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Targeting *MAPK9* in neurodegenerative diseases: mechanistic insights, phytochemical modulators, and emerging computational approaches

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Abstract

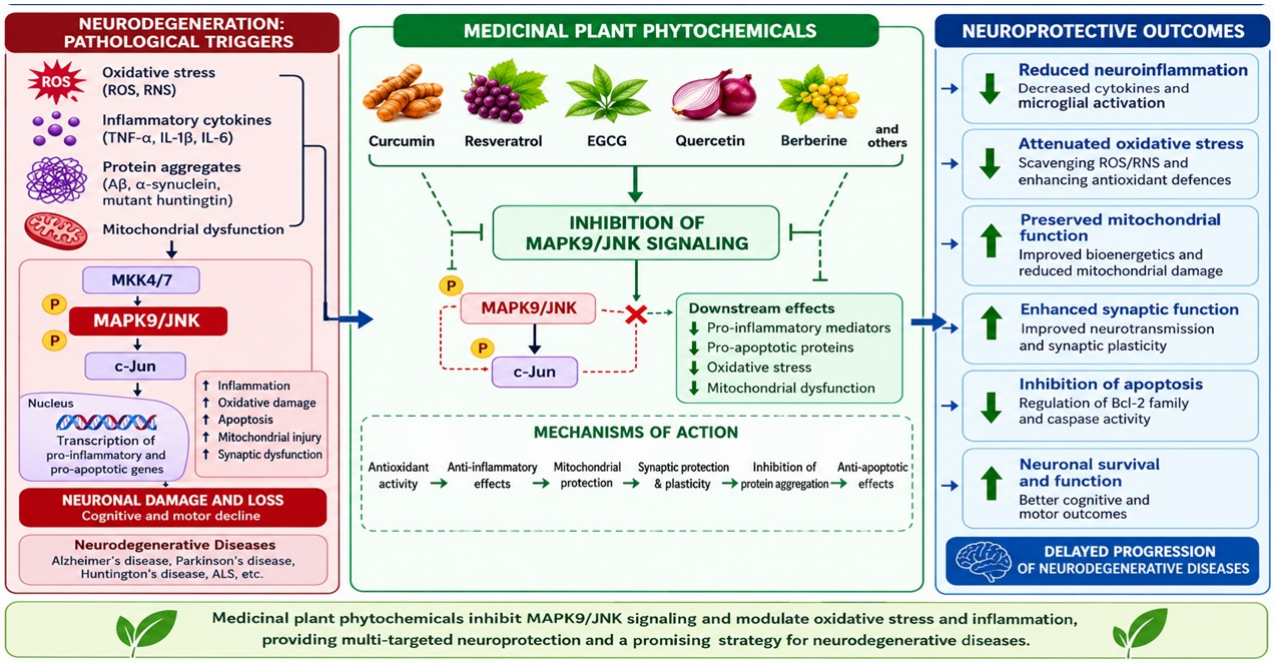
The protein Mitogen-activated protein kinase 9 (*MAPK9*) (c-Jun N-terminal kinase 2 [*JNK2*]) is a critical signalling molecule involved in cellular survival, inflammation, oxidative stress, and the programming of cell death. This is because there has been emerging evidence of the effects of the abnormal activation of *MAPK9* in the pathogenesis and progression of neurodegenerative disorders like Alzheimer's disease, Parkinson's disease, and Huntington's disease. However, many medicinal plants possess multiple phytoconstituents with neuroprotective activity that can modulate the *MAPK9* signalling cascade and protect neurons against injury. Thus, this review focuses on the biology and signalling pathways of *MAPK9*, its function in neurodegeneration, and medicinal plants and phytochemicals targeting *MAPK9*, together with their biological mechanism(s) of action. Recent advancements in drug design and discovery, involving computational techniques such as molecular docking, network pharmacology, and artificial intelligence, were also discussed. Additionally, current problems, limitations, and possibilities in the clinical translation of these natural compounds were highlighted. Therefore, knowledge of how these phytochemicals modulate the *MAPK9* signalling pathway may offer safer, more effective preventive and therapeutic approaches for neurodegenerative disorders.

Keywords

MAPK9, neurodegeneration, medicinal plants, curcumin, resveratrol, molecular docking, network pharmacology

Introduction

Neurodegenerative diseases remain one of the major public health problems affecting many parts of the world due to their characteristic gradual degradation of neuronal structure and function, causing cognitive



Graphical abstract. Phytochemicals targeting *MAPK9*/*JNK* signalling.

impairment, loss of mobility, and eventually, severe disability [1]. Some of the common neurodegenerative diseases include Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), which affect their respective patients in terms of morbidity and even death in many cases [2, 3]. AD is mainly known for causing dementia, with major hallmarks of amyloid β (Aβ) plaques, neurofibrillary tangles, synaptic dysfunction, and cognitive decline [3]. Similarly, the pathogenesis of PD involves the loss of dopaminergic neurons from the substantia nigra along with the formation of proteinaceous aggregates called α-synuclein, producing symptoms such as tremor, rigidity, and dyskinesias [4]. Furthermore, HD involves inherited genetic mutations that cause cytosine-adenine-guanine (CAG) repeat expansions in the huntingtin gene, resulting in neuronal malfunction and the development of motor and neuropsychiatric symptoms [5]. Likewise, in ALS, there is degeneration of both upper and lower motor neurons, leading to muscle weakness and ultimately death due to respiratory insufficiency [6].

However, the burden from neurodegenerative disorders remains on the rise due to the increase in the elderly population and life expectancy globally [1]. Such diseases present significant socio-economic and health care problems, not only in terms of patient suffering but also for their caregivers and the health system. Currently, therapeutic measures for neurodegenerative disorders are mainly symptomatic, failing to prevent the disease process and even reverse it [7]. As such, acetylcholinesterase inhibitors and *N*-Methyl-*D*-aspartate (NMDA) antagonists that form part of treatment options for AD are only able to temporarily improve the symptoms, with dopamine agonists used in PD becoming less and less effective with time [8, 9]. On the same note, currently available treatments for HD and ALS only yield little improvement and are unable to address the cause of neuronal cell damage [2, 5].

In recent years, significant advances in molecular neuroscience have revealed that intracellular signal transduction pathways are essential to the pathophysiology of neurodegenerative diseases. Of these signal transduction pathways, the mitogen-activated protein kinase (*MAPK*) pathway is crucial in regulating cellular responses to stress, inflammation, apoptosis, and survival [10]. *MAPK9*, also known as c-Jun N-terminal kinase 2 (*JNK2*), plays a significant role in the induction of neuronal injury and neurodegeneration [11]. It is induced by oxidative stress, inflammatory cytokines, protein misfolding, and mitochondrial dysfunction, thereby activating downstream transcription factors and pro-apoptotic signalling pathways. However, dysfunction in *MAPK9* signalling has been associated with neuronal cell death, tau

hyperphosphorylation, amyloid toxicity, and neuroinflammation seen in many neurodegenerative conditions [12].

While the expression of *JNK3* (*MAPK10*) is largely confined to the brain and has been studied intensively as a potential therapy against neuron-specific diseases [13], recent findings suggest that *JNK2* (*MAPK9*) too has several roles to play in neurodegenerative diseases. In contrast to *JNK3*, which is selectively expressed, *JNK2* is expressed in all cell types and, besides contributing to neuronal apoptosis, also helps with oxidative stress responses, microglial activation, astrogliosis-mediated neuroinflammation, and signalling from peripheral immunity that affect disease progression [14, 15]. Therefore, targeting *MAPK9* alongside *JNK3* can be of significant advantage in treating such diseases. Hence, this review is focused on *MAPK9*.

Consequently, the use of medicinal plants has attracted increased attention due to their ability to exert antioxidative, anti-inflammatory, anti-apoptotic, and mitochondrial-protective effects. Natural compounds such as curcumin, resveratrol, quercetin, epigallocatechin gallate (EGCG), and berberine have been shown to modulate *MAPK*-related signalling cascades and reduce neuronal injury in experimental studies [16–18]. Given the rising interest in plant-based treatment modalities and the pivotal role of *MAPK9* in the development of neurological disorders, the present paper provides an overview of the existing literature on the interaction between plant bioactives and *MAPK9* signalling cascades. Besides, the paper will focus on the opportunities, barriers, and prospects of phytochemical treatment of neurological conditions.

Biology and signalling mechanisms of *MAPK9*

MAPK9, also known as *JNK2*, is a member of the *MAPK* family, which forms an evolutionarily conserved protein signalling pathway that modulates various physiological functions in cells [19]. The *MAPK* superfamily includes multiple subfamilies, including the extracellular signal-regulated kinases (ERKs), p38 *MAPK*s, and the *JNK*s [20–22]. While ERKs are mainly activated by growth factors and other stimuli associated with cell proliferation, *JNK* kinases are activated by various forms of cellular stress, including oxidative stress, pro-inflammatory cytokines, ultraviolet (UV) irradiation, DNA damage, and protein aggregation [23]. As such, they play a key role in the development of certain chronic conditions.

The *JNK* protein kinase family consists of three isoforms having unique tissue expression profiles and biological roles. *JNK*1 (or *MAPK*8) and *JNK2* (or *MAPK9*) have wide tissue expression profiles, while *JNK3* (or *MAPK10*) is mainly found in the brain, heart, and testis [23]. *JNK3* has been considered to be the primary target for central nervous system (CNS) drug design due to its predominant expression in neurons and the expectation that selective blockade of *JNK3* will decrease neuronal damage without causing systemic toxicity. However, recent evidence indicates that *JNK2* is a major player in neurodegeneration via oxidative stress, inflammatory signalling, mitochondrial dysfunction, and glia activation. The diverse biological role of *MAPK9* differentiates it from *JNK3* and justifies consideration of *MAPK9* as an independent target for therapeutic intervention [11, 24].

Structurally, *MAPK9* encodes a serine-threonine protein kinase comprising an adenosine triphosphate (ATP)-binding site along with a catalytic site that is critical for phosphorylation of substrates (Figure 1). Like other *MAPK*s, *JNK2* has a dual phosphorylation motif consisting of three amino acids: threonine-proline-tyrosine (TPY) [25]. Phosphorylation of these sites is required for kinase activation and subsequent signal transduction. In addition, the protein has docking sites that are required for interaction with scaffolding proteins, transcription factors, and regulators. Alternative splicing produces several *JNK2* isoforms, such as *All* and p46, that can differ in substrate specificity, localisation, and function. Chromosomally, the *MAPK9* gene resides on chromosome *5q35* [26].

