide. As populations age, the absolute number of people living with these conditions has risen sharply, with recent global analyses documenting substantial increases in prevalence, mortality and disability-adjusted life years (DALYs) attributable to NDDs during the past three decades (S. Wang et al., 2024).

Depressive disorders are similarly a leading contributor to the global burden of disease. Large, recent global studies report that depression remains a major cause of years lived with disability (YLDs) and that its contribution to overall mental-health burden has increased in the 2000s and 2010s trends that were further influenced by societal stresses such as the COVID-19 pandemic. The rise

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in prevalence and disability from depressive disorders has major social and economic consequences, affecting productivity, healthcare costs, and family caregiving needs (Zhao et al., 2025).

Beyond their individual impacts, neurodegenerative diseases and depression are tightly linked. Depression is common in patients with AD, PD and stroke, where it worsens clinical outcomes, accelerates functional decline, and increases caregiver burden. Conversely, there is growing evidence that depression can precede neurodegenerative syndromes and may act as a prodromal symptom or even as a risk factor for later neurodegeneration indicating a complex, possibly bidirectional relationship. Understanding this interplay is critical because coexisting depression amplifies morbidity and complicates diagnosis and management of NDDs (Pagonabarraga et al., 2023).

The combined public-health impact of NDDs and depression is striking. Rising case numbers for common NDDs such as AD and PD, paired with persistent high rates of depressive disorders, create overlapping needs for long-term care, mental-health services, and caregiver support stretching health systems, especially in low- and middle-income regions where ageing populations are growing fastest. These trends demand stronger integration of neurological and psychiatric care, better screening for mood disorders in patients with NDDs, longitudinal research to clarify causal links, and investment in prevention and support services that target both cognitive and affective outcomes (M. Li et al., 2025).

- *Limitations of Classical Neurotransmitters Theories:*

A large fraction of patients do not respond to monoamine-based treatments (treatment-resistant depression, TRD) Real-world and systematic studies consistently report that roughly 30% or more of people with major depressive disorder meet criteria for treatment-resistant depression (failure of ≥2 adequate trials), and long-term remission rates after standard therapies are often low (many studies report remission in the 20–50% range depending on the cohort). These figures show that monoamine targeting alone leaves a substantial unmet need (McIntyre *et al*., 2023).

Overall response and remission rates for conventional antidepressants are modest. Large treatment cohorts and randomized trials since 2020 report response rates commonly 25–35% and remission rates often below 35% in more difficult-to-treat samples again highlighting that many patients receive incomplete benefit from monoamine-centric drugs. These empirical rates are why clinicians and researchers pursue alternative mechanisms (Ruberto et al., 2020).

The delayed clinical onset of classical antidepressants is not explained by simple neurotransmitter level. Modern reviews note that although SSRIs and SNRIs change synaptic monoamine levels within hours, meaningful symptomatic improvement usually takes weeks for many patients. This dissociation (fast biochemical change vs slow clinical change) is a persistent mechanistic gap for classical models and motivates investigation of downstream processes (synaptic plasticity, neurogenesis, circuit remodeling) (Zelek-Molik & Litwa, 2025).

Rapid-acting non-monoaminergic treatments demonstrate different mechanisms and timeline. Intravenous ketamine and related glutamatergic agents can produce clinically meaningful improvement within hours to days, including in patients who previously failed multiple monoaminergic treatments. Multiple clinical trials and reviews (2021–2024) document rapid symptom reduction and anti-suicidal effects, supporting the idea that non-monoaminergic mechanisms (glutamate, synaptogenesis) are clinically important. This is direct experimental evidence that monoamine models are incomplete (Riggs & Gould, 2021).

Inflammatory markers correlate with disease and predict poorer response to monoamine antidepressants.Meta-analyses and cohort studies show that elevated peripheral cytokines (for example, IL-6, CRP) are statistically higher in many depressed patients and that higher baseline inflammation is associated with lower probability of response to standard antidepressants. This links immune processes to treatment outcome in a way classical neurotransmitter theories do not address (Gasparini et al., 2022).

- *Emergence of Transcription Factor Based Mechanism*

In recent years, the understanding of depression (and other mood disorders) has shifted beyond classical neurotransmitter theories to highlight transcription factor (TF) based mechanisms. Rather than just focusing on synaptic monoamines, research increasingly shows that TFs mediate long-term changes in gene expression, linking environmental stress, neuroinflammation, and cellular plasticity to the biology of depression.

One important piece of evidence comes from transcriptomic analyses of human patients. For example, a large-scale RNA-seq study comparing 79 unmediated individuals with major depressive disorder (MDD) to 80 healthy controls found significantly elevated activity of the NF-κB pathway (among other TFs) in the MDD group (Savitz et al., 2025a). This suggests that the inflammatory and immune-related transcriptional programs driven by NF-κB are more active in depressed patients, and that myeloid immune cells (monocytes) are likely a major cellular source of this change (Savitz et al., 2025b).

- *Introduction of NF-Kb as a Key Intracellular Signaling Hub*

NF-κB (nuclear factor-kappa B) has emerged as a central intracellular signaling hub in modern neurobiology and inflammation research. Originally identified as a transcription factor in immune cells, NF-κB is now understood as a master regulator integrating signals from psychological stress, infection, oxidative injury, and neuronal activity, thereby deciding whether a cell activates inflammation, initiates repair, or promotes survival. In the

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brain, chronic stress and elevated pro-inflammatory cytokines (such as TNF-α and IL-1β) activate NF-κB via receptors including TLR4, TLR2, and TNF receptors. For example, in mouse models, stress has been shown to elevate HMGB1 (a damage-associated molecular pattern), activate TLR4, and thereby trigger NF-κB signaling and the NLRP3 inflammasome, contributing to neuroinflammation and depression-like behavior (Cheng et al., 2016).Once activated, NF-κB translocate to the nucleus and promotes expression of key inflammatory mediators such as IL-6, COX-2, and iNOS, as well as genes involved in synaptic plasticity, neuronal resilience, and stress response (Shih et al., 2015).

