Neuroprotective potential of traditional Ayurvedic Kadha: age-related neurological disorders: a comprehensive literature review

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Abstract
Despite modern medicine’s advancements, age-related neurological diseases like Alzheimer’s disease and Parkinson’s disease remain challenging due to high costs, side effects, and limited accessibility. Ayurveda, a traditional Indian medicine system, offers Kadha tea as a potential herbal option. This review explores Kadha’s components (basil (Ocimum basilicum L.), black pepper (Piper nigrum L.), Cinnamon (Cinnamomum verum J. Presl), ginger (Zingiber officinale Roscoe), and raisin (Vitis vinifera L.) and their interaction with various neurological disorders. Studies suggest Kadha exhibits anti-inflammatory, antioxidant, and antiviral properties, potentially impacting Alzheimer’s disease, Parkinson’s disease, neurotoxicity, neuroinflammation, and brain trauma. By focusing on specific disease mechanisms and Kadha’s intergrade effects, this review aims to elucidate its potential role in managing age-related neurological disorders.

Keywords: Ayurveda; Kadha; neuroprotective; neurological disorders; traditional medicine

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Highlights
In the context of traditional medicine, Kadha emerges as a potent blend of ingredients with promising therapeutic potential against age-related neurological disorders. Kadha, a concoction consisting of ginger, basil, black pepper, cinnamon, and raisins, has been traditionally utilized for its anti-inflammatory and antioxidant properties. The use of Kadha in Chinese and Egyptian civilizations is abundantly described in 2500 B.C.E. and is widely recommended for the treatment of a variety of chronic diseases. While ancient medicinal practices have long revered these components for their neurological benefits, contemporary research underscores their efficacy in combating conditions such as Alzheimer’s disease, stroke, parkinsonism, and oxidative stress-induced neuropathies.

Medical history of objective
Historically, Kadha’s ingredients, including basil, ginger, and raisins, have been esteemed in ancient medicinal records for their cognitive enhancement and neuroprotective qualities. Charak Samhita by Maharshi Charak is believed to have been composed around the 1st century B.C.E. to 2nd C.E. This ancient book is focused on herbal formulation. Another ancient book, Sushruta Samhita is dated around 600 B.C.E. to 1st century C.E. The author was the scholar, surgeon and teacher named Sushruta. This text is focused on surgery but also includes information about branches of Ayurveda and the use of medical herbs.

Background
Neurological disorders, particularly those associated with aging, pose a significant global health challenge. In 2016, they accounted for nearly 12% of disability-adjusted life years worldwide [1, 2]. Age-related conditions like Alzheimer’s disease (AD) and Parkinson’s disease (PD) are leading causes of morbidity, disability, and mortality, placing a substantial economic burden on healthcare systems worldwide [3]. For example, AD affects over 50 million individuals globally, progressively impairing daily activities and cognitive functions such as memory, language, reasoning, and mobility [4, 5]. Current treatment options for AD are limited, with only one new medication approved in the past 18 years [6]. Similarly, PD primarily affects movement with rigidity, slowness, and tremors, affecting over 6 million people worldwide [7]. While treatments exist for managing these symptoms, many neurological disorders remain incurable, and available options often come with side effects. For instance, the three approved AD treatments donepezil, galantamine, and rivastigmine can cause nausea, vomiting, anorexia, dizziness, and diarrhea [8].

Therefore, the development of safer and more effective strategies to reduce neurological disabilities is crucial to improving patient well-being and alleviating the burden on healthcare systems. This pressing need has spurred our exploration of herbal options as potential therapeutic approaches for neurological disorders.

Ayurveda, a traditional Indian medical system, utilizes various methods for preparing herbal remedies, including decoctions known as “Kadha”. The Ministry of AYUSH (Ayurvedic, Yoga and Naturopathy, Unani, Siddha and Homeopathy) identifies five common ingredients in Kadha: basil (Ocimum basilicum L.), black pepper (Piper nigrum L.), cinnamon (Cinnamomum verum J. Presl), ginger (Zingiber officinale Roscoe), and raisin (Vitis vinifera L.) [9].

Research suggests potential benefits of Kadha related to neurological disorders. Studies have demonstrated the antioxidant and anti-inflammatory properties of both individual Kadha components and the combined formula itself [10–14]. For instance, Choudhuri et al. confirmed the synergistic antioxidant effect of specific herbs blended in Saptarangi Plus Kadha [15]. Other studies, like Srivastava et al.’s, suggest Kadha’s potential to enhance the immune system, which might contribute to neurological health [16]. However, the potential benefits of consuming Kadha as a unified beverage compared to its individual components remain largely unexplored.

This paper aims to delve into the potential interaction between Kadha and neurological diseases. We will explore the evidence supporting the neuroprotective properties of Kadha’s individual components and discuss the potential advantages of consuming Kadha as a whole compared to its separate ingredients.

Methods

Results
Neuroprotective potential of Kadha
Previous research has proved the neuroprotective potential of Kadha such as the management of diabetic neuropathy, immunity booster, and antioxidant activity. Also, all properties of the Kadha components have been proven in different articles.

Ayurvedic medicines such as Kadha are seen as immunity boosters and they have been used as a treatment of viral diseases for a long time [17]. They also have many therapeutic effects on neurodegenerative diseases (Figure 1, 2) [18].

Diabetic peripheral neuropathy (DPN)
Diabetic peripheral neuropathy frequently occurs as a common chronic complication of diabetes [19]. Diabetes mellitus (DM) prevalence increases with age, specifically, 19.9% of those between the ages of 65 and 79 will develop DM. Moreover, up to 50% of patients with DM develop neuropathy which is associated with increasing age and duration of DM [20].

A study by Amitha et al. investigated the potential of Kadha, a traditional Ayurvedic herbal decoction, in managing DPN. They employed a combination of topical and oral treatments: Kanjika Taila Shanika Abyangya and Dhanyamala Parishkeya for the first 10 days, followed by 30 days of oral administration of 50 mL Paripathadi Kadha twice daily (morning and evening) before meals. The study assessed various DPN symptoms (pins and needles, skin color changes, hyperesthesia, electric shock sensations, burning, alldynia, and altered pin prick threshold) at three-time points: day 0, day 11, and day 31. The results revealed significant improvement in DPN symptoms after the intervention, suggesting the combined approach may be a promising option for managing DPN [21].

Oxidative stress

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**Figure 1** The underlying mechanism of therapeutic effects of Kadha and its main ingredients on neurological disorders; AD, stroke, multiple sclerosis (MS), and migraine. Symbols “↑” and “↓” are to demonstrate the increase and decrease, respectively. Grape seed extract was an exception in inducing the increase in interleukin-6 (IL-6) production in astrocytes. APP, amyloid precursor protein; Aβ, amyloid-beta; CysLTIIR, cysteinyi leukotriene receptor 1; GSK-3β, glycogen synthase kinase three beta; AChE, acetylcholinesterase; BChE, butyrylcholinesterase; GR, glucocorticoid receptor; Akt, activated protein kinase; T Reg, regulatory T cells; COX, cyclooxygenase; LPO, lipid peroxidation; MDA, malondialdehyde; P-CaMKII, phosphorylated-CaMKII; α-Calmodulin-Dependent Protein Kinase II; PD-95, postynaptic density protein of 95 kDa; NR-2B, N-methyl-D-aspartate receptor subunit NR2B; IL, interleukin; TNF, tumor necrosis factor; MCF, monocyte chemoattractant protein; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; TRAF6, TNF receptor associated factor 6; GSH, glutathione; TH, T helper cells; DHODH, dihydroorotate dehydrogenase; NO, nitric oxide.