The cellular localisation of *MAPK9* is dynamic and directly correlates with its biological function [22]. In a basal state, inactive *JNK2* is localised to the cytoplasm; however, once activated, it translocates to the nucleus and phosphorylates multiple transcription factors that regulate stress-induced genes. In neurons, activated *JNK2* has also been found localised to mitochondria, synapses, and axons, thereby emphasising its

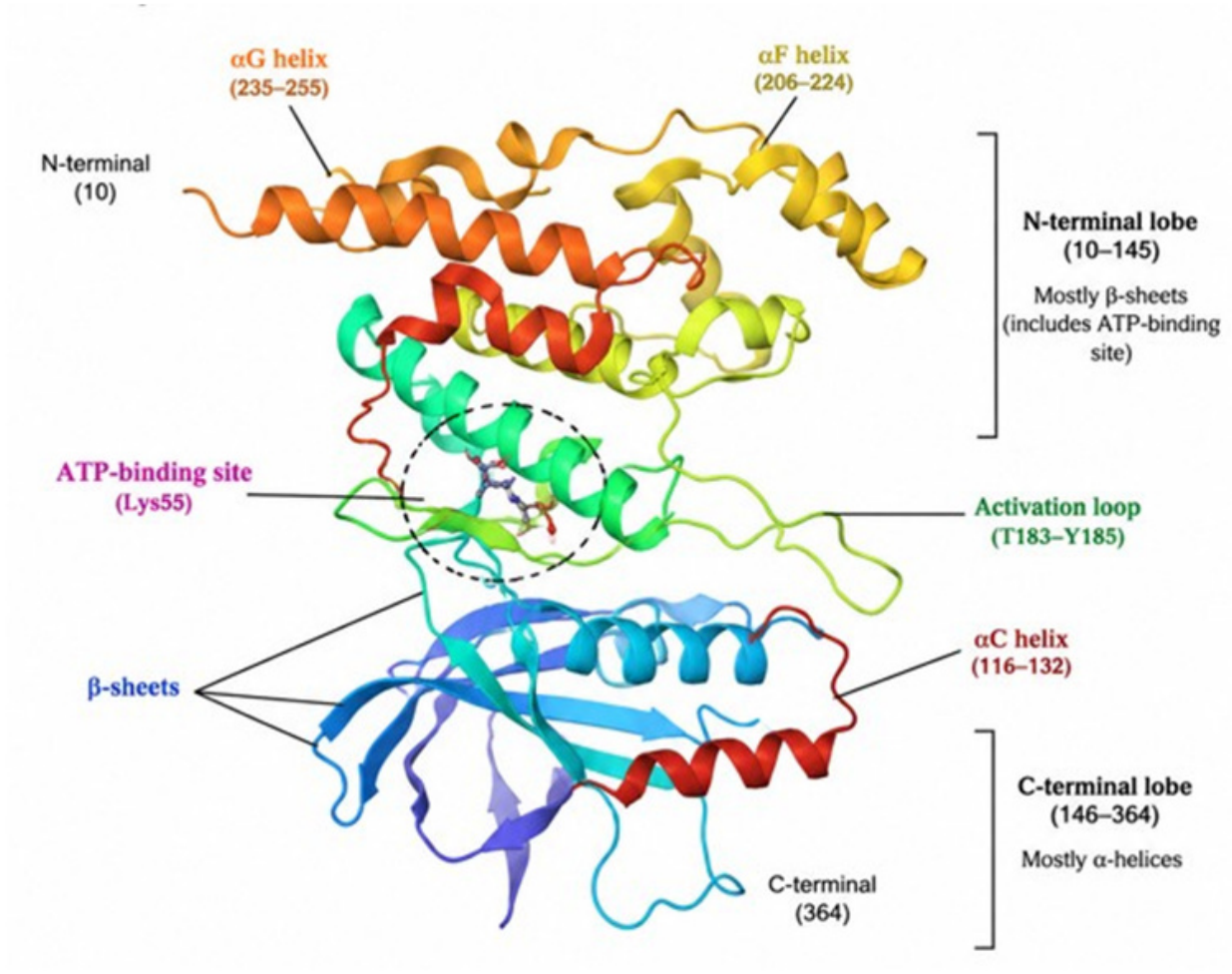


Figure 1. Crystal Structure of *JNK2*. The three-dimensional structure of *JNK2* highlights its unique kinase domain, which includes α-helices, β-sheets, and the ATP-binding site. *JNK2* is an important molecule that participates in the control of cellular stress response, inflammation, cell death, and neurodegeneration. Source: UniProt: P45984 · MK09_HUMAN *MAPK9:* PDB: 8ELC.

diverse physiological and pathological functions. In the mitochondria, *JNK2* plays an important role as it is responsible for causing mitochondrial dysfunction, release of cytochrome C, and the activation of intrinsic apoptosis pathways [27]. For example, mitochondrial *JNK* activation in response to oxidative stress has been shown to cause the death of dopaminergic neurons in PD models [28].

MAPK9 signalling cascade

The activity of *MAPK9* occurs in an organised manner within a signalling cascade that involves phosphorylation steps [20]. *MAPK* pathway activation occurs primarily through upstream kinases called MAP kinase kinase kinases (MAP3Ks), such as apoptosis signal-regulating kinase 1 (ASK1), MLKs, TAK1, and MEKK1-4. MAP3K activation occurs in response to cellular stimuli, including oxidative stress, endoplasmic reticulum stress, inflammatory cytokines, and excitotoxicity (Figure 2). Afterwards, MAP3K phosphorylates the downstream kinases known as MAP kinase kinases (MAP2Ks), such as MKK4 and MKK7, and these proteins phosphorylate the TPY motif of *JNK* family proteins, causing *JNK2* activation [29].

The involvement of the stress-activated pathway via *MAPK9* is critical in influencing cell fate in disease states. Oxidative stress constitutes one of the most powerful activators of *JNK2* signalling. The accumulation of excessive amounts of reactive oxygen species (ROS) causes the disruption of the cell redox balance and initiates the phosphorylation cascades mediated by ASK1, which in turn results in the constant activation of *JNK* [30]. Furthermore, inflammatory cytokines like tumour necrosis factor-alpha (TNF-α) and interleukin (IL)-1β activate *JNK* signalling in response to receptor-mediated signals [31]. In neurodegenerative disorders, the activation of the *MAPK9* pathway leads to continuous neuroinflammation and neurological

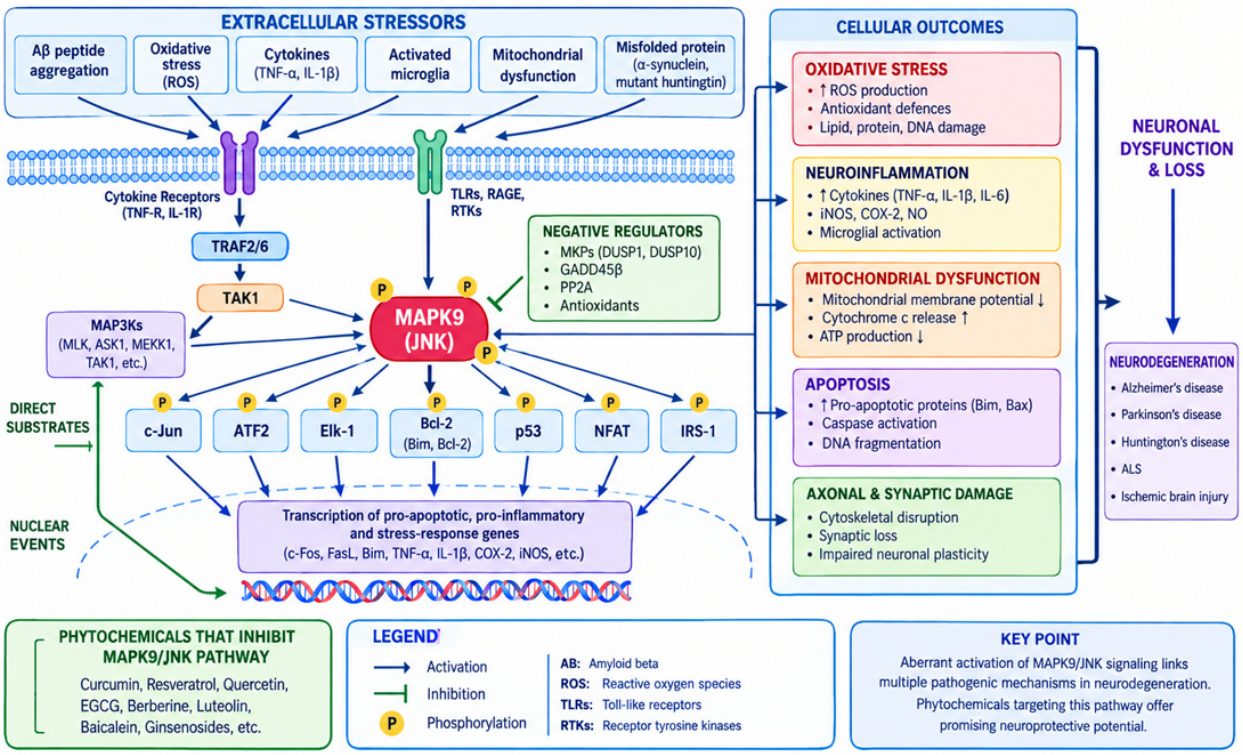


Figure 2. *MAPK9*/*JNK* signalling pathway in neurodegeneration. A schematic representation of the *MAPK9*/*JNK2* signalling pathway in neurodegeneration. Extracellular stressors activate *MAPK9* (*JNK2*) via upstream kinases, leading to phosphorylation of transport factors and induction of pro-apoptotic, inflammatory, and oxidative pathways. This results in neuronal dysfunction and loss. Negative regulators and phytochemicals can also inhibit *MAPK9* signalling and confer neuroprotection.

dysfunction. Overexpression of c-Jun activation correlates strongly with the development of neuronal cell death and neurodegeneration. Increased phosphorylation of c-Jun in degenerating neurons under conditions of oxidative stress and excitotoxicity has been reported in experimental models [32].

Physiological roles of *MAPK9*

From a physiological perspective, *MAPK9* has several vital functions in maintaining cellular homeostasis and neural health. When activated under normal conditions, *JNK2* triggers various adaptive stress responses to protect cells from damage and support their recovery [33]. The temporary activation of *JNK* signalling might increase antioxidant levels and facilitate the disposal of damaged cellular structures via autophagy. On the contrary, prolonged activation usually triggers *JNK*-mediated apoptotic cascades. In general, *JNK*-induced apoptosis occurs via two major processes: nuclear activation of AP-1, which induces pro-apoptotic genes, and the mitochondrial pathway, involving caspase activation and cytochrome c release [34].

In addition to the apoptotic pathway, *MAPK9* has been found to play a role in neuronal development and differentiation. Signalling through *JNK* affects cytoskeletal remodelling, axon growth, and neuronal migration during early brain development [35]. *JNK* signalling has been shown to affect neuritogenesis and synapse formation, processes crucial to the formation of functional neural circuits. In one instance, *JNK*-dependent phosphorylation of microtubule-binding proteins plays a critical role in the formation of neuronal architecture and intracellular transport. Also, *MAPK9* is involved in synaptic plasticity, a vital process essential for learning and memory [36]. Regulated *JNK* signalling influences the dynamics of synaptic protein turnover, receptor trafficking, and long-term potentiation (LTP). On the other hand, dysregulated *JNK* signalling leads to deterioration of synaptic function and impaired cognition, especially in AD patients, where increased *JNK* signalling activity is associated with synaptic loss and memory impairment. There have been reports that aberrant *JNK* signalling activity is implicated in the phosphorylation of tau protein. The combination of *MAPK9*/*JNK2* forms a vital stress-response kinase that

mediates signals from the external environment and within the cell to control neuronal survival, inflammatory response, and cell death [37].

MAPK9 in neurodegenerative diseases

Neurodegenerative diseases refer to a group of chronic diseases that are progressive in nature and cause deterioration of neurons through structural changes and impaired function, ultimately resulting in cognitive and movement disabilities [38]. Several studies have shown that *MAPK9* (*JNK2*), a kinase in the *JNK* family, is an important regulator of the biological mechanisms underlying such pathologies [21, 24, 39]. The activation of *MAPK9* is driven by stress, inflammation, oxidative stress, and protein aggregation, factors characteristic of neurodegeneration. The involvement of *MAPK9* dysregulation in neuronal cell death has been demonstrated in neurodegenerative diseases like AD, PD, and HD, which are further discussed.

MAPK9 and neuroinflammation

Neuroinflammation is considered an important feature of several neurodegenerative disorders, in which microglial cells and astrocytes become chronically activated, resulting in the continuous production of pro-inflammatory factors that lead to neuronal death [40, 41]. However, the importance of *MAPK9* (*JNK2*) lies in its ability to regulate neuroinflammatory pathways in response to cellular and oxidative stress. After activation, the *MAPK9* pathway increases the expression of pro-inflammatory factors such as TNF-α, IL-1β, and IL-6 [31, 42].