II. STRUCTURAL AND FUNCTIONAL OVERVIEW OF NF-KB

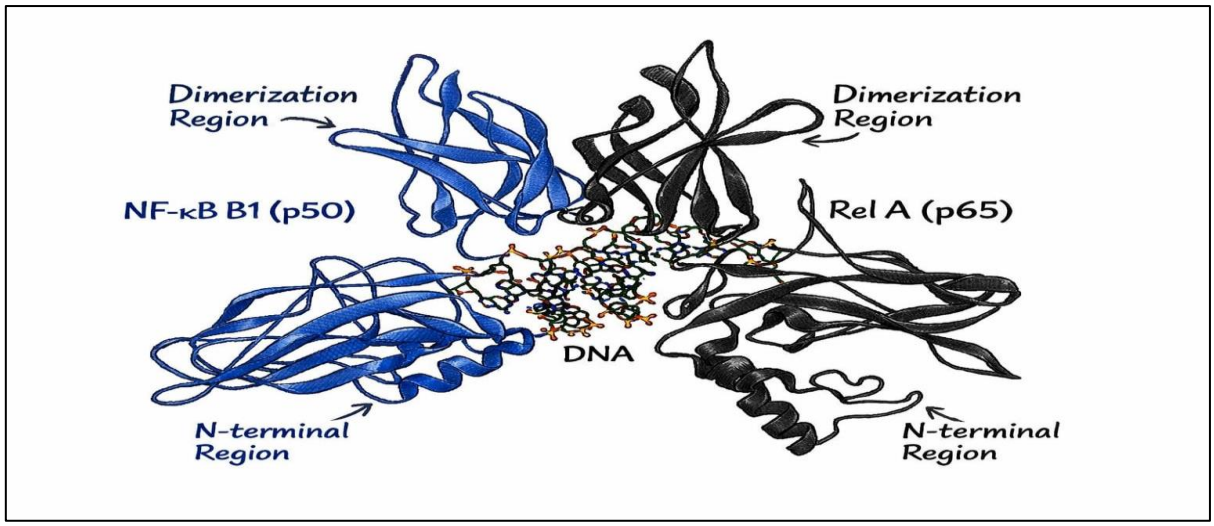

Fig 1 Structural and Functional Overview of NF-κB

➢ *Nf-Kb Family Proteins (p50, p65, p52, Rel B, c-Rel):-*

The NF-κB family is a group of five related transcription factors: RelA (p65), RelB, c-Rel, p50 (from p105) and p52 (from p100)**.** These proteins form different homo- or hetero-dimers that control many genes involved in inflammation, immunity, cell survival and stress responses (T. Zhang et al., 2021a) . All five proteins share a 300-amino-acid Rel Homology Domain (RHD) at their N-terminus. The RHD does three main things: **(a)** lets subunits dimerism, **(b)** binds specific κB DNA sites, and **(c)** contains the nuclear localization signal (NLS) needed for the complex to enter the nucleus. Because of the RHD, these proteins can pair in many combinations and thus regulate different gene sets (Msweli et al., 2024a).

- *Two Functional Groups — Who has a Transactivation Domain (TAD)*

✓ *TAD-Containing Subunits (can Activate Transcription):*

RelA (p65), RelB, c-Rel. When these are part of a dimer, they usually turn genes on (T. Zhang et al., 2021b).

✓ *No-TAD Subunits (Weak/ No Activation Alone):*

p50, p52 (generated by proteasomal processing of p105 and p100). As homodimers (p50:p50 or p52:p52) they often act as transcriptional repressors or neutral DNA binders; as heterodimers with a TAD partner they contribute to gene activation (Msweli et al., 2024b).

✓ *P65 (RelA):*

The most studied activator in the canonical pathway; when paired with p50 it strongly induces pro-inflammatory and survival genes (IL-6, TNF, anti-apoptotic genes). p65 dynamics (nuclear pulses/oscillations) are important for how genes are read (T. Zhang et al., 2021c).

✓ *P50 (from p105):*

Lacks a transactivation domain; p50:p50 homodimers often repress transcription or occupy κB sites to modulate responses. When paired with p65 or c-Rel it helps form transcriptionally active dimers. Genetic defects in NF-κB1 (p50/p105) are clinically relevant (immune dysregulation) (Fathi et al., 2023).

✓ *P52 (from p100):*

Produced by selective processing of p100 in the non-canonical pathway; commonly forms active dimers with RelB (p52: RelB) that regulate genes distinct from the canonical set. p100 itself can act as an inhibitor until processed (Iacobazzi et al., 2023a).

✓ *RelB:*

Preferentially functions in the non-canonical pathway, commonly pairing with p52 (and sometimes p50). RelB-containing dimers often regulate immune-organ development and long-term inflammatory programs (Iacobazzi et al., 2023b).

✓ *C-Rel:*

Strongly expressed in immune cells and important for cytokine gene regulation and lymphocyte function; c-Rel also contributes to certain innate immune responses and is being studied as a target in immune-driven diseases. Recent

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studies highlight stimulus-specific roles of c-Rel in immunity (A. R. Liu et al., 2024).

➢ *Inhibitory Proteins (Ikb):-*

The IκB (inhibitor of κB) proteins constitute the principal inhibitory regulators of the NF-κB transcription factor family. In resting cells, classical IκB (notably IκBα, IκBβ and IκB) bind NF-κB homo or hetero-dimers via their ankyrin-repeat domains and mask the NF-κB nuclear-localization signals, thereby retaining NF-κB in the cytoplasm and preventing target-gene transcription. On exposure to pro-inflammatory or stress signals, the IκB kinase (IKK) complex is activated and phosphorylates IκBα on conserved N-terminal serine residues (Ser32/Ser36). Phosphorylated IκBα is then recognized by ubiquitin E3 ligases (e.g. SCF^β-TrCP), polyubiquitinated (commonly at Lys21/Lys22) and degraded by the 26S proteasome; this liberation allows NF-κB to translocate into the nucleus and induce transcription of genes involved in inflammation, immunity, and cell survival. Importantly, IκBα itself is a direct NF-κB target gene, so newly synthesized IκBα re-enters the nucleus, removes NF-κB from DNA and shuttles the inactive complex back to the cytoplasm creating a rapid negative-feedback loop that limits and times NF-κB responses. Beyond the canonical phosphorylation–ubiquitination–degradation axis, IκB proteins are regulated by multiple post-translational modifications (phosphorylation at non-canonical residues, SUMOylation, ubiquitin-editing), and by dynamic nucleocytoplasmic shuttling; nuclear or "atypical" IκBs (e.g. IκBs, Bcl-3, IκBs) can also modulate NF-κB activity at the chromatin/transcriptional level, producing gene-specific effects. Because IκB regulation determines both the amplitude and duration of NF-κB signaling, dysregulation of IκB turnover or modification contributes to chronic inflammation, neuroinflammation, cancer and other pathologies and the IKK–IκB–NF-κB module remains a major therapeutic target (X. Wang et al., 2020).