**Figure 2** The underlying mechanism of therapeutic effects of Kadha and its main ingredients on neurological disorders; neuroinflammation and oxidative stress, depression, PD, neurotoxicity, neuropathy, traumatic brain injury, seizure, and tumor. Symbols “↑” and “↓” and “–” are to demonstrate increase, decrease, and no change, respectively. TLR, toll-like receptor 4; NLRP3, NACHT, LRR, and PYD domains-containing protein; ROS, reactive oxygen species; HSP70, 70 kilodalton heat shock proteins; MPO, myeloperoxidase; SOD, superoxide dismutase; CAT, catalase; FRAP, ferric reducing/anti-oxidant power; MAO-A, monoamine oxidase A; BDNF, brain-derived neurotrophic factor; GFAP, glial fibrillary acidic protein; iNOS, inducible nitric oxide synthase; GDNF, glial cell line-derived neurotrophic factor; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; BCL, B-cell lymphoma; BAX, Bcl-2-associated X protein; TRPV1, transient receptor potential cation channel subfamily V; NMDAR, N-methyl-D-aspartate receptor; IENF, intraepidermal nerve fiber.

Oxidative stress has been suggested as an etiology of neurodegenerative diseases. Accumulation of reactive oxygen species (ROS) can cause mitochondrial dysfunction in AD patients and also induces reduced activity in Complex I of the respiratory chain in PD patients [22, 23]. Several studies have investigated the antioxidant potential of herbal Kadhas. Sheth et al. found that Raktavardhak Kadha contained flavonoids, known for their antioxidant properties [24, 25].
Choudhari et al. further explored the antioxidant activity of Saptarangi Plus Kadha, a blend containing Salacia chinensis L., Curcuma longa L., and Tinospora cordifolia [15]. Using three different assays, they confirmed the inherent antioxidant activity of each herb and, more importantly, demonstrated a synergistic antioxidant effect when combined with the Saptarangi Plus Kadha formula.

Immunity booster

The intricate relationship between the immune system and the nervous system plays a crucial role in maintaining both neurological and overall health. The blood-brain barrier, a protective shield against harmful molecules, heavily relies on the immune system’s cytokine pathways for its function. In the brain itself, macrophages process antigens that cross the blood-brain barrier, while T-lymphocytes in the cerebrospinal fluid manage inflammatory processes. Notably, the brain’s lower white blood cell count compared to blood reflects its “privileged” status, where immune system interactions are carefully controlled. However, disruptions in this delicate balance can lead to various autoimmune CNS diseases [26]. Conversely, compromised immunity leaves the brain vulnerable to infections from bacteria (S. aureus, Nocardia, and Bacteroides), viruses (e.g., Cytomegalovirus), and fungi (Aspergillus species) [27]. Notably, several syndromes associated with primary immunodeficiencies also manifest neurological symptoms, such as Ataxia-Telangiectasia and Riddle Syndrome [28]. Studies like Srivastava et al.’s suggest that Kadha, in tablet form, can enhance the immune system [16]. This potential immune-boosting effect could not only support the nervous system’s proper function but also potentially prevent neurodegenerative processes by modulating the immune system in a beneficial way.

Anti-inflammatory

Neurological disorders like AD, PD, and MS often involve inflammatory responses, leading to symptoms like fever, swelling, and pain. Recent research suggests that inflammation plays a crucial role in many neurological diseases, not just as a reaction to injury [29-32]. This opens up promising avenues for exploring anti-inflammatory agents like Ayurvedic Kadha for managing these conditions. Studies on individual components of Kadha, including basil (Ocimum basilicum L.), black pepper (Piper nigrum L.), cinnamon (Cinnamomum verum J. Presl), ginger (Zingiber officinale Roscoe), and raisin (Vitis vinifera L.), demonstrate their anti-inflammatory properties [10-14]. These findings suggest that Kadha itself could potentially modulate inflammation associated with neurological disorders, potentially contributing to treatment strategies for neuroinflammation.

While research on Kadha’s combined effects is limited, the promising results from its individual components warrant further investigation. More comprehensive studies directly examining Kadha’s anti-inflammatory potential in neurological disorders are crucial to validate its therapeutic efficacy.

Basil

Basil is a tropical annual plant with a long history of use in traditional medicine. Its therapeutic potential lies in its ability to modulate inflammatory pathways. Studies have shown that basil reduces the production of specific cytokines, including interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNF-α), and chemokine (CC-motif) ligand 2 (CCL2), which are key players in inflammation. This anti-inflammatory effect extends to suppressing the activity of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a crucial transcription factor responsible for cytokine expression [32].

Beyond its anti-inflammatory properties, ancient wisdom and recent research highlight the effectiveness of basil leaves in treating various ailments. From relieving diarrhea, asthma, flu, cough, and fever to managing menstrual irregularities, ear pain, arthritis, and anorexia, basil offers a promising range of potential health benefits [33].

AD, AD. A progressive neurodegenerative disorder, manifests as a relentless decline in memory, cognitive abilities, and even personality. This deterioration arises from the progressive dysfunction and death of neuronal populations responsible for information storage and processing [34]. Interestingly, hypercholesterolemia, characterized by elevated blood cholesterol levels, has been associated with both the accumulation of amyloid-beta (Aβ) plaques in the brain and impaired cognitive function in AD patients [35]. This compelling association suggests the potential of targeted dietary interventions to mitigate the risk of developing age-related neurodegenerative diseases like AD and potentially improve cognitive function in individuals already diagnosed [36].

Several studies have investigated the neuroprotective potential of Ocimum basilicum L. Sarahroodi et al. examined the memory survival as well as memory retrieval of mice using a green Ocimum basilicum hydro-alcoholic extract. The hydro-alcoholic extract of green Ocimum basilicum L. was utilized at doses of 100, 200, 400, and 800 mg/kg. The results demonstrated that basil extract resulted in a severe increase in memory retrieval, with 400 mg/kg being the most effective [37]. Mohammadali et al. further investigated the beneficial effects of Ocimum basilicum L. on cognitive deficits due to hypercholesterolemia and oxidative stress in rat hippocampal tissues. Consumption of Ocimum basilicum L. extract increases the anti-oxidant power in serum and hippocampus and reduces the harmful effects of a high-cholesterol diet. Basil extract surprisingly delays the deposition of Aβ plaques and normalizes hippocampal morphology. As a result, it protects the hippocampal tissue from the harmful effects of hypercholesterolemia and also improves learning and memory disorders. Since Kadha contains Ocimum basilicum L., its consumption is essential in protecting the nervous system [38]. Mohd Zahid et al. evaluated Ocimum basilicum var. thyrsiflora for its ability to protect SK-N-SH neuroblastoma cells against hydrogen peroxide-induced oxidative stress. It has been shown that oxidative stress contributes to AD and PD diseases characterized by the imbalance between antioxidant defense mechanisms and the generation of free radicals.

The results showed that Ocimum basilicum L. protects neurons against oxidative damage by up-regulating superoxide dismutase (SOD) leading to, scavenging free radicals, restoring SOD activity, and preventing cell death [39].

Cerebral vascular damage.

Chronic arterial hypertension alters the structure of the brain’s vasculature, leading to a decline in blood supply. This reduced blood flow increases the brain's sensitivity to ischemic injury, which can result in neuronal death and synapse loss in areas crucial for memory and learning [40]. As the population ages, the risk and burden of cerebrovascular disease, a consequence of these changes, is expected to rise [41].

Alegra-Herrera et al. investigated the effects of standardized ethyl acetate extracts of Ocimum selloi and Ocimum basilicum L., enriched with rosmarinic acid, on various parameters in mice with chronic hypertension induced by angiotensin II. They found that the extracts lowered anxiety and memory deficits, reduced pro-inflammatory cytokines and macrophage chemotactic protein 1, and restored serum corticosterone levels. They suggest that Ocimum basilicum L. plays its anti-inflammatory role by modulating the activity of NF-κB, a protein involved in inflammation. By affecting NF-κB, basil could potentially reduce the production of pro-inflammatory cytokines and chemokines, leading to decreased levels of inflammatory markers like TNF-α and IL-1β. These findings suggest that the extracts may protect against angiotensin II-induced injury by modulating the inflammatory response and restoring hormonal balance [42].