Numerous studies have shown the importance of *JNK* signalling in neuroinflammation. For instance, genetic depletion or inhibition of *JNK2* significantly reduces α-synuclein production and inflammatory responses in neuronal models of PD [43], indicating that *JNK2* is a key factor in the neuroinflammation associated with the pathology. Additionally, studies of neuroinflammation in AD models have found elevated activation of *MAPK* pathway components in microglia, and this increase, in turn, corresponded to the induction of inflammation. Therefore, *MAPK9* serves as a mediator between cellular stress and inflammation [44]. Hence, blocking *MAPK9* activity may be a useful approach for treating neuroinflammation.

MAPK9 and neuronal apoptosis

Programmed cell death, also known as neuronal apoptosis, is a significant pathophysiological hallmark of neurodegeneration, as it underlies the progressive loss of neurons seen in conditions such as AD, PD, and HD [45, 46]. *MAPK9* (*JNK2*) is involved in inducing apoptosis by transducing intracellular signals in response to cellular stress from oxidative stress, inflammation, mitochondrial dysfunction, and accumulation of abnormal proteins [47]. Following its activation, *MAPK9* phosphorylates transcription factors such as c-Jun, thus activating pro-apoptotic genes. Several studies have also shown that modulation of *JNK* signalling results in better autophagy-mediated degradation of aggregated Aβ and α-synuclein [48, 49].

For example, in PD models, treatment with the neurotoxin 6-hydroxydopamine (6-OHDA) led to an increase in *JNK* pathway activity and c-Jun phosphorylation, followed by apoptosis [50]. *JNK* inhibition showed a decrease in neuronal death and enhanced survival. Likewise, in AD models, Aβ peptides were found to activate the *JNK* signalling pathway, which led to mitochondrial dysfunction as well as neuronal death [51]. Inhibition of *JNK* caused a reduction in the activation of caspases, thus protecting neurons from amyloid neurotoxicity.

MAPK9 in AD

MAPK9 also plays a vital role in the pathogenesis of tau in AD. Tau proteins normally play a significant role in stabilising microtubules within the neurons [52]. However, in cases of hyperphosphorylation, tau leads to its aggregation, resulting in the formation of neurofibrillary tangles [53]. *JNK2* phosphorylates tau, resulting in microtubule destabilisation. Increased levels of phospho-*JNK* and tau proteins in postmortem AD brain samples indicate a link between *MAPK9* activity and AD pathogenesis.

Synaptic dysfunction in AD may be related to *JNK* signalling. Continuous activation of *MAPK9* disrupts synaptic plasticity and neurotransmission, subsequently resulting in memory problems. Research shows that continuous activation of *JNK* prevents LTP, a physiological phenomenon necessary for learning and memory [54]. Therefore, *MAPK9*-induced synaptic damage in AD is a contributing factor towards impaired cognition.

MAPK9 in PD

Another factor linked to the aggregation of alpha-synuclein, a hallmark feature of PD, is *MAPK9*. The misfolding of α-synuclein leads to the stimulation of inflammation and oxidative stress, which then activates the *JNK* pathway [55]. This, in turn, causes increased protein aggregation and cell death, forming a vicious cycle. Furthermore, the experimental model that uses 6-OHDA, a neurotoxin, to produce a Parkinson-like degeneration of dopamine neurons has been extensively used to investigate this mechanism. In these studies, 6-OHDA induces the activation of *JNK* signalling, including *MAPK9*, that results in c-Jun phosphorylation and apoptosis gene expression [56]. The pharmacological inhibition of *JNK* signalling increases cell survival by preventing neuronal cell death.

Furthermore, a widely used model of induced Parkinsonism consists of treating mice with the toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). It was found that exposure to MPTP increases *JNK* activation in dopaminergic neurons. Moreover, pharmacological inhibition of *JNK* or the knockout of *JNK2* decreases neurodegeneration and maintains mouse motor function [57]. Also, according to Ruan et al. [58], the protective effect of nicotine against PD was studied using an MPTP-induced mouse model, which induces loss of dopaminergic neurons. The results demonstrated that nicotine administration prior to MPTP exposure improved motor activity, reduced anxiety-related behaviours, and protected dopaminergic neurons in the substantia nigra and striatum. In addition, it inhibited neuronal cell death, reduced phosphorylated α-synuclein levels, and also suppressed neuroinflammation-related microglial activation. Mechanistically, nicotine was observed to regulate *MAPK* signalling pathways by inhibiting the *JNK* pathway and increasing *ERK* signalling, without altering the p38 pathway. This resulted in a decrease in degeneration and neuroinflammation processes in the brain.

MAPK9 in other neurodegenerative disorders

The relevance of *MAPK9* (*JNK2*) as a kinase associated with various stresses that contribute to neuronal death has recently been elucidated and is considered alongside classical experimental models of neurodegenerative diseases such as PD and AD. It has been found that *MAPK9* is a major mediator of oxidative stress, excitotoxic injury, and inflammatory damage, each of which is prevalent in many neurological disorders [20, 21]. Activation of *JNK* signalling has been implicated in delayed neuronal cell death following cerebral ischemia, with increased activation of *JNK2* and *JNK3* observed after ischemic injury [59].

The activation of *MAPK9* cascades is initiated in traumatic brain injury (TBI) when mechanical injury affects brain tissue. Such injury induces neuronal cell death via c-Jun phosphorylation, followed by upregulation of pro-apoptotic gene expression. Animal experiments indicate that blocking *JNK* signalling decreases lesion size and enhances recovery after injury. The involvement of *MAPK9* has also been found in multiple sclerosis (MS), in which demyelination induced by inflammation is linked to increased *JNK* activity in glia and neurons. In experimental demyelination, *JNK* suppression was shown to reduce inflammatory damage and maintain neuronal structural integrity. Collectively, these studies reveal the involvement of *MAPK9* in several types of neurodegenerative disorders in which neuronal damage results from cellular stress, thus making it a valuable candidate for developing neuroprotective therapies [60].

Furthermore, recent evidence has also shown that *MAPK9* is involved in vascular changes that contribute to neurodegeneration [61, 62]. Chronic cerebral hypoperfusion, dysfunctional endothelium, and neurovascular unit damage lead to cognitive impairment because of increased oxidative stress, inflammatory response, and blood-brain barrier (BBB) damage [62, 63]. The activation of the *JNK* pathway in cerebrovascular endothelial cells leads to increased synthesis of pro-inflammatory factors, increased

vascular permeability, and more severe neurotoxic effects after ischemia. Therefore, the development of vascular inflammation can potentiate the effect of *MAPK9* on neuronal apoptosis and promote the development of vascular dementia and mixed neurodegenerative diseases.

Moreover, the common pathway in both traumatic and vascular neurodegeneration includes the *MAPK9* signalling pathway, which could also play an important role in chronic traumatic encephalopathy (CTE), which is characterised by progressive neuroinflammation and brain injuries resulting from repetitive mild brain injuries. Contemporary studies on CTE emphasise the possible value of various diagnostic modalities, including diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy (MRS), susceptibility weighted imaging (SWI) and positron emission tomography (PET), together with cerebrospinal fluid biomarkers, including phosphorylated tau, *TREM2*, *CCL11*, *NfL* and GFAP [64]. Importantly, both stroke and neurodegenerative disease have similar secondary pathological mechanisms such as cerebral hypoperfusion, dysfunction of the endothelium, disruption of the BBB, oxidative stress, neurovascular inflammation, mitochondrial dysfunction, and secondary neuron death. These overlapping secondary pathological mechanisms can lead to persistent activation of *MAPK9*/*JNK* signalling and exacerbate neuronal damage after the primary insult. Thus, the targeting of *MAPK9*-induced secondary injury mechanisms could be relevant for treatment of both conditions [65]. This implies that neuroprotection targeting *MAPK9* might be applicable to other diseases as well, given similarities in secondary injury mechanisms. *MAPK9*/*JNK* is a stress-signalling pathway, not a disease-specific one. The role of *MAPK9* in neurodegeneration may vary in patients with AD, PD, stroke-induced neurodegeneration, and CTE since there will be different stresses acting upstream [64, 65]. Thus, treatment of *MAPK9*-mediated neurodegeneration needs to be aetiology-based. Table 1 summarises some neurodegenerative diseases associated with *MAPK9* dysregulation.

Table 1. Neurodegenerative diseases associated with *MAPK9* dysregulation.

Neurodegenerative disease	Role of *MAPK9* (*JNK2*)	Major pathological mechanisms	Key outcomes
Alzheimer's disease (AD)	Increased *MAPK9* activation in response to amyloid β accumulation and oxidative stress	Amyloid β toxicity, tau hyperphosphorylation, neuroinflammation, synaptic dysfunction	Cognitive decline, neuronal loss, memory impairment [51]
Parkinson's disease (PD)	*MAPK9*-mediated apoptosis of dopaminergic neurons	α-Synuclein aggregation, mitochondrial dysfunction, oxidative stress, and neuroinflammation	Dopaminergic neuronal degeneration, motor dysfunction
Huntington's disease (HD)	Activation by mutant huntingtin-induced cellular stress	Oxidative stress, mitochondrial impairment, apoptotic signalling	Striatal neuron degeneration, cognitive and motor deficits [66]
Ischemic brain injury	Rapid activation following cerebral ischemia and reperfusion	Excitotoxicity, oxidative stress, inflammatory cytokine release, apoptosis	Neuronal death and neurological impairment [67]
Vascular dementia	*MAPK9* contributes to inflammation and ischemic neuronal damage	Chronic cerebral hypoperfusion, endothelial dysfunction, blood-brain barrier disruption, oxidative stress, neurovascular inflammation, and *MAPK9*-mediated apoptosis	Cognitive impairment and neuronal dysfunction [68]
Multiple sclerosis (MS)	*MAPK9* participates in inflammatory and demyelinating processes	Immune cell activation, cytokine production, oxidative stress	Demyelination and neurodegeneration [69]
Frontotemporal dementia (FTD)	Dysregulated *MAPK9* signalling is associated with protein aggregation and neuronal loss	Tau pathology, neuroinflammation, apoptotic signalling	Behavioural and cognitive dysfunction [70]

MAPK9: mitogen-activated protein kinase 9; *JNK2*: c-Jun N-terminal kinase 2.

Medicinal plants and neuroprotective phytochemicals

Medicinal plants are considered rich in secondary metabolites, called phytochemicals, that exhibit remarkable neuroprotective effects [71]. Natural products have become more popular in neurodegenerative studies owing to their antioxidant, anti-inflammatory, anti-apoptotic, and

mitochondrial-protective properties. Important classes of neuroprotective phytochemicals include polyphenolic, flavonoid, alkaloid, and terpenoid compounds. One of the most studied groups of phytochemicals is polyphenols because of their strong antioxidant nature. These molecules have more than one phenolic group, which can scavenge free radicals or reduce oxidative stress. Polyphenols are abundant in fruits, vegetables, teas, and herbal medicines [72]. For instance, curcumin is a polyphenol extracted from *Curcuma longa* that exhibits neuroprotective effects against oxidative stress, inflammation, and apoptotic pathways [41].

Resveratrol, another polyphenol found in grapes and berries, also acts as an antioxidant and anti-inflammatory agent against neuronal injury in AD and PD [73, 74]. Flavonoids are an example of sub-groups of polyphenols defined on the basis of a shared flavone structural backbone. Flavonoids occur in abundance in medicinal plants, fruits, and beverages, including green tea. Flavonoids exhibit potent antioxidant activity and control several cellular signalling mechanisms involved in neuronal survival. Quercetin, luteolin, kaempferol, and EGCG have received extensive attention due to their potential in neuroprotection. Research has demonstrated that EGCG, isolated from *Camellia sinensis,* exhibits anti-aggregation activity toward Aβ and exerts neuroprotection by inhibiting neuroinflammation and oxidative stress [75].