➢ *Canonical Vs Non- Canonical Activation Pathways:*

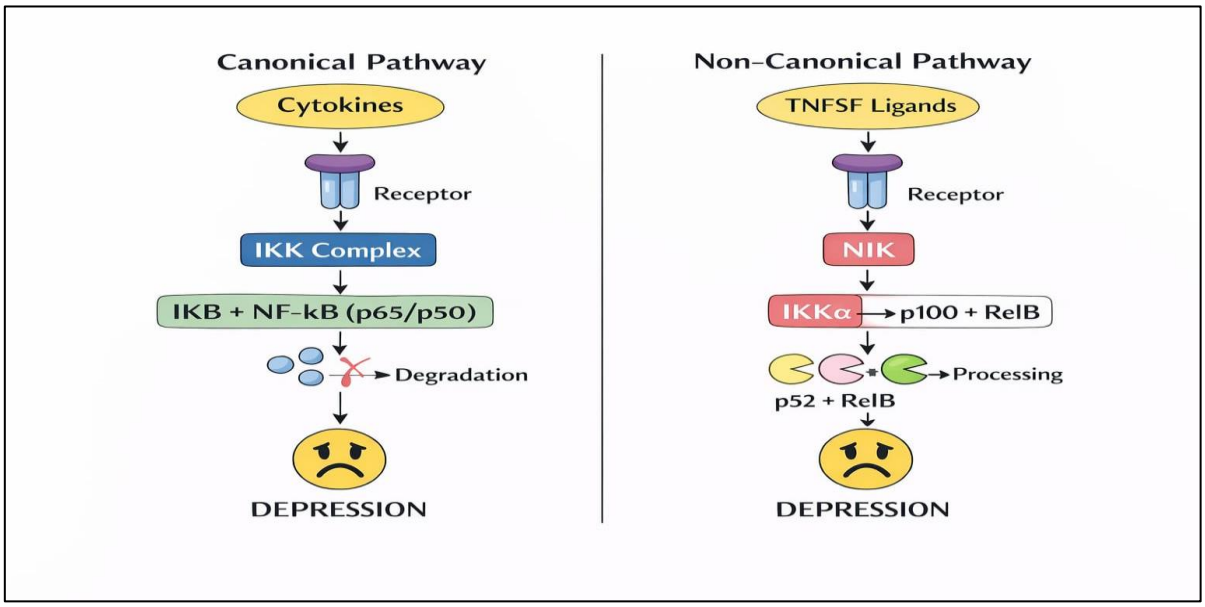

Fig 2 Canonical Vs Non- Canonical Activation Pathways

- *The Canonical Pathway:*

The canonical pathway is activated by a variety of stimuli, including pro-inflammatory cytokines, pattern-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) binding to cognate receptors. This triggers a signaling cascade culminating in the activation of the IKK complex through phosphorylation of series (S177 and S181 of IKKβ) in their kinase activation loop. The IKKβ subunit is thought to be the predominant component contributing to canonical NF-κB activation because IKKβ (*Ikbkb*) and p65 (*Rela*) knock out (KO) mice show a similar phenotype. It exists in a complex with IKKα and NEMO. The signaling complex that coordinates activation of the IKK complex is referred to as the signal some complex (SC) and is specific to the receptor, and hence ligand, stimulating the pathway. Canonical signaling is exemplified by the response to tumor necrosis factor α (TNFα) where, upon binding of TNFα to the TNF receptor (TNFR), TRADD and RIPK1 are recruited to the receptor via its death domain. TRAF2 is recruited via TRADD which itself recruits the E3 ligases cIAP1 and 2, which polyubiquitinated RIPK1. These ubiquitin chains act as anchors binding TAB/TAK1, allowing TAK1 to phosphorylate and activate the IKKs. Furthermore, the formation of linear methionine 1 (M1) ubiquitin chains can also activate the IKK complex when the E3 ligase LUBAC is recruited by TRADD, TRAF2 and cIAP1/2 and then ubiquitylates NEMO. This is thought to activate IKKs by promoting Trans auto phosphorylation. The canonical pathway is also activated by other ligands including interleukin-1 (IL-1) as recognized by the IL-1 receptor (IL-1R), the gram-negative bacterial component lipopolysaccharide (LPS) as recognized by Toll-like receptor 4 (TLR4), and T-cells as recognized by the T-cell receptor (TCR). These lead to different signaling components being recruited. In the case of IL-1R and TLRs,

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binding of their cognate ligands allows their intracellular Toll Il-1 receptor (TIR) domains to recruit TIR-containing adapter proteins such as MyD88, TRIM, Mal or TRAM, depending on the specific ligand and receptor .Dimerised MyD88 recruits IRAK4 which binds IRAK1 and this leads to the recruitment of the E3 ligase TRAF6. TRAF6 conjugates K63-linked polyubiquitin chains onto IRAK1. This facilitates the binding and phosphorylation of IKKs by TAK1.Upon activation, the IKKs phosphorylate the classical IκB proteins (at S32/S36 on IκBα), triggering their K48-linked polyubiquitylation by the $SCF^{\beta TrCP}$ E3 ligase complex, marking them for degradation by the 26S proteasome Canonical signaling liberates predominantly p65- and c-Rel-containing NF-κB dimers which enter the nucleus to bind to their DNA targets and promote gene expression (Prescott et al., 2021).

- *The Non-Canonical Pathway*

The non-canonical NF-κB pathway is activated by the wider TNF superfamily receptors (TNFSFR) including CD40, lymphotoxin β receptor (LTβ-R), B-cell activating factor receptor (BAFF-R) and receptor activation of NF-κB (RANK). Non-canonical NF-κB activation is mediated through an IKK complex that is proposed to consist of an IKKα homodimer without NEMO, and is dependent upon the cellular accumulation of NF-κB-inducing kinase (NIK). In the absence of a stimulus TRAF3 and cIAP1/2 bind to NIK and target it for K48 polyubiquitylation and proteasomal degradation. Upon receipt of an activating signal, TRAF2 recruits and K63-polyubiquitylates cIAP1/2. TRAF3 acts as an adaptor molecule that facilitates the formation of a complex composed of NIK, TRAF2 and cIAP1/2 which K48-polyubiquitylates TRAF3 causing it to be degraded by the proteasome. Since TRAF3 normally represses NIK levels this leads to the accumulation of NIK and activating phosphorylation of IKKα at S866/870 which activates it; IKKα then phosphorylates the NF-κB precursor protein, p100. This acts as a signal causing p100 to be recognised and polyubiquitylated by $SCF^{\beta TrCP}$, marking it for the partial peroteolytic processing of its C-terminal ankyrin repeat domain (ARD). This releases its N terminus, now known as the p52 subunit of NF-κB, which dimerises with RelB, translocates to the nucleus and drives gene expression. This processing event also eliminates the IκB property of p100. The C-terminus of p100 is structurally similar to other IκB proteins, containing multiple ARDs. It is not only able to sequester RelB: p52 NF-κB dimers in the cytoplasm, but also p65:p50 dimers which are traditionally considered effectors of canonical NF-κB signalling. Such cross-talk between the two activation pathways has led some to propose that NF-κB signalling should be viewed as a single system (Prescott et al., 2021).