Stroke.

Stroke, a disruption of blood flow to the brain, can severely impair function. Aging, the main risk factor, increases mortality, and morbidity, and lowers recovery in stroke patients compared to younger individuals [43, 44]. Other risk factors include diabetes, high blood pressure, cholesterol, smoking, inactivity, and alcohol abuse. During a stroke, blood flow is disrupted, depriving brain tissue of oxygen and nutrients, leading to cell death. Research suggests potential benefits of pre-treating with Ocimum basilicum L. for stroke [45]. Inflammation, triggered by activated microglia (the brain’s immune cells) within hours of stroke, is a key risk factor. Inflammation is also heavily influenced by cyclooxygenase-2 [47]. Lipopolysaccharide (LPS) stimulates the synthesis of prostaglandin E2 in human microglia via inducing cyclooxygenase-2 (COX-2) [48].
Several preclinical studies have investigated the potential neuroprotective effects of Ocimum basilicum L. in the context of stroke prevention and recovery. Bora et al. employed a murine model of stroke induced by bilateral carotid artery occlusion, followed by reperfusion. They observed significant reductions in cerebral infarct size, lipid peroxidation, and motor coordination impairment in mice pre-treated with a standardized ethyl acetate extract of Ocimum basilicum L. compared to the control group. Additionally, pre-treatment with the extract was associated with increased levels of glutathione, a crucial antioxidant molecule. Since Kadha contains Ocimum basilicum L., its consumption plays a vital role in protecting the nervous system [49].

Furthermore, Singh et al. evaluated the neuroprotective potential of Ocimum basilicum leaf extract in a model of traumatic brain injury in mice. Their study demonstrated a significant reduction in brain infarct size and oxidative stress markers in mice treated with the extract compared to the control group [50]. These findings provide further support for the potential neuroprotective properties of Ocimum basilicum L. and warrant further investigation into its therapeutic potential for various neurological disorders. Building upon these observations, Thongwong et al. explored the development of a novel neuroprotective supplement containing Ocimum basilicum L. alongside other bioactive components. Their investigation utilized an orodispersible film loaded with silkworm pupae and a combined extract of holy basil and ginger. In a model of ischemic stroke induced by right middle cerebral artery occlusion, administration of the supplement at various doses resulted in a dose-dependent reduction in brain infarct volume and improvement in neurological deficits [51]. This study highlights the potential of utilizing Ocimum basilicum-based formulations as a complementary therapeutic approach for stroke prevention and management.

Seizures. The incidence of epilepsy and seizures exhibits a significant increase in the elderly population (≥ 60 years old) compared to other age groups. This rise in new-onset epilepsy among older adults is frequently linked to underlying etiologies, such as cerebrovascular diseases, neurodegenerative disorders, intracerebral tumors, and traumatic brain injuries [52].

Epilepsy is a chronic neurological condition characterized by recurrent seizures, which are episodes of uncontrolled electrical activity in the brain. These episodes can manifest as changes in feelings, behavior, consciousness, or movement [53]. A diagnosis of epilepsy typically requires experiencing two or more unprovoked seizures separated by at least 24 h [54]. Seizures themselves can vary greatly in presentation, ranging from staring blankly for a few seconds to experiencing rapid arm or leg movements. Fortunately, for many people with epilepsy, effective medication or even surgery can control their seizures. While some individuals require lifelong treatment, others experience spontaneous remission, meaning their seizures eventually cease over time [55].

Multiple preclinical studies have investigated the potential application of Ocimum basilicum L. in the management of epilepsy. Khodabakhsh et al. employed a murine model of seizures induced by pentyleneetrazole and observed a significant reduction in brain malondialdehyde levels following administration of a hydro-alcoholic extract of Ocimum basilicum L. This finding suggests the extract’s potential to mitigate oxidative stress, a contributing factor in epilepsy pathogenesis. Notably, these observations align with existing reports acknowledging the antioxidant and anticonvulsant properties of Ocimum basilicum L. extracts [56].

Further evidence supporting the potential benefits of Ocimum basilicum L. in epilepsy management was presented by Shakiri et al. Their study, conducted on an animal model, demonstrated various positive effects, including a reduction in seizure frequency, duration, and mortality rate. Additionally, the study observed a delay in seizure onset, improved recovery time, and diminished oxidative damage to brain tissue. Furthermore, the researchers reported increased levels of antioxidant enzymes (SOD, glutathione peroxidase, and catalase (CAT)) and decreased malondialdehyde levels, suggesting enhanced cellular protection and improved antioxidant capacity. Notably, Shakiri et al. also observed improvements in short-term memory and motor coordination, suggesting potential neuroprotective effects beyond seizure control [57]. Because Kadha contains Ocimum basilicum L., its use has a great effect on the protection of the nervous system.

Cinnamon

Cinnamon, a spice derived from the Lauraceae family, has a long history of traditional use for various ailments, including digestive, respiratory, and gynecological conditions [58-61]. Modern research supports these historical applications, highlighting cinnamon’s anti-inflammatory and antioxidant properties. Additionally, studies suggest that cinnamon may play a role in improving health outcomes in individuals with conditions like diabetes, dyslipidemia, high blood pressure, and infections [59, 60]. The potential mechanism underlying cinnamon’s health benefits may involve its influence on inflammatory factors like NF-κB, IL-1β, IL-6, and antioxidant enzymes including glutathione peroxidase, CAT, and SOD [61].

Cinnamomum cassia (Chinese cinnamon) and Cinnamomum verum (true cinnamon) is the most common species which has the highest concentration of cinnamaldehyde [62]. Bioactive compounds derived from cinnamon are therapeutically effective against DM, cancer, oxidative stress, cardiovascular disease, fungal and bacterial diseases, wound healing, inflammatory syndromes, cholesterol levels, and immunomodulatory effects [63-73].

Cerebral ischemia-induced brain injury. Multiple preclinical studies have explored the potential neuroprotective properties of trans-cinnamaldehyde (TCA), a bioactive compound found in cinnamon, against ischemic stroke. Chen et al. employed an animal model of ischemia/reperfusion-induced brain injury and observed a significant reduction in infarct area, neurological deficit scores, and the expression of inflammatory markers (inducible nitric oxide synthase (iNOS) and COX-2) following TCA administration. These findings suggest a potential mechanism of neuroprotection through the downregulation of the NF-κB signaling pathway, a key player in inflammatory responses [74].

Supporting these observations, Qi et al. conducted in vitro experiments demonstrating the protective effects of TCA on rat adrenal pheochromocytoma cells exposed to simulated ischemic conditions (glucose and oxygen deprivation/reperfusion) [75]. This study provides further evidence for the potential benefits of TCA in mitigating cellular damage associated with stroke.

Furthermore, Zhao et al. investigated the therapeutic potential of TCA in a permanent middle cerebral artery occlusion model in mice. Their study demonstrated significant neuroprotective effects, including reduced neurological deficits, brain edema, and infarct volume. Additionally, they observed downregulation of inflammatory mediators, namely toll-like receptor 4 (TLR4), tumor necrosis factor receptor-associated factor 6 (TRAF6), and NF-κB, further supporting the anti-inflammatory properties of TCA [76]. Cinnamaldehyde has been shown to exhibit anti-inflammatory properties through various mechanisms. Studies have demonstrated its ability to suppress LPS-induced activation of the TLR4 pro-inflammatory signaling pathway, thereby inhibiting the expression of high mobility group box 1, an endogenous ligand for TLR4 [70, 77]. Additionally, cinnamaldehyde has been found to block the overexpression of TLR4 and TRAF6 in macrophages [78]. Furthermore, Heiss et al. reported that cinnamaldehyde regulates NF-κB activation by reacting with the free sulfhydryl groups of cysteine. Collectively, these findings suggest that cinnamaldehyde may exert its anti-inflammatory effects by acting upstream of TLR4 activation, thus inhibiting the expression of TLR4/TRAF6 and subsequent nuclear translocation of NF-κB [79].