Alkaloids are nitrogen-containing chemical compounds with diverse biological actions in living organisms, including neuroprotective effects. There are several alkaloids extracted from medicinal herbs that have anti-inflammatory and anti-apoptotic functions useful in neurodegenerative disorders [76]. One example is berberine, which is an isoquinoline-type alkaloid obtained from species like *Berberis vulgaris* [77]. The compound reduces oxidative stress, neuroinflammation, and neuroapoptosis. Huperzine A, which is an acetylcholinesterase inhibitor obtained from *Huperzia serrata*, has been found effective in treating AD by enhancing cognitive abilities and preventing neuronal degeneration [78].

Terpenoids represent another type of neuroprotective agents obtained from isoprenoids. The compounds have antioxidant, anti-inflammatory, and neuroregulatory properties. Examples of terpenoids include ginsenosides from *Panax ginseng* and withanolides from *Withania somnifera*, both of which possess neuroprotective properties. They have the ability to modulate apoptosis, mitochondrial activity, and neuroinflammation [79]. For instance, withanolides have been noted to lower oxidative stress and increase neuron survival [80].

Mechanisms of phytochemical neuroprotection

The protective effect of phytochemicals from medicinal plants against neurological damage occurs through several mechanisms. The first mechanism involved in the neuroprotective properties of phytochemicals is their antioxidant activity. Oxidative stress is one of the main causes of neurological disorders, as it leads to the oxidation of macromolecules and impairment of neurons' function [40]. Phytochemicals can protect neurons from oxidative damage by donating electrons to free radicals and strengthening the antioxidant system in cells (Figure 3). Some phytochemicals, such as curcumin, quercetin, and resveratrol, stimulate activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) and increase production of such enzymes as superoxide dismutase, catalase, and glutathione peroxidase [81].

Another essential mechanism underlying the neuroprotective action of phytochemicals is their anti-inflammatory effects. Neuroinflammation plays an important role in neuronal death through microglial activation and the subsequent release of inflammatory cytokines. A number of phytochemicals have been found to block inflammation via NF-κB, *MAPK*s, and *JNK* pathways. EGCG and curcumin, for example, have been found to block microglial activation and down-regulate TNF-α, IL-1β, and IL-6 [82]. In addition, resveratrol has been found to suppress inflammation induced by the release of inflammatory cytokines in models of PD and cerebral ischemia.

Phytochemicals also possess anti-apoptotic properties by regulating both the intrinsic and extrinsic apoptotic pathways. Diseases associated with neurodegeneration are characterised by progressive neuronal cell death caused by the activation of apoptotic cascades. Various phytoconstituents can prevent apoptosis by modulating *Bcl-2* proteins, caspases, and mitochondrial-related mechanisms. It has been found

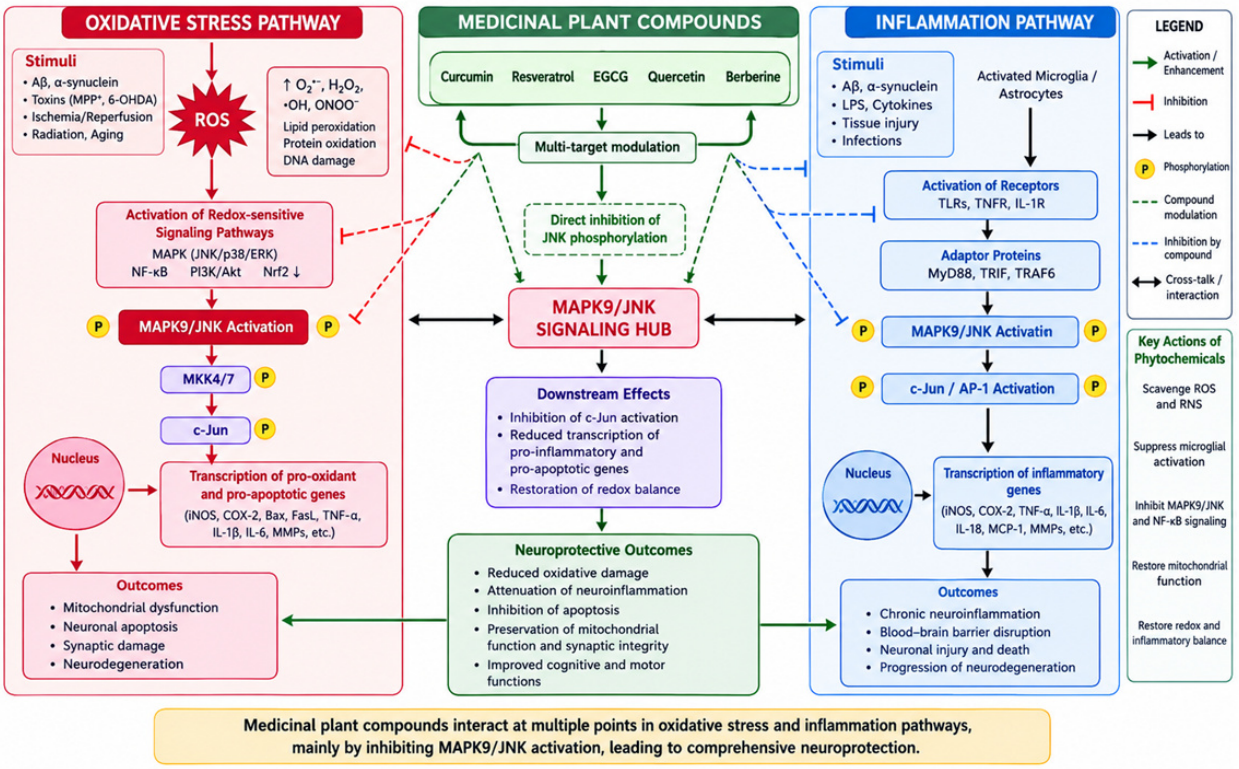


Figure 3. Interaction of medicinal plant compounds with oxidative stress and inflammation pathways. Overview of how medicinal plant bioactives modulate oxidative stress and inflammatory signalling. Phytochemicals suppress ROS generation, inhibit *MAPK9*/*JNK* and NF-κB activation, reduce pro-inflammatory cytokine production, restore redox balance, and ultimately protect neurons from degeneration. EGCG: epigallocatechin gallate; ROS: reactive oxygen species.

that curcumin and berberine can downregulate Bax gene expression and upregulate the expression of anti-apoptotic *Bcl-2* proteins, thereby preventing mitochondrial membrane depolarisation. Quercetin also prevents the activation of caspase-3 [83].

Common medicinal plants with neuroprotective potential

A number of medicinal herbs have been explored to discover their neuroprotective actions and usefulness in neurodegenerative disorders. The plant *Curcuma longa*, popularly known as turmeric, is one of the most commonly studied medicinal herbs because of the presence of curcumin, which has excellent antioxidant and anti-inflammatory activities [84]. Curcumin has proven capabilities for inhibiting the formation of Aβ and reducing inflammation and oxidative stress in AD.

The other medicinal plant under discussion is *Camellia sinensis* (Green tea), which contains catechins such as EGCG. The major effects of EGCG include reducing oxidative stress, inhibiting protein aggregation, and attenuating the inflammatory response in neurodegeneration models. There are reports indicating that green tea catechins enhance cognitive function and protect dopaminergic neurons in PD models [85].

Ginkgo biloba is yet another well-known medicinal plant used for cognitive enhancement and neuroprotection. The active components of *Ginkgo biloba* are flavonoids and terpenoids, which enhance cerebral blood flow and provide protection against apoptosis and oxidative stress. Studies show promising results in improving memory and cognitive functions in mild cognitive impairment (MCI) and AD [86].

Withania somnifera (Ashwagandha) is one of the valuable medicinal herbs used in Ayurveda. Active phytochemicals present in the plant, called withanolides, possess antioxidant, anti-inflammatory, and anti-apoptotic activities. In experiments, it was found that Ashwagandha exerts its protective effect on neurons in AD, PD, and cerebral ischemia through anti-oxidation [87]. *Bacopa monnieri* is an Ayurvedic herb famous for its ability to enhance cognition and protect nerve cells. Bacosides are the main active components of *Bacopa monnieri*; they stimulate synaptic activity, decrease oxidative stress, and improve memory. Laboratory studies suggest that *Bacopa monnieri* prevents neurons from damage due to Aβ exposure and positively affects cognitive functions in neurodegenerative diseases [88].

In totality, the medicinal properties of plants and their bioactive phytochemicals are strong therapeutic candidates for neurodegenerative diseases because of their multitarget mechanisms. The modulation of oxidative stress, neuroinflammation, apoptosis, and mitochondrial dysfunction by these plants makes them strong candidates in the development of neuroprotective drugs focusing on the *MAPK9* pathway.

Medicinal plant bioactives targeting *MAPK9*

Phytochemicals from medicinal plants have been of interest for their use in the treatment of neurodegenerative diseases based on their ability to influence stress-activated signalling pathways, which include *MAPK9*/*JNK2*. Many natural products have been found to have neuroprotective activity based on their ability to inhibit oxidative stress, neuroinflammation, mitochondrial dysfunction, and apoptosis, processes that are highly correlated with *MAPK9* activity (Figure 4). Some phytochemicals have been shown to influence *JNK* pathways in models of neurodegenerative disorders such as AD, PD, HD, and ischemia.

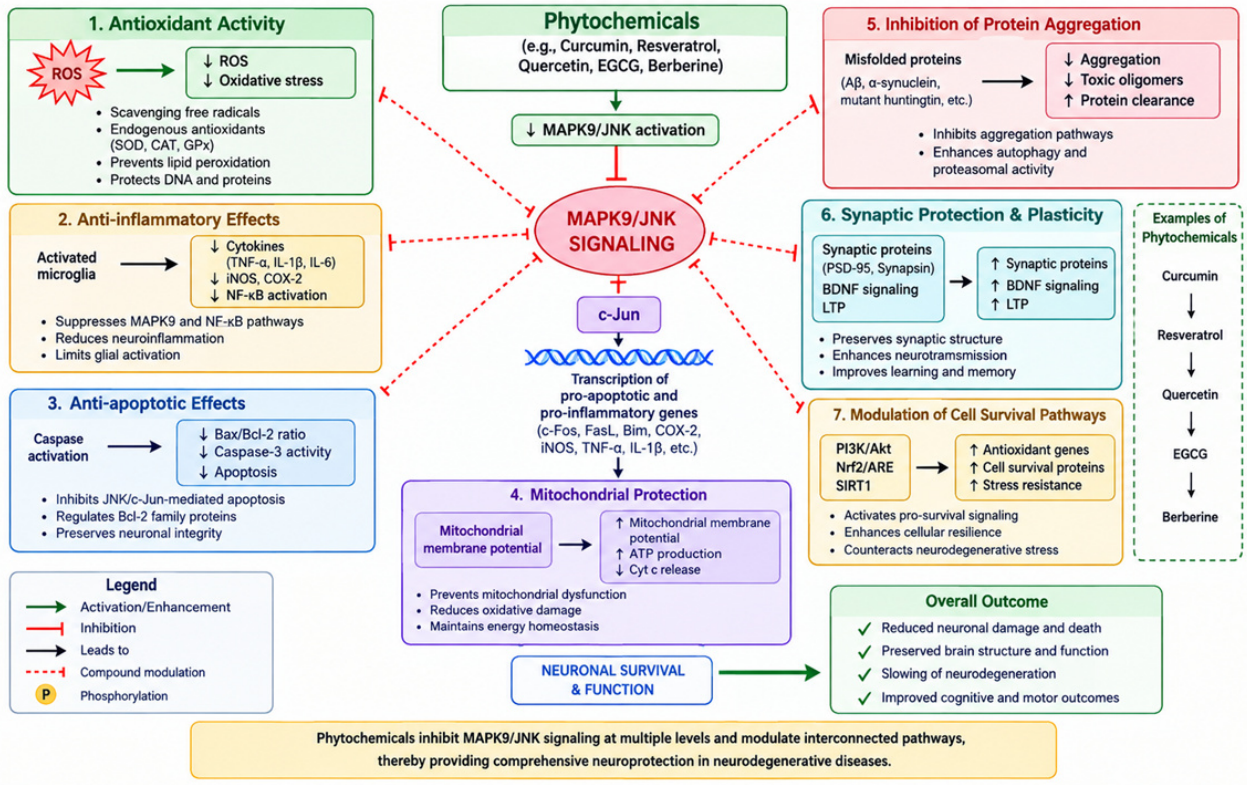


Figure 4. Mechanisms of phytochemical-mediated neuroprotection. An illustration of the neuroprotective actions of phytochemicals, including antioxidant, anti-inflammatory, anti-apoptotic, and mitochondrial protective effects. Bioactive compounds inhibit *MAPK9*/*JNK* signalling, reduce oxidative stress and protein aggregation, preserve synaptic function, and promote neuronal survival in neurodegenerative conditions. EGCG: epigallocatechin gallate.