➢ *Triggers in Neuronal Cells (ROS, Cytokines, Stress, Calcium Imbalance):*

In neurons (and other brain cells), NF-κB can be activated by several stress- or damage-related signals. Key triggers include:

- *Reactive Oxygen Species (ROS) / Oxidative Stress:*

✓ Excessive ROS / oxidative stress are common in neurodegenerative conditions and brain injury. Such oxidative stress can activate NF-κB signaling, leading to expression of inflammatory genes, cytokines, and other mediators (Hsieh & Yang, 2013a).
✓ Thus, ROS functions not only as damaging agents causing oxidative damage, but also as second messengers that stimulate redox-sensitive pathways including NF-κB (Hsieh & Yang, 2013b).

- *Pro-Inflammatory Cytokines and Neuroinflammation:*

✓ Cytokines such as Tumor Necrosis Factor-alpha (TNF-α), which are elevated in inflammatory or neurodegenerative conditions, can trigger NF-κB activation in neurons or glial cells (Fischer & Maier, 2015).
✓ This can also lead to production of ROS/RNS (reactive oxygen/nitrogen species), further amplifying oxidative stress and inflammatory signaling. This cross-talk between inflammation and oxidative stress forms a vicious cycle: cytokine → NF-κB → more pro-inflammatory genes + ROS generation → further NF-κB activation (González-Reyes et al., 2017).

- *Calcium Imbalance:*

✓ Disturbances in intracellular calcium homeostasis e.g. calcium overload, excitotoxicity, ischemia-reperfusion injury represent potent triggers of NF-κB activation in neuronal cells. Recent reviews on cerebral ischemia-reperfusion and neuronal injury highlight that elevated intracellular Ca^{2+} can lead to activation of signaling cascades (e.g. via Ca^{2+}-dependent kinases, calmodulin, calcineurin) culminating in NF-κB activation and neuroinflammation (Y.-W. Li et al., 2025).
✓ Calcium-mediated NF-κB activation may contribute to neuronal damage especially under excitotoxicity or ischemic conditions where Ca^{2+} influx, mitochondrial dysfunction, ROS generation and inflammatory signaling converge(Y.-W. Li et al., 2025).

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III. NF-KB IN NEURODEGENERATIVE DISEASES

S. No	Disease	Role of NF-κB Pathway	Therapeutic Uses	Contraindications	Mechanism / Key Factors	Reference
1	Parkinson Disease	NF-kB mediated neuroinflammation contributes to dopaminergic neuron loss	NF-κB inhibitors may reduce neuroinflammation and protect dopaminergic neurons	Long-term inhibition may suppress normal immune response	Oxidative stress, cytokine releases	Ghosh A et al. J Neuroimmune Pharmacol.2017
2	Alzheimer Disease	NF-KB regulates inflammatory genes involved in neuronal degeneration	Anti-inflammatory drugs targeting NF-κB may reduce amyloid-induced inflammation	Anti-inflammatory drugs targeting NF-κB may reduce amyloid-induced inflammation	Activation in microglia and astrocytes leading to Beta amyloid toxicity	Shih Rhet al. Cell Mol Neurobiol.2015
3	Depression	NF-kB activation promotes neuroinflammation and cytokines production contributing to depressive symptoms	Anti-inflammatory or NF-κB-modulating agents may improve depressive symptoms	Not suitable in patients with immune deficiency or severe infection	Increased IL-6,neuronal damage	Miller AH &Raison CL Brain Behav Immun.2016
4	Rheumatoid Arthritis	NF-kB regulates inflammatory mediators causing joint inflammation	NF-κB inhibitors help reduce inflammation and joint damage	Long-term suppression may increase risk of infection	Increased IL-6,cartilage degradation	Liu Tet al. signal Trans duct Target Ther.2017
5	Cancer	NF-kB promotes tumor survival ,proliferation ,and metastasis	Targeting NF-κB may enhance cancer therapy and induce tumor cell apoptosis.	May affect normal cell survival and immune defense	Anti-apoptotic gene expression, angiogenesis	Xia Y et al. Cell Death Dis.2022

A. Alzheimer's Disease:

Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by memory loss, synaptic dysfunction, extracellular amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles of hyper phosphorylated tau. In the last decade, chronic neuroinflammation has emerged as a central driver that links these pathological hallmarks to neuronal dysfunction and clinical decline. The transcription factor NF-κB is a key regulator of inflammatory and stress responses in the brain and therefore occupies a pivotal position in AD pathogenesis. NF-κB signaling contributes to Aβ production, tau pathology, glial activation, and maladaptive immune-neuronal crosstalk — making it both a marker and a potential therapeutic target in AD (Sun et al., 2022).

➢ *Amyloid-Beta (Aβ) and Tau-Induced NF-kB Activation:*

Amyloid-beta (Aβ) and tau induce NF-κB activation, fueling neuroinflammation in Alzheimer's disease (AD) through distinct yet interconnected pathways in microglia and neurons (T. Wang et al., 2025).

- *Aβ-Induced NF-KB Activation:*

Aβ oligomers trigger NF-κB signaling in microglia by phosphorylating IκBα and p65, activating the NLRP3 inflammasome and elevating proinflammatory cytokines like IL-1β. This process sustains chronic neuroinflammation, with NTN-1 treatment shown to inhibit Aβ-stimulated NF-κB and shift microglia toward an anti-inflammatory M2 phenotype in 2025 rat AD models. NF-κB up regulation by Aβ also links to oxidative stress and plaque progression (J. Zhang et al., 2024).