PD. There are many de facto factors known to impact PD pathogenesis. PD is an age-related neurodegenerative disease that is mainly caused by the selective loss of the dopaminergic pathway. As preclinical and clinical indication reports that α-synuclein accumulation and autophagy inequality are linked with the genesis and progression of PD, a new study suggests that cinnamon could be helpful in halting the progression of α-synuclein [80-86].
Preclinical studies suggest potential neuroprotective effects of cinnamon in PD. Notably, cinnamon treatment protected mice from developing Parkinson’s-like symptoms induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [87]. Studies further demonstrated that sodium benzoate, a metabolite of cinnamon, inhibited the loss of parkin and protein diglycine, both crucial for dopaminergic neuron survival, and regulated neurotransmitter levels, ultimately improving motor function in PD mice [88, 89].

Mechanistically, sodium benzoate has been shown to inhibit the activation of p21ras, a small G protein, leading to the subsequent suppression of NF-κB, a key inflammatory pathway. This inhibition ultimately decreases nitric oxide synthase expression and production, mitigating neuroinflammation in PD models [88-90]. Additionally, cinnamon metabolism promotes the expression of the Glial cell line-derived neurotrophic factor, a neurotrophic factor known to support dopaminergic neuron survival [81]. Overall, these studies provide preliminary evidence for the potential neuroprotective properties of cinnamon in PD. However, further research, including clinical trials, is necessary to establish the safety and efficacy of cinnamon for the treatment of PD in humans.

AD. Preclinical studies suggest the potential benefits of TCA in improving synaptic function and mitigating neuroinflammation in AD models. Administration of TCA to mice with AD-like pathology has been shown to increase synaptic markers in the hippocampus and frontal cortex, suggesting enhanced neuronal connectivity [52, 71]. Additionally, TCA appears to inhibit neuroinflammatory responses by suppressing microglial activation and pro-inflammatory mediator production, potentially contributing to its neuroprotective effects [71]. TCA exerts neuroprotective effects by potently suppressing neuroinflammation. This is supported by its ability to diminish LPS-induced changes in primary microglia, including morphological alterations, nitric oxide (NO) production, and IL-1β release. Notably, TCA uniquely targets LPS-induced iNOS expression by shortening its mRNA half-life. This effect appears to be mediated through interference with the MEK1/2-ERK1/2 signaling pathway in primary microglia. Similar reductions in iNOS mRNA abundance were observed in the hippocampus of LPS-challenged mice treated with TCA, suggesting its potential to modulate neuroinflammation within the brain [71].

Do et al. investigated the potential of TCA to reduce Aβ pathology in a transgenic mouse model of Alzheimer’s disease (SNFAD) [92]. Their study revealed that TCA treatment improved cognitive function and decreased Aβ deposition in the brains of these mice. Interestingly, this effect was accompanied by a decrease in β-site APP-cleaving enzyme 1 (BACE1) levels, an enzyme critical for Aβ production. Additionally, TCA treatment increased the expression of silent information regulator 1 (SIRT1), coactivator 1α (PGC1α), and peroxisome proliferator-activated receptor γ (PPARγ), regulators known to suppress BACE1 activity. Previous research supports these findings. Li et al. demonstrated that TCA activates both PPARγ and retinoic X receptor (RXR) [93]. The PPAR-PPAR-RXR complex binds to specific DNA sequences (PPREs) to regulate gene expression, and studies by Heneka et al. and Katsouri et al. show that PPARγ agonists and PGC1α enhance BACE1 expression [94, 95]. Furthermore, SIRT1 plays a role in activating PGC1α and deacetylating PPARα, promoting its function [96]. Collectively, these studies suggest that TCA might exert its therapeutic effects in AD by reducing BACE1 levels through the SIRT1-PGC1α-PPARγ pathway, potentially interacting with the promoter region of the BACE1 gene [97].

Furthermore, Sajadi et al. observed that the administration of insulin and cinnamon has a positive effect on the rat models with AD. They indicated that administration of insulin and cinnamon improved the behavioral tests due to increased glucose transporter gene expressions in the hippocampus since decreased hippocampal insulin signaling leads to memory impairment and probably AD [98].

Supporting these preclinical findings, a systematic review by Sakkhaee et al. highlighted the potential benefits of cinnamon and its bioactive compounds (eugenol, cinnamaldehyde, and cinnamic acid) on brain function and behavior. Notably, the review suggests that cinnamon may reduce tau and Aβ aggregation, both implicated in AD, thus potentially impacting memory and learning. These findings suggest that cinnamon and its components warrant further investigation as potential adjuvants for preventing and alleviating cognitive decline [99].

Subarachnoid hemorrhage. Subarachnoid hemorrhage, primarily caused by a ruptured aneurysm, is a severe neurological condition with diverse outcomes ranging from mild cognitive impairment to catastrophic cerebral infarctions or death. Its incidence significantly increases with age. Following the initial bleeding, two primary factors contribute to negative outcomes: cerebral vasospasm, a narrowing of blood vessels, and early brain injury [100, 101]. Cinnamaldehyde, a compound found in cinnamon, has been investigated for its potential to address these challenges due to its established vasodilatory and neuroprotective properties.

Preclinical studies, such as one by Gürer et al., support the potential use of cinnamaldehyde in treating subarachnoid hemorrhage complications. Their study demonstrated that cinnamaldehyde reduced arterial wall thickness, increased the cross-sectional area of the basilar artery (a critical blood vessel in the brain), and mitigated hippocampal degeneration, a marker of brain injury [102].

MS. MS is a chronic, neurodegenerative disease characterized by progressive demyelination, leading to various neurological symptoms and disabilities [1]. The disease course can be classified into several stages, with subsequent presentation often being a clinically isolated syndrome. Patients may then progress to secondary progressive MS, primary progressive MS, or progressive-relapsing MS, which combines features of both relapsing-remitting MS and progressive MS [103]. Given the inflammatory nature of MS, researchers have explored the potential use of anti-inflammatory agents, including natural products like cinnamon. Delaviz et al. investigated the effect of cinnamon supplementation on inflammatory markers in a group of patients with progressive-relapsing MS. Their study demonstrated a significant reduction in IL-6 levels in the cinnamon group compared to the control group, suggesting cinnamon’s potential role in modulating inflammatory pathways in MS patients [104].

Neuroinflammation. Multiple studies support the potential anti-inflammatory and neuroprotective effects of TCA, a key component of cinnamon. Ho et al. investigated the potential of cinnamon as a dietary supplement for neurodegenerative diseases, focusing on its ability to suppress neuroinflammation [105]. They employed LPS-activated BV2 microglial cells, a commonly used model for studying neuroinflammatory processes. Their results demonstrated that the cinnamon ethanol extract at 50 μg/mL significantly suppressed the production of various pro-inflammatory mediators, including NO, TNF-α, IL-1β, and IL-6, as well as the activation of the pro-inflammatory transcription factor NF-κB. Furthermore, Ho et al. compared the anti-inflammatory effects of five individual compounds found in cinnamon. They found that at 100 μM, only cinnamaldehyde, 2-methoxy cinnamaldehyde, α-methyl cinnamaldehyde, and eugenol significantly suppressed NO, TNF-α, and IL-6 production. Notably, cinnamaldehyde demonstrated the strongest inhibitory effect against all four pro-inflammatory mediators and was the only compound to significantly suppress IL-1β production. Mechanistically, the study suggests that cinnamaldehyde does not prevent LPS binding to its receptor (TLR4) but rather inhibits its subsequent oligomerization and associated signaling pathways. Additionally, cinnamaldehyde reduces LPS-induced intracellular ROS formation, thereby restoring redox balance and attenuating the activation of NF-κB through multiple signaling pathways including NF-κB inducing kinase/IκB kinase, extracellular signal-regulated kinases and p38 mitogen-activated protein kinases [106, 107].