Neuroprotection mediated through the preservation of mitochondria is yet another key role played by phytochemicals. Mitochondria are extremely sensitive to oxidative stress and are key organelles in the generation of ATP and the regulation of apoptosis. Deterioration of mitochondria results in increased ROS formation, calcium imbalance, and ultimately leads to neuronal cell death in neurodegeneration. There are several phytochemicals that aid in the preservation of mitochondrial function by increasing the stability of mitochondria, enhancing ATP synthesis, and protecting mitochondria from oxidative stress [39].

Curcumin

Curcumin, the main polyphenol extracted from *Curcuma longa*, also known as turmeric, is one of the best-studied natural agents used in neurodegenerative disorders. The ability of curcumin to act as an antioxidant, anti-inflammatory, and antiapoptotic compound has been demonstrated experimentally, and many of its actions can be attributed to the inhibition of the *MAPK9*/*JNK* pathway.

For instance, a study carried out by Wang et al. [89] demonstrated that curcumin reduced *JNK*-3 expression and phosphorylation and attenuated neuronal apoptosis in the hippocampus of rats with Aβ-induced AD. Curcumin has also been found to inhibit activation of NF-κB and pro-inflammatory cytokines, including TNF-α and IL-1β, which could explain its anti-inflammatory effects. Moreover, curcumin prevents mitochondrial depolarisation and cytochrome c release, protecting the mitochondria [90]. As for PD, curcumin showed protective effects when administered to patients suffering from rotenone-induced and MPTP-induced neurodegeneration. In particular, curcumin inhibited *JNK*-mediated apoptosis, resulting in decreased loss of dopaminergic neurons and improved motor function [91].

Several in vitro and in vivo studies have reported that curcumin attenuates *JNK* phosphorylation and reduces neuronal apoptosis induced by oxidative stress or Aβ exposure. However, these effects vary across experimental models, doses, and formulations, and may also involve indirect regulation through upstream antioxidant and anti-inflammatory pathways, including Nrf2 and NF-κB, rather than direct inhibition of *MAPK9*.

Resveratrol

Resveratrol is a polyphenolic compound naturally occurring in grapes, berries, and red wine. This compound possesses strong antioxidant and anti-inflammatory activities, along with exhibiting neuroprotective effects in multiple models of neurodegeneration [92]. The most prevalent pathway through which resveratrol exerts neuroprotective activity is its antioxidant and anti-apoptotic actions by inhibiting oxidative stress and *JNK* signalling pathways. Inhibitory effects of resveratrol on *JNK* signalling pathways involve decreased production of ROS and improved antioxidant defense by activation of sirtuin 1 (SIRT1) and Nrf2 signalling pathways. Although resveratrol can decrease the activation of *JNK* in various models of neurodegenerative disorders [93], the effectiveness of the treatment is determined by many factors, including the disease model used, dosage, and the duration of the treatment, as well as the decrease in oxidative stress and SIRT1/Nrf2 activation rather than *MAPK9* inhibition.

Furthermore, resveratrol modulates neuroprotective pathways involving neuron survival and synaptic transmission. In models of ischemic stroke, resveratrol alleviated neuronal injury by decreasing the inflammatory response and inhibiting phosphorylation of *JNK* [94]. Moreover, it increased the synthesis of ATP through promoting mitochondrial biogenesis in neurons. Based on multiple actions described above, resveratrol is considered an efficient phytochemical capable of modulating *MAPK9*-related neurodegeneration.

Quercetin

Quercetin is a type of flavonoid found abundantly in fruits, vegetables, onions, apples, and various medicinal herbs. Quercetin is notable due to its strong antioxidant properties and ability to regulate cellular signalling pathways involved in oxidative stress and inflammation. Quercetin's protective actions on the nervous system involve ROS scavenging and regulation of *MAPK* signalling pathways, including *JNK* activation.

In vitro experiments have established that quercetin can reduce neuronal injury induced by oxidative stress due to its ability to remove free radicals and increase the activity of antioxidant enzymes [95]. In neurons exposed to hydrogen peroxide, quercetin has been found to decrease *JNK* phosphorylation and apoptosis of neurons under oxidative stress conditions. Yet, clinical studies have not been conducted, and its neuroprotective action most probably involves the regulation of more than one signalling pathway, both antioxidative and anti-inflammatory [96]. Quercetin also acts as an anti-inflammatory agent by suppressing *NF-κB* activation and the secretion of pro-inflammatory cytokines. In AD animal models, quercetin has been demonstrated to reverse Aβ-mediated neuronal damage and enhance cognitive function. Moreover, quercetin provides protection against mitochondrial dysfunction by stabilising mitochondrial membranes and reducing ROS generation. In PD animal models, quercetin caused a decrease in dopaminergic neuron degeneration and improvement of motor dysfunction caused by oxidative stress-induced *MAPK* signalling pathways. The aforementioned evidence highlights the potential of quercetin in treating *MAPK9*-mediated neurological disorders.

EGCG

EGCG, the main catechin in *Camellia sinensis* (green tea), is a widely studied phytochemical known for its neuroprotective properties through interactions with the *MAPK* pathway. The first mechanism underlying the neuroprotective action of EGCG is its ability to inhibit protein aggregation. It was found that EGCG prevents the accumulation of Aβ protein and reduces protein aggregation. Moreover, EGCG can reduce *JNK* activation in response to exposure to Aβ and induce a decrease in cell apoptosis [97]. Another effect of EGCG is the inhibition of hyperphosphorylation of the tau protein, thereby inhibiting the development of neurofibrillary tangles.

Another neuroprotective property of EGCG is mitochondrial protection. It reduces ROS generation, stimulates ATP production, and maintains mitochondrial membrane stability. EGCG protects dopaminergic neurons from oxidative stress and mitochondria-mediated apoptosis in animal models of PD. Moreover, EGCG can inhibit microglial activation and inflammatory cytokine production. Thus, these studies have shown a decreased activation of *JNK* due to treatment with EGCG in animal models of AD and PD. However, such observations are not always consistent, and the effect might be a consequence of decreased oxidative stress, mitochondrial preservation, and neuroinflammation suppression.

Berberine and other emerging compounds

The isoquinoline alkaloid berberine, isolated from herbs such as *Berberis vulgaris*, has great potential as a neuroprotective agent due to its anti-inflammatory and antioxidant properties. Specifically, berberine regulates several pathways related to neuronal survival, including the *MAPK* and NF-κB pathways. Several studies have found that berberine can inhibit *JNK* phosphorylation in neuroinflammatory and ischemic models. Nevertheless, it appears from existing studies that such an effect is part of a more complex regulation of *MAPK*s and NF-κB signalling pathways, which complicates ascribing neuroprotective effects only to *MAPK9* inhibition [98].

Moreover, berberine alleviates oxidative stress through increased antioxidant enzyme activity and inhibition of ROS production. For instance, berberine enhances cognitive outcomes and reduces Aβ levels in Alzheimer's models. Additionally, the phytochemical acts on mitochondria by boosting ATP synthesis and protecting mitochondrial membranes.

Other new phytochemicals that can regulate *MAPK9*-mediated pathways include luteolin, kaempferol, and ginsenosides. Particularly, luteolin is a flavonoid found in celery and green peppers that can inhibit the activation of microglia and block *JNK*-induced inflammatory signalling. On the other hand, kaempferol reduces oxidative stress and neuronal death in ischemia models. Ginsenosides are compounds derived from *Panax ginseng* that induce neuroprotection by modulating *MAPK* and mitochondrial pathways. Medicinal plant bioactives constitute novel candidates in *MAPK9*-related neurodegenerative diseases. This is attributed to their ability to regulate numerous pathological processes, including neuroinflammation, oxidative stress, apoptosis, and mitochondrial dysfunction. Table 2 highlights some reported medicinal plants and active phytochemicals targeting *MAPK9* (*JNK2*) in neurodegenerative diseases.

Table 2. Medicinal plants and active phytochemicals targeting *MAPK9* (*JNK2*) in neurodegenerative diseases.

Medicinal plant	Active phytochemical(s)	Neurodegenerative model/Disease	Effect on *MAPK9*/ *JNK* signalling	Neuroprotective mechanism	Key references
Curcuma longa (Turmeric)	Curcumin	Alzheimer's disease (AD), Parkinson's disease, cerebral ischemia	Inhibits *JNK* phosphorylation and c-Jun activation	Anti-inflammatory, antioxidant, anti-apoptotic	[84]
Camellia sinensis (Green Tea)	Epigallocatechin gallate (EGCG)	AD, Parkinson's disease	Suppresses *JNK* activation and downstream inflammatory signalling	Inhibits amyloid aggregation, mitochondrial protection	[85, 97]
Vitis vinifera (Grape)	Resveratrol	Parkinson's disease, cerebral ischemia, AD models	Reduces oxidative stress-mediated *JNK* activation	Activates SIRT1, antioxidant, anti-inflammatory	[3, 99]

Table 2. Medicinal plants and active phytochemicals targeting *MAPK9* (*JNK2*) in neurodegenerative diseases. (*continued*)

Medicinal plant	Active phytochemical(s)	Neurodegenerative model/Disease	Effect on *MAPK9*/ *JNK* signalling	Neuroprotective mechanism	Key references
Berberis vulgaris	Berberine	Neuroinflammation, AD models	Attenuates *MAPK*/ *JNK* and NF-κB signalling	Reduces reactive oxygen species (ROS) production and cytokine release	[98, 100]
Ginkgo biloba	Ginkgolides, Bilobalide, Flavonoids	AD, vascular dementia	Modulates *MAPK*-mediated inflammatory pathways	Antioxidant, anti-apoptotic, improves cerebral blood flow	[86, 101]
Withania somnifera (Ashwagandha)	Withanolides	AD, Parkinson's disease	Downregulates stress-induced *MAPK* activation	Anti-inflammatory, mitochondrial protection	[80, 102]
Bacopa monnieri	Bacosides A and B	Cognitive impairment, AD models	Suppresses oxidative stress-associated *JNK* signalling	Enhances synaptic function and antioxidant defences	[103]
Panax ginseng	Ginsenosides (Rg1, Rb1, Rd)	Parkinson's disease, ischemic injury	Regulates *MAPK*/ *JNK*-mediated apoptosis	Mitochondrial stabilisation and neuronal survival	[104]
Scutellaria baicalensis	Baicalein, Baicalin	Parkinson's disease, neuroinflammation	Inhibits *JNK* phosphorylation and microglial activation	Antioxidant and anti-inflammatory activity	[105]
Allium cepa (Onion)	Quercetin	AD, oxidative stress models	Suppresses *JNK*/c-Jun signalling	ROS scavenging and apoptosis inhibition	[96]
Glycyrrhiza glabra (Licorice)	Liquiritigenin, Glycyrrhizin	Neuroinflammation and ischemic injury	Modulates *MAPK*-mediated inflammatory responses	Anti-inflammatory and antioxidant effects	[17]
Centella asiatica	Asiaticoside, Madecassoside	Cognitive impairment, AD models	Reduces stress-induced *MAPK* activation	Neurogenesis promotion and antioxidant activity	[18]

While there are many reports on the ability of several phytochemicals to inhibit *JNK* phosphorylation, care should be taken when drawing conclusions from these results. The majority of these data are based on in vitro and animal experiments, in which various disease models and doses were used. Furthermore, most of the time, the decrease in *JNK* phosphorylation was due to a reduction in oxidative stress, improvement in mitochondrial function or alteration of upstream signalling pathways instead of inhibition of *MAPK9* itself.