- *Tau-Induced NF-KB Activation:*

Pathological tau fibrils activate microglial NF-κB, promoting tau propagation and neurofibrillary tangle formation while amplifying inflammatory cascades. This tau-NF-κB axis intersects with Aβ pathology, creating a feedback loop that exacerbates neuronal loss, with NF-κB1 identified as a shared biomarker in AD and related disorders in studies. Inhibition of this pathway reduces tau seeding in experimental models (Povala et al., 2025).

B. Parkinson's Disease:

NF-κB activation drives neuroinflammation in Parkinson's disease (PD) by regulating proinflammatory cytokine production in microglia and astrocytes, contributing to dopaminergic neuron loss in the substantia nigra (Dolatshahi et al., 2021).

- *Mechanisms of NF-Kb in PD:*

Alpha-synuclein aggregates trigger NF-κB signaling in neurons and glia, leading to apoptosis and release of cytokines like TNF-α and IL-1β that amplify neurodegeneration. Both canonical and non-canonical NF-κB pathways activate in response to oxidative stress and

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mitochondrial dysfunction, sustaining chronic inflammation during PD progression. Misfolded alpha-synuclein from dying neurons further activates glial NF-κB, worsening synaptic loss and dopaminergic degeneration (Singh et al., 2020).

- *Dual Role and Therapeutic Potential:*

NF-κB exhibits a dual function in PD, promoting neuronal survival via mitochondrial maintenance at low activity levels while driving toxicity chronically. Inhibitors targeting NF-κB pathways, such as those blocking IKKβ or using natural compounds like tocotrienols, reduce microglial inflammation and protect dopamine neurons in PD models. Chinese medicine derivatives also suppress NF-κB to mitigate PD symptoms, highlighting its viability as a therapeutic target (Chaturvedi & Beal, 2008).

➢ *Dopaminergic Neuronal Loss and Microglial Activation:*

Parkinson's disease (PD) pathogenesis involves progressive dopaminergic neuronal loss in the substantia nigra pars compacta (SNpc), driven by alpha-synuclein aggregation, mitochondrial dysfunction, oxidative stress, neuroinflammation, and impaired protein clearance mechanisms (Morris et al., 2024).

- *Dopaminergic Neuronal Loss Mechanism:*

Selective vulnerability of SNpc dopaminergic neurons arises from high energy demands, dopamine metabolism generating oxidative stress, and alpha-synuclein misfolding into Lewy bodies that impair axonal transport and synaptic function. Mitochondrial defects, including PINK1/Parkin-mediated mitophagy failure and complex I inhibition, trigger apoptosis, necroptosis, and ferroptosis, leading to dopamine release deficits before overt cell death. Genetic factors like SNCA, LRRK2, and GBA mutations accelerate this loss, while environmental toxins exacerbate protein aggregation and neuronal degeneration (Chaudhary et al., 2025).

- *Microglial Activation and Neuroinflammation:*

Microglia become chronically activated by extracellular alpha-synuclein aggregates via TLRs and NLRP3 inflammasome, releasing TNF-α, IL-1β, and ROS that amplify dopaminergic toxicity and synaptic pruning. This creates a feed-forward loop where dying neurons release damage-associated molecular patterns, sustaining microglial hypertrophy and impairing lysosomal/autophagy pathways. Gut-brain axis dysbiosis may initiate peripheral inflammation that propagates centrally via vagal nerves (Jankovic & Tan, 2020).

C. Multiple Sclerosis:

NF-κB signaling is central to Multiple Sclerosis (MS) pathogenesis, orchestrating immune cell activation, proinflammatory cytokine production, and chronic neuroinflammation that drive demyelination, axonal damage, and neurodegeneration in the central nervous system (Guo et al., 2024). Multiple Sclerosis (MS) is a chronic autoimmune disorder characterized by neuroinflammation-driven demyelination and neurodegeneration within the central nervous system (CNS). The hallmark of MS pathology is the immune-mediated destruction of myelin sheaths produced by oligodendrocytes, which results in impaired nerve conduction, axonal injury, and neuronal loss. The process is initiated and perpetuated by a complex interplay between peripheral immune cell infiltration, resident glial cell activation, and molecular signaling that disrupts myelin integrity and blocks demyelination attempts (Garton et al., 2024)

- *Cellular and Molecular Mechanism:*

NF-κB activates in T cells, B cells, microglia, astrocytes, and oligodendrocytes via canonical (IKKβ-dependent) and non-canonical pathways triggered by stimuli like TNF-α, cytokines, and microbial products, leading to nuclear translocation of p65/RelA and p50 subunits. Genome-wide association studies identify MS risk variants in NF-κB pathway genes (e.g., NFKB1, REL, NFKBIZ), enhancing IκBα degradation and sustaining transcription of IL-1β, TNF-α, IL-6, and chemokine's that promote blood-brain barrier breach and lymphocyte infiltration. In active MS lesions, heightened NF-κB DNA-binding correlates with microglial hypertrophy, T cell perivascular cuffing, and impaired myelin repair, while genetic polymorphisms reduce NF-κB inhibitors like A20, amplifying glial inflammation (Leibowitz & Yan, 2016).

- *Dual Role and Disease Progression:*

NF-κB exhibits context-dependent effects: protective in regulatory B/T cells via anti-apoptotic genes early in MS, but pathogenic chronically by shifting microglia to pro-inflammatory M1 states and exacerbating oxidative stress in relapsing-remitting and progressive forms. It intersects with EBV infection, where viral proteins up regulate NF-κB to foster auto reactive B cells, and with gut dysbiosis influencing peripheral immune priming. Experimental autoimmune encephalomyelitis models confirm NF-κB knockout in myeloid cells reduces disease severity by curbing macrophage infiltration and cytokine storms (Goodin, 2025).

➢ *Neuroinflammatory Demyelination in MS:*

Neuroinflammation plays a pivotal role in MS by recruiting auto reactive T cells, B cells, and myeloid cells across a compromised blood-brain barrier into the CNS. These immune cells release proinflammatory cytokines (such as TNF-α, IFN-γ, and IL-17), reactive oxygen and nitrogen species, and complement proteins that damage oligodendrocytes and myelin. Microglia and macrophages engulf myelin debris but can also adopt pro-inflammatory phenotypes leading to ongoing tissue injury. Despite early preservation of oligodendrocytes numbers in active lesions, chronic lesions show progressive oligodendrocytes loss and failed demyelination associated with inhibitory factors and glial scar formation (Boutitah-Benyaich et al., 2025).