Pyo et al. investigated its effects on inflammatory cells and dopaminergic neurons in mice. They found that TCA suppressed the production of inflammatory mediators, such as iNOS and COX-2, in LPS-activated microglial cells. These findings suggest that TCA may exert its anti-inflammatory effects by influencing NF-κB activation. Since NF-κB regulates the expression of pro-inflammatory mediators like iNOS and COX-2, its inhibition by TCA could potentially maintain...
the basal expression levels of these enzymes, thereby mitigating inflammatory responses [108]. Furthermore, preclinical studies demonstrate that TCA can mitigate neuroinflammation in AD models by suppressing microglial activation and pro-inflammatory mediator production [109].

**Neurotoxicity.** Methamphetamine (N-methyl-1-phenylpropan-2-amine, also known as METH) is a highly addictive central nervous system stimulant with significant abuse potential [110]. Its lipophilic and cationic nature allows it to readily cross the blood-brain barrier, leading to neurotoxicity within the central nervous system [111, 112]. Chronic methamphetamine exposure can cause degeneration of dopaminergic and serotonergic neurons, resulting in long-term neurological damage [113].

Rashidi et al. investigated the potential neuroprotective effects of TCA against METH-induced cytotoxicity. They treated pheochromocytoma cell line 12 cells with varying doses of TCA, followed by exposure to METH (2.5 nM). Cell viability, DNA fragmentation, ROS generation, and glutathione content were assessed to evaluate apoptosis and oxidative stress responses. The study demonstrated that exposure to METH significantly reduced cell viability and glutathione levels while increasing ROS generation and DNA fragmentation, indicating cellular damage. However, treatment with TCA mitigated these effects, increasing cell survival, reducing ROS levels, boosting glutathione content, and lessening signs of apoptosis. These findings suggest that TCA may have neuroprotective properties against METH-induced neurotoxicity, potentially acting through antioxidant and antiapoptotic mechanisms [114].

Emamghoreishi et al. investigated the neuroprotective potential of cinnamaldehyde against Aβ toxicity in SHSY5Y neurons, a cell line commonly used in neurodegenerative disease research [115]. The study explored the involvement of various receptors, including N-methyl-D-aspartate (NMDA), ryanodine, and glycogen synthase kinase-3β, in cinnamaldehyde’s protective effects. Their findings revealed that cinnamaldehyde significantly reverses Aβ-induced toxicity and suppressed the Aβ-mediated increase in glycogen synthase kinase-3β protein levels in SHSY5Y neurons. Additionally, the study observed that dantrolene, a ryanodine receptor antagonist, significantly reduced the neuroprotective effects of cinnamaldehyde. These results suggest that suppression of ryanodine receptors may play a crucial role in the neuroprotective mechanisms of cinnamaldehyde against Aβ-induced neurotoxicity.

**Safety and toxicity to humans.** The food and drug administration and the Council of Europe have approved cinnamaldehyde as a safe, natural ingredient. However, in vitro and in vivo testing revealed that the high and non-nutritional consumption of this product may cause genotoxicity and hepatitis [115]. Currently, no dosage is established to determine how much Cinnamomum verum J. F res is toxic to humans, although high concentrations may be harmful.

**Ginger**

Originating from Southeast Asia, ginger (Zingiber officinale Roscoe) belonging to the Zingiberaceae family has been extensively employed in traditional medicine throughout history. Its therapeutic efficacy is attributed to the presence of a diverse array of phytochemicals, exhibiting various health benefits. Ginger demonstrates pharmacological potential in addressing a spectrum of ailments, including rheumatic diseases, constipation, hypertension, vomiting, and diabetes. Additionally, its antioxidant and anti-inflammatory properties offer a promising avenue for the prevention of age-related decline [116]. Notably, ginger has also been shown to be effective in alleviating menstrual pain [117].

Mechanistically, ginger’s diverse spectrum of effects is attributed to its interaction with the 5-HT3 receptor, its anti-therapeutic properties, and its ability to suppress pro-inflammatory cytokines like interleukin-1 (IL-1) [118].

AD. Choi et al. investigated the neuroprotective effects of fermented ginger extract on Aβ-induced neurotoxicity in rat hippocampal cells. Their study focused on the ability of the yeast Schizosaccharomyces pombe to convert 6-shogaol, a bioactive compound in ginger, to 6-paradol during fermentation. While maintaining 6-gingerol levels, the study demonstrated successful biotransformation of 6-shogaol to 6-paradol. Furthermore, the fermented extract exhibited significant neuroprotective effects in rat hippocampal cells, increasing cell viability following Aβ exposure. These findings suggest that fermentation could be a valuable strategy to enhance the neuroprotective potential of ginger by generating 6-paradol [119].

In an animal study, Arumugam et al. used a comparative molecular docking technique to find putative anti-Alzheimer receptors for ginger bioactive phytochemicals, including gingerol, shogaols, zingerone, also related molecules. The most promising favorable anti-therapeutic AD target, acetylcholinesterase, was discovered through an analysis of binding energy, projected inhibition constant, as well as hydrophobic/hydrophilic interactions of ligands with target receptors [120].

Two studies by Zeng et al. investigated the effects of traditional Chinese medicinal ginger root extract in AD models. The first study investigated the potential of traditional Chinese medicinal ginger root extract to prevent a behavioral decline in an AD rat model. The rats received the extract, and their memory and learning were assessed after 35 days. Notably, the extract reversed behavioral dysfunction and alleviated AD-like symptoms, suggesting potential therapeutic benefits. However, the research also revealed a seemingly contradictory finding. Ginger extract triggered increased in NF-κB and IL-1β markers associated with an inflammatory response. While NF-κB activation can be a stress response triggered by IL-1β, further research is required to clarify the specific role and downstream effects of this upregulation within the context of AD treatment [121]. Interestingly, the high-dose extract also increased the levels of antioxidant enzymes (SOD and CAT) and decreased MDA levels, suggesting a potential to mitigate oxidative stress in the brain despite the initial rise in inflammatory markers. These observations highlight the complex interplay between ginger’s anti-inflammatory and antioxidant properties, necessitating further investigation to fully understand their combined impact on AD pathology [122]. The second study by Zeng et al. delved deeper into the individual components of ginger by examining the effects of 6-shogaol, a primary gingerol compound, on AD treatment. This study demonstrated that 6-shogaol exerted neuroprotective effects in rat cells by reducing oxidative stress, suppressing inflammation, and activating protein kinase B, ultimately inhibiting Aβ-induced apoptosis. These findings suggest the potential of 6-shogaol as a therapeutic agent for both treatment and prevention of AD [123]. These studies unveil the intricate nature of ginger’s impact on AD. While ginger root extract demonstrates promising potential in improving behavior and mitigating oxidative stress, further research is crucial to elucidate the specific roles and potential interactions of its various components within the complex context of AD pathophysiology.

Hoseini et al. highlighted the potential of ginger’s unique combination of vitamins (particularly E and C) and shogaol to improve memory, and focus, and alleviate AD symptoms [124]. Vitamin E, acting as an antioxidant, protects cell membranes from oxidative damage. Interestingly, vitamin C, being water-soluble, can be oxidized and reduce fat-soluble vitamin E. However, it also facilitates the scavenging of free radicals by vitamin E, offering a synergistic protective effect [122].

In a report, Na et al. studied the effect of 6-shogaol on AD. CysteinyI leukotriene receptor one and a (cysteine protease) cathespin B (CatB) are involved in Aβ generation. According to the results, administration of 6-shogaol inhibits cysteinyI leukotriene receptor one and CatB. They suggested that 6-shogaol can be beneficial for treating AD as cysteinyl leukotriene receptor one and CatB inhibitor [125]. In another study, Park et al. showed that 6-paradol (240 µg/mL of shogaol for 60 h), a metabolite of 6-shogaol, has an acetylcholinesterase inhibitory effect. So, it is a valuable ingredient for treating AD [126].