Why target *MAPK9* instead of *JNK3*?

While *JNK3* has been found to be the most studied isoform in relation to neurodegenerative disorders due to its primary neuronal expression, inhibition of *JNK3* alone may not be enough to inhibit the complicated inflammatory and oxidative responses involved in the pathogenesis of such disorders. In contrast to *JNK3*, *MAPK9* (*JNK2*) has been found to be expressed in neurons, astrocytes, microglial cells, and immune cells [14]. This enables *MAPK9* to regulate not only neuronal apoptosis but also neuroinflammation. From experimental evidence, it has been seen that *JNK2* participates in cytokine secretion, oxidative stress enhancement, mitochondrial damage, and protein aggregation [106]. However, the widespread occurrence of *JNK2* has its own dangers, as the side effects in the system after long-term inhibition need to be considered. Thus, future research efforts should be concentrated on the creation of brain-specific inhibitors for *MAPK9* that could provide maximum protection to the neurons without causing any toxic effects outside the nervous system. *JNK2* and *JNK3* proteins can thus be considered complementary members of the *JNK* pathway rather than competing therapeutic targets.

Therapeutic potential and translational relevance

BBB considerations

Bioactive molecules extracted from medicinal plants that could act on *MAPK9*/*JNK2*, a *MAPK* pathway, have shown considerable neuroprotective effects against neurodegeneration in animal studies. Nevertheless, the

clinical efficacy of these drugs is often determined by the permeability of the molecules through the BBB. The BBB acts as a natural barrier that regulates the transport of foreign particles into brain tissue while protecting it from harm caused by external sources [107]. As such, several neuroprotective phytochemicals fail to enter the brain due to the BBB.

Most natural bioactives have physicochemical constraints, including low solubility, poor membrane permeability, and rapid metabolic degradation, resulting in minimal BBB permeation [108]. In addition to acting as a barrier to drug delivery, BBB dysfunction is a key pathology associated with neurodegenerative diseases. It has been observed that *MAPK9*-mediated inflammatory signalling leads to endothelial cell damage, loss of tight junction protein function, and dysfunction of neurovascular units, and thus facilitates immune cell entry and chronic neuroinflammation. This means that therapy targeting *MAPK9* can serve a double purpose.

There is substantial evidence for curcumin's anti-inflammatory and *MAPK9*-inhibitory actions, although its clinical application is hindered by limited brain uptake and poor pharmacokinetics [41, 90, 109]. Furthermore, the antioxidant and anti-apoptotic actions of quercetin and resveratrol are significant in mitigating cellular damage, although they exhibit poor CNS bioavailability when administered orally [110]. Despite these challenges, phytochemicals such as EGCG and berberine have exhibited BBB penetration and protective effects in experimental models of neurodegenerative conditions. Knowledge of the physiological factors that determine BBB permeation of compounds is vital to the design of therapies based on plant derivatives.

Bioavailability challenges

Another key drawback is that poor bioavailability poses a significant constraint in the use of medicinal plants' phytochemicals for therapeutic purposes. Many phytochemicals get degraded and metabolised quickly, thereby posing a challenge to their therapeutic efficiency due to reduced bioavailability. Curcumin is one such compound, which, despite having excellent neuroprotective effects, shows poor bioavailability due to its poor absorption rate, metabolic rate, and short plasma half-life [111]. Another such compound is resveratrol, which shows a high first-pass effect [112]. For example, Almeida et al. [113] conducted a randomised, double-blind, placebo-controlled clinical study assessing the pharmacokinetics and safety profile of trans-resveratrol in a randomised, double-blind and placebo-controlled study among healthy human volunteers. They were administered doses ranging from 25 to 150 mg, six times per day. The study indicated that trans-resveratrol is highly absorbed and achieves maximum plasma levels within 0.8 to 1.5 hours following dosing. While the drug showed high tolerance and produced only minor side effects, its plasma levels were still low because of low bioavailability and quick clearance from the body [113].

Some approaches used to address the above-mentioned barriers to the effective delivery of phytochemicals include structural modification, formulation optimisation, and various encapsulation techniques. Nano-curcumin (NCMN) has demonstrated improved bioavailability, enhanced ability to cross the BBB, and more pronounced neuroprotective effects in AD [107, 108].

Pan-Assay Interference Compounds (PAINS): a critical consideration

Although many phytochemicals have been found to display significant activity towards pathways associated with *MAPK9*, care must be taken in the interpretation of their positive results from biochemical and cellular assays. A number of polyphenols commonly used in research, including curcumin, display structural features typical of PAINS [114]. These compounds might create biological activity by non-specific mechanisms, such as redox cycling, protein aggregation, fluorescence interference, covalent modification, or metal chelation. Hence, the observed biological activity does not automatically translate into the selectivity of a certain *MAPK9* pathway. This problem is especially important in kinase drug discovery, since false positives resulting from interference in the assay might occur and increase the overestimation of the therapeutic value of certain compounds [115]. However, the classification of a phytochemical as a PAINS compound does not mean it lacks biological activity. Instead, it means the necessity of rigorous validation with orthogonal biochemical assays, target engagement studies, cellular mechanistic assays, and

pharmacology in vivo. The future study should involve computational modelling, biophysical binding assays, selective kinase profiling, and proper experimental validation of the results.

Drug delivery systems

Development of novel drug delivery systems has greatly increased the potential of neuroprotective phytochemicals. Nanotechnological formulations, including nanoparticles, liposomes, polymeric micelles, dendrimers, and solid lipid nanoparticles, serve as efficient tools to increase BBB penetration and targeted delivery to neuronal cells. Such systems protect phytochemicals against degradation, improve their solubility, and facilitate controlled drug delivery [108].

The use of nanoparticle delivery of curcumin led to higher brain uptake and decreased neurotoxicity caused by Aβ deposition in AD models [116, 117]. Also, delivery of EGCG via nanoparticles was effective in protecting mitochondria and inhibiting dopaminergic neuronal loss in PD models [118]. The development of intranasal drug delivery systems is gaining popularity as it does not require passage across the BBB and uses the olfactory route to deliver drugs directly into the brain. Such an approach can increase the efficiency of therapy for *MAPK9*-dependent neurodegenerative diseases.

Combination therapies

Another potentially effective approach to enhancing neuroprotective efficacy is combination therapy. Given that neurological diseases such as AD and PD have several interrelated pathological pathways, monotherapies are unlikely to deliver significant benefits. A combination of phytochemicals from medicinal plants with pharmaceutical drugs or other biologically active compounds could offer improved efficacy through synergistic effects. A number of studies have shown the benefits of using combination therapies of phytochemicals. Combination therapy of curcumin and donepezil was more effective in improving cognitive function and neuroinflammation than each agent alone in AD [119]. Beltagy et al. [119] examined the therapeutic value of NCMN, both alone and in combination with donepezil, in a rat model of AD. The findings revealed that NCMN significantly enhanced cognitive function, locomotor ability, and neuronal protection through antioxidant, anti-inflammatory, anti-tau hyperphosphorylation, and anti-cholinesterase properties. It should be noted that NCMN also acted as an active agent in modulating the *PI3K/AKT/GSK-3β* signalling pathway, which is very important in neuronal protection and survival. The use of NCMN along with donepezil showed better results than either alone [119].

Similarly, Resveratrol combined with levodopa (LD) was more effective at increasing dopaminergic neuronal survival and reducing oxidative stress in PD. For example, Liu et al. [120] studied the synergistic effect of LD and resveratrol on rotenone-induced neurodegeneration in PD using cellular and animal models. Their study results revealed that the combination of LD and resveratrol inhibited ROS generation, improved mitochondrial function, and prevented cell death. Additionally, they inhibited inflammation by downregulating the toll-like receptor (TLR)-2 and TLR-4 signalling pathways, thereby reducing the secretion of inflammatory cytokines. In rotenone-exposed rats, there were improvements in motor function, enhanced superoxide dismutase (SOD) activity, and diminished malondialdehyde (MDA) levels [120]. Thus, combination therapies can reduce doses of pharmaceutical drugs and lower their side effects. In addition, combination therapies targeting *MAPK9* and other related signalling pathways could provide more effective neuroprotection.

Potential for precision medicine

Precision medicine holds promise for advancing personalised neuroprotective strategies against *MAPK9*. Neurodegenerative disorders are characterised by significant heterogeneity in terms of their pathogenesis due to genetic predispositions, differences in inflammation profiles, disease progression, and responsiveness to therapy among different patients [121]. Modern advances in genomics, proteomics, transcriptomics, and computational biology have enabled the identification of biomarkers that correlate with *MAPK9* dysfunction and neuronal stress responses. These biomarkers can help classify patients and apply an individualized phytochemical approach. For instance, individuals exhibiting signs of increased

oxidative stress or activation of the *MAPK9* pathway are likely to respond positively to antioxidant compounds such as curcumin, quercetin, or EGCG [122]. Moreover, innovative computational techniques, such as molecular docking, artificial intelligence (AI), and network pharmacology, can help identify novel plant bioactives with selective activity against *MAPK9*.

On balance, bioactive compounds from medicinal plants targeting *MAPK9* hold great promise for the treatment of neurodegenerative conditions (Table 3). Despite the considerable difficulties posed by issues such as the penetration of these drugs across the BBB, insufficient bioavailability, and limited clinical translatability, several potential solutions are emerging.

Table 3. Advantages and limitations of phytochemical therapeutics in neuroprotection.

Aspect	Advantages	Limitations
Multi-target activity	Simultaneously modulate multiple pathological pathways, including *MAPK9*/*JNK*, oxidative stress, neuroinflammation, mitochondrial dysfunction, and apoptosis.	Multi-target effects may complicate mechanistic interpretation and target validation.
Safety profile	Generally exhibit lower toxicity and better tolerability compared to many synthetic drugs.	Long-term safety data are often lacking, particularly at therapeutic doses.
Natural origin	Derived from medicinal plants with extensive historical use in traditional medicine systems.	Variability in plant source, cultivation conditions, and harvesting practices can affect quality and efficacy.
Antioxidant activity	Efficiently scavenge reactive oxygen species (ROS) and enhance endogenous antioxidant defences.	Antioxidant effects observed in vitro may not always translate into clinical efficacy.
Anti-inflammatory effects	Suppress pro-inflammatory cytokines and signalling pathways such as *MAPK9* and NF-κB.	Limited understanding of optimal dosing regimens required to achieve sustained anti-inflammatory effects in humans.
Neuroprotective potential	Protects neurons from apoptosis, mitochondrial dysfunction, excitotoxicity, and protein aggregation.	Most evidence is derived from preclinical studies rather than large-scale clinical trials.
Blood-brain barrier (BBB) penetration	Certain compounds, such as berberine, resveratrol, and epigallocatechin gallate (EGCG), demonstrate partial BBB permeability.	Many phytochemicals exhibit poor BBB penetration, limiting therapeutic concentrations within the brain.
Bioavailability	Some compounds can be optimised through formulation technologies and structural modifications.	Poor solubility, rapid metabolism, and low oral bioavailability remain major challenges for compounds such as curcumin and quercetin.
Drug development potential	Serve as valuable lead compounds for the design of novel neuroprotective drugs targeting *MAPK9*.	Isolation, purification, and large-scale production may be costly and technically challenging.
Combination therapy	Can be combined with conventional drugs to enhance efficacy and reduce adverse effects through synergistic mechanisms.	Potential herb-drug interactions may influence pharmacokinetics and treatment outcomes.
Precision medicine applications	It may be tailored to individual molecular profiles and disease mechanisms in future personalised therapies.	Biomarkers for patient stratification and treatment monitoring remain inadequately validated.
Computational drug discovery	Integration with molecular docking, AI, machine learning, and network pharmacology accelerates candidate identification.	Computational predictions require extensive experimental and clinical validation before translation.
Standardisation and quality control	Advances in phytochemical characterisation improve consistency and reproducibility.	Lack of universal standards for extraction, formulation, and quality assessment remains a significant challenge.
Clinical translation	Growing interest from academia and industry supports further development.	Significant translational gaps exist between promising laboratory findings and successful clinical outcomes.