Humoral immune components, including antibodies and complement cascade activation, contribute significantly to myelin destruction. Oligoclonal bands in cerebrospinal fluid reflect local antibody production supporting

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inflammatory demyelination. Complement activation leads to formation of membrane attack complexes that directly lyse myelin membranes. TNF receptor 1 signaling promotes oligodendrocytes apoptosis, while TNF receptor 2 activates survival pathways, highlighting the dual cytokine roles in demyelination and repair (Mahajan et al., 2025).

- *Glial Cell Interaction:*

Astrocytes and microglia respond robustly to the inflammatory milieu. Reactive astrocytes release cytokines and chemokine's further recruiting immune cells and contribute to blood-brain barrier dysfunction. Microglia become chronically activated, displaying hypertrophy and upregulated inflammatory mediators that further exacerbate oligodendrocytes stress and myelin damage. Subtypes of oligodendrocytes precursor cells (OPCs) exhibit reduced proliferative and demyelinating capacities under inflammatory cytokine exposure (e.g., IFN-γ), contributing to demyelination failure (Coutinho Costa et al., 2023).

- *Molecular Pathways and Therapeutic Insights:*

Signaling pathways including p38-MAPK, NF-κB, and integrated stress responses regulate inflammatory activation and cell death processes in MS lesions. Therapies aimed at modulating TNF signaling, promoting OPC differentiation, and reducing ER stress show promise for enhancing demyelination. Immune-modulatory drugs such as sphingosine 1-phosphate receptor modulators and monoclonal antibodies target peripheral immune infiltration and glial activation, thereby limiting demyelination. This neuroinflammatory demyelination process results in diverse clinical manifestations depending on lesion location, from sensory-motor deficits to cognitive impairment, making it essential to understand the multifactorial interplay between immune cells, glia, and oligodendrocytes for developing effective MS treatments (Bando, 2020).

➢ *Shared Mechanism in NF-Kb:*

NF-κB serves as a shared molecular hub integrating oxidative stress, mitochondrial dysfunction, apoptosis, and cytokine toxicity across neurodegenerative and inflammatory diseases like Alzheimer's, Parkinson's, and multiple sclerosis. Activated by reactive oxygen species (ROS), NF-κB translocates to the nucleus to transcribe proinflammatory genes, creating feedback loops that amplify cellular damage. This convergence positions NF-κB as a therapeutic nexus for mitigating common pathological cascades in these conditions (Zong et al., 2024).

- *Oxidative Stress and NF-Kb Crosstalk:*

Oxidative stress from excess ROS activates the canonical NF-κB pathway via IKK phosphorylation and IκBα degradation, while NF-κB up regulates NADPH oxidases (e.g., NOX1/2) and iNOS, perpetuating ROS production and peroxynitrite formation. Mitochondrial superoxide leakage further fuels this cycle, impairing antioxidant defenses like GSH/GSSG ratios. Recent studies confirm NF-κB inhibition reduces ROS in disease models, restoring redox balance (Mariappan et al., 2010).

- *Mitochondrial Dysfunction via NF-Kb:*

NF-κB localizes to mitochondria, where it disrupts electron transport chain complexes (e.g., complex III), elevates mitochondrial ROS, and alters dynamics through OPA1 regulation, leading to fission/fusion imbalance and ATP depletion. This dysfunction triggers bioenergetics failure and cytochrome c release, linking NF-κB directly to organelle integrity loss in neurodegeneration. Pharmacological blockade (e.g., PDTC) preserves mitochondrial structure and function in oxidative stress models (Laforge et al., 2016).

✓ *Apoptosis and Cytokines Toxicity Pathway:*

NF-κB promotes apoptosis by inducing pro-death cytokines (TNF-α, IL-1β, IL-6) that engage death receptors, activating caspases and JNK/p38 MAPK while suppressing anti-apoptotic genes like XIAP in chronic states. Cytokine storms exacerbate mitochondrial outer membrane permeabilization, amplifying Bax/Bak oligomerization. Dual-role dynamics show early NF-κB neuroprotection shifting to toxicity with sustained activation (Adlimoghaddam & Albensi, 2021).

IV. NF-KB AND DEPRESSION MECHANISTIC LINK

NF-κB (Nuclear Factor kappa B) signaling plays a crucial mechanistic role in depression by regulating neuroinflammation, neural plasticity, and stress responses. Chronic stress and inflammatory stimuli activate NF-κB in brain regions such as the hippocampus and prefrontal cortex, leading to the transcription of proinflammatory cytokines (IL-1β, IL-6, TNF-α) that disrupt neurogenesis and synaptic function, which are key contributors to depressive symptoms. NF-κB activation mediates stress-induced reduction in neural stem cell proliferation and plasticity, underlying anhedonia and mood dysregulation in depression models (Koo et al., 2010a).

NF-κB activation occurs via phosphorylation and degradation of its inhibitor IκB-α, resulting in nuclear translocation of p65/p50 subunits, which promote expression of inflammatory and apoptotic genes. Studies have shown increased NF-κB signaling in depressive patients and animal models, linking its activity to cytokine toxicity, oxidative stress, and neuronal apoptosis. The neuroinflammatory cascade driven by NF-κB amplifies depression severity and persistence, partly through dysregulation of brain-derived neurotrophic factor (BDNF) and impaired neuroplasticity(Cui et al., 2024).

Emerging evidence illustrates a bidirectional relationship where NF-κB activation also modulates BDNF signaling, forming a feedback loop critical for antidepressant effects. Inhibiting NF-κB or modulating its downstream targets has shown antidepressant-like effects in preclinical studies, highlighting therapeutic potential. Agents like ketamine exert anti-inflammatory actions partially through NF-κB pathway inhibition, reducing proinflammatory cytokines and restoring synaptic function (Sokołowska et al., 2023).

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➢ *Chronic Stress → NF-Kb Activation in Brain Cells:*

Chronic stress activates NF-κB signaling in brain cells, particularly in the hippocampus, prefrontal cortex, and nucleus accumbens, driving neuroinflammation, impaired neurogenesis, and behavioral deficits associated with mood disorders(Koo et al., 2010b).

- *Mechanism of NF-Kb Activation by Chronic Stress:*

Chronic stress triggers NF-κB via the canonical pathway, where stressors elevate glucocorticoids and proinflammatory cytokines (e.g., IL-1β), leading to IKK phosphorylation, IκBα degradation, and nuclear translocation of p65/p50 dimers in neural stem cells (NSCs), microglia, and neurons. This activation selectively inhibits NSC proliferation in the hippocampal sub granular zone without affecting early progenitors, reducing neurogenesis by 50% in stress models. The cAMP-PKA/EPAC pathway further amplifies NF-κB by altering phosphorylation states, sustaining cytokine release (TNF-α, IL-6) and oxidative stress(Z. Liu et al., 2025).