Both red and white ginger extracts have the ability to inhibit acetylcholinesterase activities during AD. Oboh et al. conducted an
experiment to compare acetylcholinesterase inhibitory activities of two varieties of *Zingiber officinale* Roscoe in induced lipid peroxidation rat brain models. They found that white ginger had higher acetylcholinesterase inhibitory activity than red ginger, which could be related to its phytochemicals, such as flavonoids, and tannins [127].

**PD.** Park et al. evaluated the anti-neuroinflammatory impact of 6-shogaol, an active compound of *Z. officinale* PD models. In an in vivo experiment, C57/BL mice were pre-treated with 6-shogaol administered orally at a dose of 10 mg/kg body weight per day for 3 days. Subsequently, they received MPTP injections intraperitoneally at a dose of 30 mg/kg for 5 days. MPTP is a neurotoxin that induces permanent symptoms of PD in experimental animal models. It converts to 1-methyl-4-phenylpyridinium in the brain leading to toxic injury and dopaminergic cell degeneration. Furthermore, 1-methyl-4-phenylpyridinium remarkably suppressed microglial activation and raised TNF-α, NO, INOS, and COX-2 [132]. This study demonstrated that 6-shogaol has a protective effect on dopaminergic neurons against 1-methyl-4-phenylpyridinium and MPTP neurotoxicity in the PD model [128, 129].

**Diabetic neuropathy.** Painful diabetic neuropathy (PDN) is a consequence of chronic DM, where prolonged hyperglycemia leads to metabolic imbalances and nerve damage [130]. The transient receptor potential vanilloid 1 (TRPV1), strongly expressed in the peripheral nervous system and spinal cord, is implicated in PD nerve development. Additionally, TRPV1 interacts with N-methyl-D-aspartate receptors (NMDARs), further contributing to pain signaling [131–133].

Fajrín et al. investigated the effects of 6-shogaol, a ginger component, on allopndia in a PDN mouse model [134]. They focused on whether 6-shogaol could alter TRPV1 and NMDAR type 2B (NMDAR2B) mRNA expression within the spinal cord. Using quantitative real-time polymerase chain reaction, they found significantly reduced TRPV1 and NMDAR2B expressions in the spinal cords of mice treated with ginger extract (400 mg/kg body weight) and 6-shogaol (15 mg/kg body weight) compared to the diabetic control group. These findings suggest that ginger extract and 6-shogaol may alleviate PDN pain sensations by downregulating TRPV1 and NMDAR2B expression in the spinal cord.

**Brain damage associated with diabetes.** Ginger has been shown to have beneficial effects on brain injury related to diabetes. El-Akahawy et al. investigated the potential neuroprotective effects of ginger in a rat model of diabetic brain injury. Following eight weeks of streptozotocin-induced diabetes, they administered ginger treatment. Their findings revealed that ginger alleviated brain damage by mitigating oxidative stress, inflammation, and apoptosis. Notably, the elevated TNF-α expression observed in the diabetic group was reversed in various brain regions of the ginger-treated animals. This suggests a potential role for ginger’s anti-inflammatory properties in counteracting diabetes-induced ROS production. Additionally, ginger treatment significantly reduced the expression of iNOS, the number of apoptotic cells, and caspase-3 positive cells, further confirming its neuroprotective potential. These findings warrant further exploration of ginger’s therapeutic potential in mitigating diabetic brain injury [135].

**Stroke.** In a study by Thongwong et al., they suggested a novel neuroprotective supplement (which also had ginger inside) for reducing the risk of ischemic stroke under stroke conditions. They also examined the neuroprotective effect of an orodispensible film derived from a rice polymer loaded with silkworm pupae and the combined extract of holy basil and ginger with 10 different doses and after that, they inspect the right middle cerebral artery occlusion. The results evidently indicated that all doses of this suggested supplement were associated with decreased brain infarct volume and improved neurological deficits [152].

**Neuroinflammation.** Wattanarathon et al. investigated the protective effect of *Zingiber officinale* Roscoe against brain damage due to oxidative stress and memory impairment due to focal cerebral ischemia. The study shows that if mice are fed ginger rhizome extract, the volume of cerebral infarction decreases, and cognitive function and neuronal density in the hippocampus increase [136]. The extract of both white ginger (*Zingiber officinale* Roscoe), as well as red ginger (*Zingiber officinale var. Rubra*), has been reported to have neuroprotective and antioxidant effects. Oboh et al. found that compared to the aqueous extract of white ginger, red ginger had an elevated protective effect against Fe2+–induced lipid peroxidation in rat brain homogenates. This neuroprotective effect of red ginger could be associated with its high phytochemical content, Fe2+ chelating ability, and OH scavenging ability, as well as reducing power [127].

Abolaji et al. conducted an experiment to investigate the protective effects of 6-gingerol-rich fraction (6-GFR) on chlorpyrifos-induced oxidative damage and inflammation in the brains of rats. The results showed that 6-GFR protected against chlorpyrifos-induced increases in oxidative stress, and improved the activities of antioxidant enzymes in the brains of rats exposed to chlorpyrifos [137].

To evaluate the ameliorating effects of ginger on nervous damage, Singh et al. treated Wistar rats with orally administered dichlorvos and lindane, followed by post-treatment of ginger juice. They found that dichlorvos, as well as lindane-induced tissue impairment, was improved by ginger juice [138]. Histone deacetylase inhibitors increase 70 kilodalton heat shock proteins which is an essential part of the protein folding mechanism. It is found out that 6-shogaol has the same effect on the level of 70 kilodalton heat shock proteins as histone deacetylase inhibitor. Results also showed both histone deacetylase inhibitors and 6-shogaol suppressed the proinflammatory cytokine production. They have concluded that 6-shogaol can be a therapeutic agent for neuroinflammatory disorders by up-regulating 70 kilodalton heat shock proteins [139].

Pyo et al. studied the anti-inflammatory effects of *C. chinensis* and the neuroprotective effects on the mice explored the inflammatory cells and dopaminergic degeneration. In the LPS-induced inflammatory BV2-microglial cells, TCA inhibited INOS and COX-2 upregulation. These results suggest that *C. chinensis* has neuroprotective effects on dopaminergic neurons linked to the inhibition of inflammatory reactions. These results propose that *C. chinensis* could protect against inflammation-induced neurodegenerative diseases [108].

**Neurotoxicity.** Mehdizadeh et al. examined the effect of ginger on 3,4-methylenedioxymethamphetamine-induced neurotoxicity in rat brains. This study was conducted on three groups of rats (control, 3-methoxy-4,5-methylenedioxymethamphetamine, and 3-methoxy-4,5, methylenedioxymethamphetamine plus ginger). According to the results, unlike the 3-methoxy-4,5-methylenedioxymethamphetamine group, the 3-methoxy-4,5-methylenedioxymethamphetamine plus ginger group caused up-regulation of B-cell lymphoma two also down-regulation of B-cell lymphoma two associated X, apoptosis regulator, Bcl-2-associated X protein (BAX) expression [140]. BAX is an apoptosis stimulator and B-cell lymphoma two inhibits apoptosis by preventing BAX [141]. So, ginger can be used as a therapeutic agent to prevent brain damage in the 3-methoxy-4,5-methylenedioxymethamphetamine treated rats.

Farombi et al., in their study, evaluate the neuroprotective effects of 6-ginger-rich ginger against neurotoxicity caused by acrylonitrile in male Wistar rats. Since acrylonitrile is a neurotoxin and is widely used to make synthetic fibers, plastics, and glass, in this study, they investigated the protective effects of ginger on acrylonitrile induced damage to the brain in male rats. The researchers found that growth hormone-releasing factors restored malondialdehyde, tumor necrosis factor, IL-6, and NO levels induced by acrylonitrile. In addition, the growth hormone-releasing factor prevented acrylonitrile-induced cerebral cortex lesions and increased the expression of caspase-9 and -3 in the brain. These results suggest that the growth hormone-releasing factor may be a beneficial therapeutic agent for treating brain damage induced by acrylonitrile [142].