Phytochemical therapeutics offer a unique advantage in neuroprotection by simultaneously targeting multiple disease mechanisms, including *MAPK9*-mediated oxidative stress, neuroinflammation, and neuronal apoptosis. However, challenges related to bioavailability, blood-brain barrier penetration, standardisation, and limited clinical evidence must be addressed before these compounds can be widely adopted as effective therapies for neurodegenerative diseases.

Advanced nanoformulation strategies for *MAPK9*-targeting phytochemicals

While having shown promising preclinical efficacy, the clinical development of phytochemicals that target *MAPK9* faces challenges due to low aqueous solubility, fast metabolism, inability to penetrate the BBB, and inconsistency in pharmacokinetic profiles. Thus, nanoformulation technology has been recognised as an appropriate way to overcome these obstacles rather than merely being used as carriers for the drugs. For instance, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, liposomes, dendrimers, and nanoemulsions enhance the stability of phytochemicals, enable prolonged circulation in the bloodstream, control release, and increase BBB passage via receptor-mediated or adsorptive endocytosis [123]. Similarly, NCMN has significantly higher oral bioavailability and accumulation in the brain compared with curcumin, leading to better antioxidant, anti-neuroinflammatory, and anti-apoptotic effects in AD mouse models [124]. Furthermore, nanoencapsulated EGCG and resveratrol have an increased ability to enter neurons and protect mitochondria [125].

Yet, there are some limitations associated with the use of nanoformulations as well. The effectiveness of these formulations will be determined by factors such as the particle size, surface charge, entrapment efficiency, stability of the formulation, repeatability, and safety of the manufacturing process, which need to be optimised to facilitate successful transition to the clinical setting [126]. In addition, there are no examples of the nanoformulations targeting *MAPK9* that have passed preclinical testing; thus, comparative analysis of various nano-carriers under the same conditions is still very rare.

Integration of imaging and biomarker assessment

Effective translation of the *MAPK9* phytochemicals in the clinic will necessitate the development of innovative imaging and biomarker approaches in order to optimise patient stratification, therapeutic response monitoring and pharmacological drug development. Advanced neuroimaging modalities such as structural MRI, DTI, fMRI, and PET can be used to assess the presence of brain atrophy, white matter pathology, neuroinflammation, and brain metabolism non-invasively [127]. Imaging techniques involving the use of radiolabeled ligands against Aβ, tau, and activated microglia might be considered as an approach to elucidate whether targeting *MAPK9* signalling leads to a decrease in the disease-related burden. Fluid biomarkers, including p-tau, NfL, GFAP, inflammatory cytokines, and markers of oxidative stress, can serve as a quantitative measure of neuronal injury and disease progression [128]. As *MAPK9* modulates oxidative stress, apoptosis, and neuroinflammation, integration of imaging with biomarkers will allow early detection of treatment responses and personalised medicine strategies.

An equally important element to consider here is the utilisation of an extended set of biomarkers, since there are multiple pathological mechanisms which interact in order to bring about neurodegenerative disorders. As opposed to a single biomarker, a multimodal panel should be used in this case, consisting of neurofilament light chain, total and phosphorylated tau, glial fibrillary acidic protein, TNF-α, IL-1β, IL-6, MDA, glutathione, superoxide dismutase, as well as BBB integrity markers. Furthermore, incorporation of transcriptomic, proteomic and phosphoproteomic signatures that indicate the activation of *MAPK9* would make the procedure even more efficient. Altogether, with the help of neuroimaging in combination with an extended biomarker panel, it will be possible to implement precision medicine that will enable early detection of disease progression, as well as a more accurate objective measurement of *MAPK9*-targeted therapies.

Computational and emerging approaches

Due to the increased complexity of the pathologies associated with neurodegenerative disorders, as well as the complexity of the active components of medicinal plants, there has been an urgent need to incorporate computational methodologies in neuropharmacology studies. Experimental studies of natural products have proven to be costly and time-consuming processes. Therefore, computational techniques have proved highly useful for the identification, analysis, and optimisation of phytochemicals targeting *MAPK9*/*JNK2* (Figure 5). Techniques include molecular docking, molecular dynamics (MD) simulations, AI, machine learning (ML), and network pharmacology.

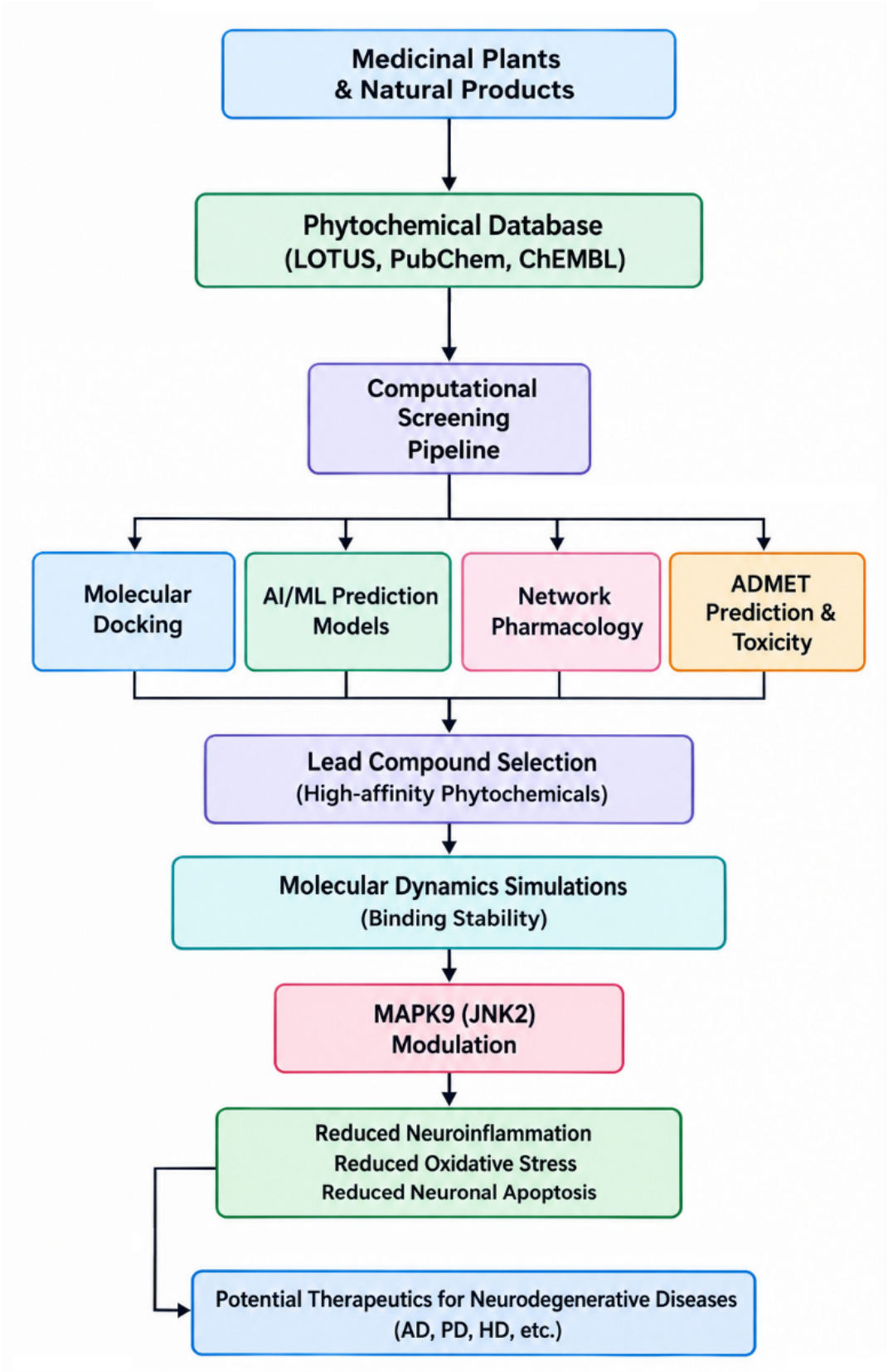


Figure 5. Computational and emerging approaches for identifying *MAPK9*-targeting phytochemicals in neurodegenerative diseases. Identification of *MAPK9*-targeting phytocompounds through computational and novel techniques. Lead identification of natural products extracted from medicinal plants through molecular docking, network pharmacology, artificial intelligence, machine learning, ADMET predictions, and molecular dynamics to determine their ability to target *MAPK9* and reduce neurodegeneration, including inflammation, oxidative stress, and neuronal apoptosis. AD: Alzheimer's disease; ADMET: Absorption, Distribution, Metabolism, Excretion, and Toxicity; HD: Huntington's disease; PD: Parkinson's disease.

Molecular docking and virtual screening

Molecular docking remains one of the most utilised methods in structure-based drug design. The technique predicts the best way that a compound docks in the receptor site of a protein and also measures the strength of interaction between a protein and a ligand [129]. In neurodegenerative diseases, molecular docking has emerged as an important technique for identifying bioactive compounds from medicinal plants that can inhibit *MAPK9* activity. Furthermore, with the availability of high-resolution crystal structures of *MAPK9*, molecular docking becomes possible and enables the identification of the binding energy of phytochemicals to crucial catalytic and allosteric sites of the protein [130]. Molecular docking studies often assess hydrogen-bond formation, hydrophobicity, electrostatic attraction, and binding energy to establish the feasibility of the interaction [131].

Among several phytochemicals, curcumin, quercetin, resveratrol, luteolin, kaempferol, and berberine exhibit good docking potential towards *MAPK9*/*JNK* proteins. For instance, molecular docking studies have revealed that curcumin can form stable hydrogen bonds with residues in the ATP-binding site of *JNK* enzymes, suggesting potential inhibition of their activity [132]. Likewise, quercetin can strongly interact with catalytic residues taking part in the phosphorylation process, thereby possibly preventing the subsequent activation of c-Jun and inflammatory pathways [133].

Virtual screening can be used in addition to docking to quickly test a large number of chemicals against the target protein. Phytochemical libraries, such as ZINC, IMPPAT, NPASS, and Traditional Chinese Medicine Libraries, may be screened for *MAPK9* inhibitors [134–136]. This technique saves time by eliminating the need to test a large pool of compounds in the laboratory. Some recent studies have successfully identified new types of flavonoids and polyphenols with high affinity for *JNK* proteins using virtual screening approaches [137, 138]. For example, dos Santos Maia et al. [139] assessed the possibility of utilising lignans as multitarget drugs for AD by applying the QSAR, docking, and Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) approaches. As a result, 139 lignans were found to exhibit activity against several targets implicated in neurodegenerative processes, including *MAPK9*-linked *JNK*-3, *PTP1B*, *NOX1*, *NQO1*, *PDE5*, *Nrf2*, *COX-2*, and *iNOS*. Six lignans, including austrobailignan 6, anolignan C, 7-epi-virolin, compound 64, ococymosin, and mappiodoinin B, exhibited high neuroprotective and antioxidant properties. It was concluded that lignans are suitable candidates for multitarget drug development against AD.