- *Cellular Impact in Brain Regions:*

In microglia, chronic stress induces NF-κB-mediated M1 polarization, releasing neurotoxic factors that prune synapses and exacerbate neuronal apoptosis in the prefrontal cortex. Hippocampal NSCs show preferential NF-κB up regulation (20-25% of cells), linking to dendritic atrophy and anhedonia. Nucleus accumbens NF-κB modulates glutamate homeostasis and neuroimmune responses, contributing to reward deficits. Astrocytes exhibit delayed NF-κB responses, promoting glial scarring and barrier dysfunction (Koo et al., 2010c).

➢ *Increased Cytokines Affecting Neuronal Structure:*

Increased proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 directly and indirectly alter neuronal structure by modulating synaptic protein expression, dendritic arborization, spine density, and axonal integrity, contributing to neuroinflammatory disorders (Zipp et al., 2023a).

- *Synaptic Structure and Plasticity Disruption:*

Elevated TNF-α reduces AMPA receptor trafficking and surface expression on postsynaptic membranes, decreasing spine head volume and excitatory synapse stability in hippocampal and cortical neurons. IL-1β impairs long-term potentiation (LTP) by elevating nitric oxide and altering actin cytoskeleton dynamics, leading to dendritic spine retraction and loss. IL-6 chronically promotes synaptic pruning via microglial activation and complement deposition, reducing synapse number by 20-30% in disease models while acutely enhancing inhibitory transmission(Zipp et al., 2023b).

- *Dendritic and Axonal Morphology Changes:*

Cytokines induce dendritic atrophy through p38 MAPK and NF-κB pathways, shrinking branch length and complexity in prefrontal cortex neurons under inflammatory conditions. TNF-α signaling via TNFR1 triggers caspases-mediated axonal fragmentation and tau hyper phosphorylation, mimicking neurodegenerative changes. Combinatorial cytokine effects (e.g., TNF-α + IL-6) amplify blood-brain barrier permeability, allowing further immune infiltration that sustains structural remodeling and impairs myelination (Martins & Harrison, 2025).

➢ *Suppression of BDNF, Impaired Neuroplasticity and Neurogenesis:*

Suppression of brain-derived neurotrophic factor (BDNF) disrupts neuroplasticity and neurogenesis, contributing to psychiatric and neurodegenerative disorders through impaired synaptic strengthening, dendritic remodeling, and neural progenitor survival(Yang et al., 2020a).

- *Mechanism of BDNF Suppression:*

Chronic stress, inflammation, and genetic variants (e.g., Val66Met polymorphism) reduce BDNF transcription via hyper methylation of promoters and glucocorticoid receptor-mediated repression, lowering mature BDNF levels in hippocampus and prefrontal cortex. This halts TrkB signaling cascades including MAPK/ERK-CREB activation, which normally drives c-Fos, Arc, and NeuroD1 expression essential for neuronal differentiation. ProBDNF accumulation binds p75NTR, promoting apoptosis and synaptic pruning over maturation, exacerbating circuit instability(Yang et al., 2020b).

- *Neurogenesis Disruption:*

Adult hippocampal neurogenesis halts due to BDNF loss, as neural progenitors fail to proliferate or differentiate into granule cells, with survival rates dropping post-mitosis. Pathways like PI3K/Akt and PLCγ, BDNF-dependent for progenitor migration and integration, shut down, linking to cognitive deficits and mood dysregulation. Antidepressants reverse this by elevating BDNF, restoring dentate gyrus proliferation and circuit embedding(Yang et al., 2020c).

➢ *Depression and Neurodegeneration Overlapping Mechanism Pathway:*

Depression and neurodegeneration share overlapping mechanistic pathways including neuroinflammation, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, impaired neuroplasticity, monoamine oxidase (MAO) enzyme hyperactivity, and genetic vulnerabilities that create bidirectional risk (Untu et al., 2025).

- *Neuroinflammation and Cytokines Dysregulation:*

Proinflammatory cytokines (IL-6, TNF-α, IL-1β) elevate in both conditions, activating microglia and astrocytes to release neurotoxic factors that prune synapses and promote protein aggregation (e.g., amyloid-β, alpha-synuclein). This chronic inflammation disrupts blood-brain barrier integrity, amplifying oxidative stress and neuronal apoptosis via NF-κB and NLRP3 inflammasome pathways. Genome-wide association studies identify shared variants in immune genes linking depression to Alzheimer's disease (AD) and Parkinson's disease (PD) progression(Hussain et al., 2020).

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- *HPA Axis Hyperactivity and Glucocorticoid Resistance:*

Chronic stress in depression induces HPA overdrive, elevating cortisol that impairs hippocampal neurogenesis and BDNF expression while accelerating tau hyper phosphorylation and amyloid genesis in neurodegeneration. Glucocorticoid resistance sustains inflammation, reducing neuroplasticity through glucocorticoid receptor dysfunction in prefrontal cortex and hippocampus. Longitudinal data show midlife depression doubles AD risk via these endocrine changes(Papa et al., 2025).

V. THERAPEUTIC TARGETING OF NF-KB

➢ *Pharmacological Inhibitors:-*

- *IKK Blockers:*

IκB kinases (IKKα/β/IKKε) phosphorylate IκB proteins, triggering NF-κB release and nuclear translocation. Blocking IKKs therefore prevents pathway activation upstream. Small-molecule IKK inhibitors (ATP-competitive or allosteric) and IKK-targeting scaffolds have been developed; these reduce NF-κB activation in cellular models and show efficacy in preclinical inflammation models. However, therapeutic translation is limited by on-target immune suppression and tissue homeostasis effects because IKKs regulate many physiological processes(Ali et al., 2020).

- *Antioxidants:*

Antioxidants play a complementary role by scavenging reactive oxygen species (ROS), which are upstream activators of NF-κB. Compounds such as N-acetyl cysteine (NAC), tempol, and edaravone reduce oxidative stress and thereby indirectly inhibit NF-κB activation, restoring mitochondrial function and reducing apoptosis in neurodegenerative models. Natural antioxidants including curcumin, resveratrol, tocotrienols, and phenolic compounds also inhibit NF-κB pathway components, adding neuroprotective effects by lowering inflammation and protein aggregation in brain cells(Tyuryaeva & Lyublinskaya, 2023).