In addition to the beneficial and protective effects of *C. chinensis* and orodispensible film, the effect of Kafta has on the nervous system, due to its ginger content, it can reduce the toxic effects of substances in agricultural products on the nervous system. To prove this, Hamzeh et al. conducted a study to investigate the effect of ginger (100 mg/kg/day, gavage, for 30 days) in reducing the
toxicity of diazinon on the nervous system. Diazinon is widely used in agriculture. Diazinon stimulates acetylcholinesterase activity and lipid peroxidation, resulting in increased oxidative stress, leading to neurotoxicity. However, ginger, due to its antioxidant properties, significantly reduces lipid peroxidation and increases glutathione; thus, the harmful effect of diazinon neutralized the increase in oxidative stress [143].

Raisin
Raisins with the scientific name *Vitis vinifera* L. are very widely used in the Mediterranean diet, and are obtained by drying grapes. Usage of raisins reduces cholesterol, blood pressure, and blood sugar, thereby reducing the risk of heart disease and diabetes. Raisins also play a role in the prevention of gastrointestinal diseases through a positive effect on the intestinal microbiota and reducing the passage time of food through the intestine [144].

AD. Ma et al. conducted a study to explore the potential benefits of *Vitis vinifera* flavonoids in the context of AD pathology. Their research delved into the effects of these flavonoids on neurotransmitter signaling, synaptic function, and memory capabilities within a murine model of AD. For a period of two weeks, rats were orally administered *Vitis vinifera* L. at varying doses of 0.5, 50, 150, and 300 mg/kg body weight. The study’s findings indicate that *Vitis vinifera* L. appears to decrease acetylcholinesterase activity while increasing choline acetyltransferase activity within the hippocampal neurons of rats. These actions potentially lead to elevated levels of the neurotransmitter acetylcholine, known to play a critical role in cognition. Moreover, the study demonstrated significant improvements in learning and memory performance among mice treated with *Vitis vinifera* L., possibly linked to an upregulation of synaptotagmin-1 (SYT1) and brain-derived neurotrophic factor (BDNF) expression — proteins implicated in synaptic plasticity [145].

The study suggests that *Vitis vinifera* L. may modulate cholinergic signaling and synaptic activity, offering a possible explanation for its observed benefits in the AD mouse model. Further research indicates that the activation of acetylcholine receptors in pheochromocytoma cell line 12 cells can initiate the CaM/CaMKII/CREB pathway. CAMP-response-element-binding protein (CREB), a primary regulator of BDNF, plays a vital role in synaptic plasticity and memory formation. Interestingly, studies have shown reduced CREB phosphorylation and downstream target gene expression (including BDNF and SYT1) in amyloid precursor protein transgenic mice, emphasizing the significance of the CREB pathway in the pathophysiology of AD [146–149].

Calapai et al. conducted a randomized, double-blind, placebo-controlled clinical trial intervention to evaluate the potential benefits of *Vitis vinifera* L.-based dietary supplement (250 mg/day) on cognitive function and the neuropsychological status of healthy elderly. This study showed that taking *Vitis vinifera* L. dietary supplements for 12 weeks can improve physiological, and cognitive features and thus eliminate the adverse neurological and psychological conditions of healthy elderly [150].

Labanca et al. performed a study to evaluate the antioxidant, anticholinesterase, and antitryosinase activities of *Vitis vinifera* L. (cv. Aglianico) leaf extracts. In this study, Aglianico leaves, as a primary source of phenols, showed the highest tyrosinase inhibition value, as well as the highest acetylcholinesterase and butyrylcholinesterase inhibitory activity. Their study demonstrated that Aglianico leaves were able to be used as a potential substance for the treatment of diseases like AD or MS due to its tyrosinase, as well as cholinesterase inhibitory activities [151].

Bakhtiari et al. investigated the anti-dementia properties of mazvi (dried grapes). Interestingly, their study revealed that while the seed extract, rich in phenolic compounds and exhibiting high in vitro radical scavenging activity, did not improve memory function, fruit extracts (both aqueous and ethanolic) containing furfurals (non-phenolic compounds) significantly inhibited memory decline and increased the activity of antioxidant enzymes catalase and SOD [152].

Marzulli et al. investigated the probable effect of fermented grape marc from negroamaro and koshu *Vitis vinifera* L. on the treatment of neurodegenerative diseases, which activate conventional regulatory T cells and reduce the release of granulys B; thus, they can be beneficial in silencing Treg cells with neurotoxic activities and also for AD cases. They found fermented grape marc preparations suspended in water are often more beneficial than ethanol suspensions. It is likely polyphenol bioavailability depends on the type of suspension used, so having improving effects in some circumstances or no effects in others [153].

Hong et al. studied the neuroprotective effect of ampelopsin A as a main compound in *Vitis vinifera* L. on scopolamine-induced dementia mice models. The results showed that the central administration of ampelopsin A improved cognitive-memory behaviors in mice given scopolamine, and it contributed the rise in neurocognitive as well as neuroprotective effects on intrinsic neuronal excitability and behaviors [154].

Rapaka et al. treated Sprague-Dawley rats with aluminium chloride (100 mg/kg/day, orally) for eight weeks, followed by a post-treatment of *Vitis vinifera* L. (250 mg/kg and 500 mg/kg, orally) for 16 weeks. They discovered that treatment with *Vitis vinifera* L. improved memory as well as learning in a dose-dependent manner and exhibited an alteration in the expression of amyloid precursor protein and tau. The results showed that *Vitis vinifera* L. protected rats from aluminium-induced AD. The mechanism of neuroprotection may be because of a reduction in oxidative stress, inflammation, and in the formation of amyloid plaques and tau tangles, suggesting that *Vitis vinifera* L. may show to be a helpful substance in the treatment of AD [155].

Dani et al. prepared in vitro rat models treated with hydrogen peroxide. They observed *Vitis labrusca* leaf extracts could diminish the lipid and protein damage in induced hydrogen peroxide rat models [156].

Overall, these studies suggest that *Vitis vinifera* L. and its components may offer diverse benefits for the central nervous system, with potential applications in preventing or mitigating the progression of AD. Additionally, Rodríguez-Gonzalo et al. performed an RCT to assess the effects of consuming 50 g of raisins on cognitive performance, quality of life, and functional activities in healthy over 70-year-olds adults so for 6 months, the intervention group consumed 50 g of raisins per day added to their usual diet, while the control group did not receive specific supplement. Overall, they detect a slight improvement in cognitive performance, quality of life, and functional activities in the elderly [157].

It is important to note that most of these studies used animal models, and further research is needed to confirm their findings in humans and elucidate the underlying mechanisms of action before drawing definitive conclusions about the therapeutic efficacy of *Vitis vinifera* L. in AD.

Diabetic neuropathy. Peripheral neuropathy is the consequence of damage to peripheral nerves that is more prevalent in the aged, diabetic, and obese populations [73].

The most common causes are diabetes, the side effects of certain medicines or drinking too much alcohol, and immune-mediated conditions. *Vitis vinifera* L. has been mentioned in many studies as an effective substance for treating peripheral neuropathy cases [158]. Jin et al. evaluated the neuroprotective effect of *Vitis vinifera* L. extract (250 mg/kg, orally) on prediabetic mice induced by a high-fat diet. The results showed increased intraepidermal nerve fibers following *Vitis vinifera* L. extract administration. According to the results, *Vitis vinifera* L. extract has therapeutic potential in peripheral neuropathy in a high-fat diet mouse model [159]. Oxaliplatin, a platinum-based third-generation anti-cancer agent, is mainly used to treat colorectal cancer. Oxaliplatin causes the DNA cross-linking that prevents cancer cells from replicating, improving cancer treatment. Oxaliplatin, however, is known to cause chemotherapy-induced neuropathy.