MD simulations

Although docking gives a static view of interactions between the protein and ligand, MD studies give a dynamic view by observing the interactions that occur during a period of time under physiological conditions [140]. It is now mandatory to validate docking results using MD simulation and also to determine the stability of plant secondary metabolite-*MAPK9* complexes. Thus, using Newtonian mechanics, the MD simulation technique helps researchers analyse the atomic movement of protein-ligand interactions. Various properties like root mean square deviation (RMSD), root mean square fluctuation (RMSF), radius of gyration (Rg), hydrogen bonding occupancy, solvent accessible surface area (SASA), and binding energy calculations help evaluate the stability and functional aspects of protein-ligand interactions [141].

For example, studies investigating the complex between curcumin and *JNK*s have exhibited protein-ligand interactions that were stable over 100 ns of MD simulation trajectories, indicating that curcumin can stabilise itself at the kinase's active site under physiological conditions [142]. Likewise, EGCG and resveratrol have been found to adopt stable conformations upon binding to *JNK*s in MD simulations, making them likely candidates for neuroprotective inhibitors [143, 144]. Therefore, MD simulation is extremely useful for studying the induced-fit effect on *MAPK9* induced by ligand binding, as it may help identify new allosteric binding sites and thus develop more selective inhibitors. Additionally, free energy calculations using MM/PBSA or MM/GBSA provide quantitative data on binding energy, making computational predictions more reliable before proceeding to experimentation.

AI and ML in natural product discovery

AI and ML techniques are transforming modern pharmaceutical discovery through fast screening and analysis of large biological and chemical datasets. They show promise in significantly accelerating the identification of medicinal plant compounds that inhibit *MAPK9* and other protein kinases linked to neurodegenerative diseases.

ML methods could be used with available data on kinase inhibitors to predict biological activities, toxicity, pharmacological characteristics, and BBB penetration capacity of phytochemicals [145]. Random forests, support vector machines, gradient boosting, and deep learning methods achieved strong performance in predicting compound-target interactions [146].

In the case of natural product discovery, AI techniques could be applied to select phytochemicals with the highest likelihood of inhibiting *MAPK9* before any docking or laboratory experiments. Moreover, ML techniques can reveal hidden structural features associated with kinase inhibition, helping to discover novel chemical scaffolds in medicinal plants [147, 148].

These advances in generative AI technology have further increased opportunities to discover neuroprotective drugs. New phytochemical compounds designed using GANs, VAEs, and transformer architectures could be developed with enhanced pharmacokinetic profiles to offset problems arising from their low bioavailability and poor target selectivity. Moreover, AI-driven predictions of compound permeability across the BBB and of their ADME/Tox properties could reduce the likelihood of failure and increase the likelihood of success in the discovery of treatments for neurological disorders.

Network pharmacology approaches

Whereas traditional medicines act on a single target site at a time, bioactive compounds from medicinal plants often exert their therapeutic effects through multiple molecular targets. Network pharmacology has become an increasingly popular field of systems biology that studies the complex mechanism of action of plants [149]. Network pharmacology combines bioinformatics, pharmacology, genomics, proteomics, and systems biology to study network interactions among natural compounds, proteins, signalling pathways, and diseases. It is especially useful for neurodegenerative conditions because of the presence of several interrelated pathological factors, including oxidative stress, neuroinflammation, mitochondrial dysfunction, protein aggregation, and apoptosis.

Network pharmacology techniques help determine key molecular hubs and signalling pathways modulated by phytochemicals from medicinal plants. Studies done on the compounds curcumin and resveratrol have shown involvement in the *MAPK9*, NF-κB, PI3K/Akt, Nrf2, and apoptotic pathways, among others [150]. This shows the importance and the wide spectrum of activity of these compounds. Similarly, studies on the plants *Withania somnifera* and *Bacopa monnieri* have shown regulation of multiple neuronal targets, including those governing neuronal survival and synaptic transmission [151, 152].

By integrating information from transcriptomics and proteomics datasets, researchers will be able to establish how phytochemicals modulate cellular signalling pathways in their entirety, rather than individual proteins. The application of molecular docking, MD simulations, AI, ML, and network pharmacology is revolutionising the screening of bioactive compounds from medicinal plants for *MAPK9* targeting.

Challenges and limitations

However, despite the considerable body of work supporting the neuroprotective effects of plant-derived, *MAPK9*/*JNK2*-specific bioactive compounds, many factors still make their effective utilisation in a clinical setting quite difficult. Although many plant-derived compounds show great promise for their antioxidant, anti-inflammatory, and anti-apoptotic properties in both cell and animal models, several issues, including pharmacokinetics, clinical validation, and extraction challenges, remain.

- **Poor pharmacokinetics:** A problem related to phytochemicals as potential therapeutic agents is their poor pharmacokinetic properties. Many plant-derived drugs are poorly soluble in water, absorbed through the intestine, quickly metabolised, and have poor bioavailability; thus, they cannot be used effectively. For instance, curcumin has proven highly effective at inhibiting the *MAPK9*-mediated inflammatory and apoptotic pathways, but it is difficult to use in clinical practice due to poor bioavailability and rapid systemic clearance [84, 109]. The same is true for resveratrol, which undergoes extensive first-pass effect; hence, it has a low plasma level despite its neuroprotective effects [73, 99].
- **Limited clinical trials:** While there is ample research demonstrating the benefits of natural bioactives, few of these agents have undergone extensive clinical testing. Most information on the potential benefits of *MAPK9*-targeting phytochemicals comes from preclinical experiments conducted in cells or animals. Although the information gained from these experiments may be informative, it does not always translate to a positive effect when the same compound is tested on humans. Clinical studies involving curcumin, EGCG, resveratrol, and *Ginkgo biloba* extracts, for example, have yielded inconclusive results in part because of disparities in dosages, treatment durations, target populations, and methodologies [86, 94, 153].
- **Variability in plant extracts:** The other important issue that must be mentioned in relation to natural products is their intrinsic variability. The chemical makeup of plants can be affected by various factors, including geography, climate, soil, harvest timing, farming techniques, and even the extraction process itself. Consequently, different extracts from the same plant type could vary greatly in their biochemical concentrations. For instance, curcuminoids and catechins can have varying quantities when taken from *Curcuma longa* and *Camellia sinensis*, respectively [84, 154].
- **Standardisation issues:** As such, it can be seen that closely related to the issue of extract variability is that of standardisation. While synthetic drugs have well-defined chemical structures due to consistent synthesis methods, natural medicinal extracts typically include complex arrays of chemicals. Without consistent standards in their extraction process, quality control, and characterisation of compounds present, it is possible to see large inconsistencies in their biochemical makeup [155]. This is especially important when studying the effects of *MAPK9*-targeted compounds, given variations in their biochemical composition.
- **Translational gaps:** Although some interesting discoveries have been made in the lab setting, there are several obstacles that impede translation from research results to therapeutic applications. Animal models of neurodegenerative disorders may lack features such as disease progression, individual variations, and the influence of the environment, which complicate human pathologies. Therefore, drugs effective in experimental models may not yield the same results when applied clinically [91, 100]. Moreover, while most investigations concentrate on single target molecules, neurodegeneration is characterised by intricate processes involving signalling pathways for oxidative stress, inflammation, mitochondrial malfunction, protein aggregation, and more.

Therefore, closing these gaps requires an interdisciplinary approach that combines methods from computational biology, pharmacology, biomarker discovery, drug delivery, and rigorous clinical trials.

Future perspectives

Increasing awareness of the vital role of *MAPK9*/*JNK2* in promoting neurodegeneration opens possibilities for designing more efficient next-generation neuroprotective agents. Research efforts ought to focus on isolating *MAPK9*-specific phytotherapeutics that modulate abnormal *MAPK9* activity while leaving the physiological activities of other *MAPK* proteins unaltered. Technological advances in phytochemical extraction, identification, and medicinal chemistry can greatly assist in identifying highly specific and effective plant-derived compounds.

Also, nanotechnology-based approaches for drug delivery have great potential to address poor pharmacokinetic properties and the limited ability of phytochemicals to cross the BBB. Nanoparticles, liposomes, dendrimers, and other drug carriers are likely to enhance the efficacy of phytotherapeutic agents due to their superior pharmacodynamics [156]. Future clinical studies should incorporate standardised neuroimaging and validated molecular biomarkers to evaluate target engagement, disease progression, and therapeutic efficacy of *MAPK9*-targeted interventions.

Thus, enhanced understanding of the indispensable role of *MAPK9*/*JNK2* in driving neurodegeneration enables the development of better next-generation neuroprotective agents. Research should focus on extracting plant-derived phytotherapeutics that act on the *MAPK9* pathway without interfering with the functions of other *MAPK* proteins. The technological advancements in phytochemistry and medicinal chemistry will play an important role in achieving such specificity and effectiveness. Drug delivery using nanotechnology holds immense promise for overcoming poor pharmacokinetics and the inability of phytochemicals to cross the BBB. Drug delivery techniques, including nanoparticles, liposomes, and dendrimers, among others, would make phytotherapeutic drugs more effective by enhancing pharmacodynamics.

Conclusions

Even though *JNK3* is still the main neuron-specific drug target, there is evidence suggesting that *MAPK9* acts through complementary roles in integrating neuronal damage with oxidative stress, neuroinflammation, and immune signalling from the periphery. This underscores the importance of investigating *MAPK9* as a separate drug target and, at the same time, calls for the development of isoform-specific inhibitors. Hence, these factors make *MAPK9* a prospective therapeutic target, while bioactive agents derived from medicinal plants (e.g., curcumin, resveratrol, quercetin, EGCG, berberine) show great ability to regulate *MAPK9*-related pathways and provide significant neuroprotection. Future studies should prioritise rigorous target validation and account for potential assay interference associated with highly reactive phytochemicals to facilitate the identification of truly selective *MAPK9* modulators.

It should be acknowledged that integrating natural product studies with advanced technologies is one of the most fascinating directions in this field. For example, thanks to recent advances in molecular modelling, AI, and network pharmacology, new approaches to identifying phytochemicals targeting *MAPK9* may emerge. However, successful implementation of such an approach would face several obstacles, including issues regarding bioavailability, standardisation, and clinical evaluation. Thus, interdisciplinary research would continue being critical in this context.

Abbreviations

6-OHDA: 6-hydroxydopamine

AD: Alzheimer's disease

AI: artificial intelligence

ALS: amyotrophic lateral sclerosis

ASK1: apoptosis signal-regulating kinase 1

ATP: adenosine triphosphate

Aβ: amyloid β

BBB: blood-brain barrier

CNS: central nervous system

CTE: chronic traumatic encephalopathy

DTI: diffusion tensor imaging

EGCG: epigallocatechin gallate

ERKs: extracellular signal-regulated kinases

fMRI: functional magnetic resonance imaging

HD: Huntington's disease

IL: interleukin

JNK2: c-Jun N-terminal kinase 2

LD: levodopa

LTP: long-term potentiation

MAP3Ks: MAP kinase kinase kinases

MAPK: mitogen-activated protein kinase

MD: molecular dynamics

MDA: malondialdehyde

ML: machine learning

MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

NCMN: nano-curcumin

NF-κB: nuclear factor kappa B

Nrf2: nuclear factor erythroid 2-related factor 2

PAINS: Pan-Assay Interference Compounds

PD: Parkinson's disease

PET: positron emission tomography

ROS: reactive oxygen species

SIRT1: sirtuin 1

TLR: toll-like receptor

TNF-α: tumour necrosis factor-alpha

TPY: threonine-proline-tyrosine

Declarations

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Author contributions

SO: Investigation, Writing—original draft. IA: Conceptualization, Supervision, Writing—review & editing. Both authors read and approved the submitted version.

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The authors declare no conflicts of interest.

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