- *Cytokines Blockers:*

Pharmacological inhibitors targeting cytokines block key proinflammatory mediators like TNF-α, IL-1β, and IL-6, disrupting NF-κB-driven neuroinflammation in neurodegenerative diseases (NDDs) such as Alzheimer's and Parkinson's by preventing IKK activation and cytokine storms from microglia (Mallick et al., 2025a)**.**

✓ *TNF-α Inhibitors:*

Etanercept and adalimumab neutralize TNF-α, reducing NF-κB p65 phosphorylation and synaptic damage in preclinical NDD models while improving cognitive outcomes in clinical trials for MS and stroke-related neurodegeneration. These biologics enhance blood-brain barrier penetration via intranasal routes, curbing amyloid aggregation and dopaminergic loss with 50-70% inflammation reduction (Sharma et al., 2025).

✓ *IL-1β and IL-6 Blockers:*

Anakinra inhibits IL-1R signaling, blocking IκBα degradation and NLRP3 inflammasome activation in PD and stroke models, yielding neuroprotection and normalized CSF cytokines in early AD trials. Tocilizumab targets IL-6R trans-signaling, suppressing STAT3/NF-κB crosstalk and astrogliosis in ALS and depression-NDD overlaps, with JAK inhibitors like baricitinib offering oral alternatives for broader cytokine control (Mallick et al., 2025b)**.**

➢ *Neuroprotective Natural Compounds:*

NF-κB is a central transcriptional regulator of neuroinflammation and cell stress responses in the central nervous system. Chronic or dysregulated NF-κB activation in microglia, astrocytes and neurons drives sustained production of pro-inflammatory cytokines (TNF-α, IL-1β), inducible enzymes (iNOS, COX-2) and chemokines that contribute to neuronal dysfunction and cell loss in Alzheimer's disease, Parkinson's disease, ischemic injury and traumatic brain injury. Modulating (rather than abolishing) NF-κB signaling therefore represents a rational neuroprotective strategy to reduce maladaptive inflammation while preserving essential homeostatic NF-κB functions (Fan & Lei, 2022a). Plant-derived compounds (polyphenols, flavonoids, alkaloids, withanolides and saponins) frequently act on multiple nodes of stress and inflammatory networks. They commonly combine antioxidant activity, mitochondrial protection and proteostasis modulation with direct effects on NF-κB pathway components (e.g., reduced IKK activation, stabilization of IκBα, decreased nuclear p65 activity). This pleiotropy can produce synergistic neuroprotective outcomes in preclinical models; however, translational success requires rigorous attention to formulation, brain exposure and target engagement(Yoon, 2025).

- *Molecular mechanisms:*

✓ *Blocking IKK Activation / Preventing IκBα Phosphorylation and Degradation:*

Several phytochemicals directly or indirectly lower IKK activity or inhibit IκBα phosphorylation, retaining NF-κB in the cytosol and decreasing inflammatory gene transcription (Fan & Lei, 2022b).

✓ *Antioxidant Upstream Effects and Nrf2 Cross-Talk:*

Because oxidative stress activates redox-sensitive kinases that feed into NF-κB, antioxidant-active compounds (and those that activate Nrf2) reduce upstream triggers and thereby blunt NF-κB activation. Cross-talk between Nrf2 activation and NF-κB suppression is repeatedly observed and offers a dual protective mechanism(Chiang et al., 2023a).

✓ *SIRT1 / Deacetylation-Based Modulation:*

Compounds such as resveratrol activate SIRT1, which deacetylates the NF-κB p65/RelA subunit and reduces its transcriptional potency a modulatory mechanism that dampens inflammatory output without fully inhibiting other NF-κB roles (Rogina & Tissenbaum, 2024).

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✓ *Interference with Nuclear Import or DNA Binding:*

Some polyphenols reduce nuclear translocation or directly impair NF-κB DNA binding, lowering downstream cytokine and enzyme expression in glia and neurons (Fideles et al., 2023).

- *Natural Compounds:*

✓ *Curcumin (Curcuma Longa):*

Curcumin reduces IKK/IκB phosphorylation, lowers microglial TNF-α/IL-1β and suppresses iNOS/COX-2 expression in multiple neuronal and glial models. Recent work emphasizes nano and carrier formulations that improve brain delivery and enhance NF-κB suppression in vivo (Fan & Lei, 2022c).

✓ *Resveratrol:*

Acting via SIRT1 and AMPK, resveratrol lowers p65 acetylation and NF-κB transcriptional activity, reducing microglial activation and improving behavioral endpoints in rodent models of neurodegeneration and hypoxic/ischemic injury. Clinical translation remains limited by dose/formulation variability (Ma et al., 2019).

✓ *Quercetin:*

Quercetin inhibits NF-κB activation and NLRP3 inflammasome signaling in neuronal and microglial models; nanoparticle formulations show improved CNS exposure and clear histological/functional benefit in preclinical studies (Chiang et al., 2023b).

✓ *EGCG (Green Tea Catechin):*

EGCG suppresses microglial NF-κB activation, reduces cytokine release and limits aggregation-related toxicity; preclinical report consistent anti-inflammatory effects linked to NF-κB modulation(Alam et al., 2024).

✓ *Berberine and Withanolides (e.g., Withaferin A):*

Berberine reduces TLR4/MyD88/NF-κB signaling and protects in stroke/SAH models; withanolides from Withania somnifera show NF-κB suppression and broad anti-inflammatory/neuroprotective activity in multiple preclinical reports(Tian et al., 2023).

VI. CONCLUSION

NF-κB acts as a central regulator of inflammation, immunity, apoptosis, and stress responses, making it a key driver in the pathogenesis of major neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, ALS, and Multiple Sclerosis. Studies shows that chronic and uncontrolled NF-κB activation promotes microglial overactivation, synaptic dysfunction, oxidative injury, and neuronal loss. At the same time, selective and balanced NF-κB signaling is necessary for neuronal survival and repair.

Targeting NF-κB through IKK inhibitors, antioxidants, cytokine blockers, or neuroprotective natural compounds offers promising therapeutic potential. However, complete inhibition may disrupt essential physiological functions. Therefore, future therapies must focus on pathway-specific, cell-specific, and context-dependent modulation. Overall, NF-κB remains a powerful therapeutic target, but precision regulation rather than broad suppression will be essential for safe and effective clinical translation.

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