Michiel et al. examined the protective effects of a hydro-alcoholic extract of *Vitis vinifera* L. (300 mg/kg, orally) red leaf on neurons treated with oxaliplatin. Their analyses showed that the hydro-alcoholic extract of *Vitis vinifera* L. red leaf can protect against
oxidative damage as well as neuropathy caused by oxaliplatin. In vitro and in vivo tests suggest that the extract can be used as a treatment for chemotherapy-induced neuropathy. Oxaliplatin-treated rats were significantly impacted by repeated daily administrations of *Vitis vinifera* L. extract, which significantly reduced the mechanical and thermal sensitivity to harmful and non-harmful stimuli. In addition to reducing oxidative damage, *Vitis vinifera* L. also reduced pain without affecting the effectiveness of treatment with oxaliplatin [160].

PD. A botanical extract from *Vitis vinifera* L. demonstrated dose-dependent inhibiting effects on reactive oxygen species. To evaluate the improvement effect of *Vitis vinifera* L. in Locomotor dysfunction due to PD, Long et al. performed a study in transgenic fly models, which were fed by the extract. They showed that extract in flies significantly improved their climbing ability, and it also significantly extended their lifespan [161].

**Stroke.** Chun et al. evaluated the neuroprotective effects of alcoholic extract of *Vitis vinifera* L. in vitro and in vivo cerebral ischemia models. This study demonstrated that alcoholic extract of *Vitis vinifera* L. promotes the cell viability of SK-N-SH human neuroblastoma cells, which were highly deprived of oxygen and glucose. It also increased the number of surviving cells in Gribis models with two vessel occlusions [162].

**Oxidative stress.** Duangan et al. found the protective effect of *Vitis vinifera* ethanol extract against glutamate-induced oxidative toxicity and HT22 hippocampal neuronal cells and juglone-induced oxidative stress. Its action is conducted through the inhibition of reactive oxygen species accumulation as well as improving endogenous anti-oxidant enzymes. These studies prove the phytochemical constituents and antioxidant properties of *Vitis vinifera* L. leaf extract [163].

Habashy et al. found that the administration of polyphenolic fraction from seedless black *Vitis vinifera* L. to carbon tetrachloride- intoxicated rats for ten days clearly boosted the carbon tetrachloride-induced systemic elevation in reactive oxygen species, NO, and thiobarbituric acid reactive substances levels, as well as myeloperoxidase activity. Based on this study, the polyphenolic fraction of *Vitis vinifera* L. had a therapeutic effect on carbon tetrachloride-induced necroinflammation as well as oxidative stress in rat brains [164].

Fujishita et al. in their study, found that grape seed extract stimulated astrocytes and increased neuroprotection against oxidative stress. As a result of their study, they showed that grape seed extract, acting on astrocytes, raised IL-6 synthesis, which functions as a neuroprotective paracrine, thereby protecting neuronal cells from oxidative stress [165].

Ghorbanian et al. conducted an experiment to examine the effects of raisins on spatial memory and morphometric parameters of the brain in aging rat models. The results indicated that raisins notably increase the antioxidant level and improve cognitive performance in aging rats, suggesting that anti-oxidants found in *Vitis vinifera* L. may prevent cells from degenerating, which typically happen due to aging, which leads to memory impairment [166].

**Neurotoxicity.** Pirinciguçu et al. in a study looking into the protective effects of Öközgüöz grape juice against oxidative stress as well as tissue damage caused by carbon tetrachloride in rats, found that the effects of carbon tetrachloride in combination with Öközgüöz grape juice or ursodeoxycholic acid are significantly reduced. The results of this study demonstrate the protective properties of Öközgüöz grape juice, indicating that this fruit is used extensively in traditional medicine for the treatment of tissue disorders. The effects of Öközgüöz grape juice were comparably positive to those of ursodeoxycholic acid. Consequently, the results of this study can be interpreted as indicating that the consumption of raisin extract has a positive effect on nervous system activity [167].

Aluminum is a mineral with relatively low oxidation potential but it can cause oxidative damage in various ways. It binds to negatively charged phospholipids in the brain. Phospholipids in the brain contain unsaturated fatty acids and are simply attacked by reactive oxygen species, including O₂⁻, H₂O₂, and OH. *Vitis vinifera* L. extract has been shown to protect the brain against aluminum-induced neurotoxicity [168].

Lakshmi et al., in a study, designed to evaluate the protective potential of *Vitis vinifera* L. hydro-alcoholic extract (400 mg/kg, orally) in improving aluminum-induced changes in behavioral and neurochemical parameters in mice showed that *Vitis vinifera* L. extract, together with aluminum, significantly increases short-term memory, cognition, mobility, muscle activity, as well as motor and muscle activity in mice. Therefore, this study confirmed the hypothesis that *Vitis vinifera* L. extract could be used as a neuroprotector in aluminum-induced neurotoxicity [169].

Boral et al. designed a study to evaluate the therapeutic effect of grape leaf polyphenols (100 mg/kg, orally for 21 days) on some biochemical and neurological markers in AlCl₃-induced AD in male rats. The neuropathogenic role of aluminum in AD can be explained by its potent and widespread toxic properties. Moreover, AlCl₃ induces changes in AD tissue. In this study, the results showed that 100 mg/kg body weight per day of virus-like particle extracts improved the cognitive and behavioral changes in AD rats. In addition, virus-like particle extract showed anti-annemics, anti-inflammatory, anti-oxidant, and neuroprotective properties against AlCl₃-induced brain injury and neurocognitive dysfunction [170].

**Black pepper**

Black pepper is one of the most widely used spices from the Piperaceae family, which also has healing properties. Some of its therapeutic properties include improving menstrual disorders and diseases of the ear, throat, and nose. It also has antimicrobial, anti-oxidant, anti-cancer, and anti-diabetic properties. Black pepper exerts its effects through mechanisms such as reducing cholesterol, reducing triglycerides, inhibiting superoxide anion, NO, and hydrogen peroxide, and affecting apoptosis [171].

AD. In the examination of Lokarat et al., acetycholinesterase inhibition, Aβ aggregation, anti-oxidant, and anti-inflammatory effects were all investigated. They analyzed black pepper oil by Gas chromatography-mass spectrometry and identified 33 combinations with limonene, d-3-carene, a-pinene, (3-β-pinene, and Caryophyllene as the major components. They concluded that black pepper oil can be useful in decreasing the hazard of AD aiment through acetycholinesterase inhibition and anti-inflammatory activity through cyclooxygenase-2 inhibition [172].

Based on the investigation of Chonpathompikunert et al. in animal models, the influence of piperine, the main active alkaloid of *Piper nigrum* L., on neurodegeneration and memory function in the hippocampus has been examined, and AD can be improved through it. For a period of two weeks before and one week after the bilateral intracerebroventricular administration of ethylcholine aziridinium ion, rats were orally administered piperine at varying doses of 5, 10, and 20 mg/kg body weight. According to this research, as a result, a decrease in lipid peroxidation and/or lower levels of acetylcholinesterase enzyme might be contributing factors. Furthermore, piperine proved to have neurotropic effects on the hippocampus [173].

In the research conducted by Hritcu et al., a methanolic extract of *Piper nigrum* L. fruits (50 and 100 mg/kg, orally, for 21 days) was analyzed for its potential antioxidant and memory-enhancing properties in a rat AD model using Aβ (1–42) particles. Aβ (1–42) rats with AD with this substance showed improvement in memory impairment by reducing brain oxidative stress. Also, the level of glutathione peroxidase, CAT, and SOD-specific activities were measured in the hippocampus, along with malondialdehyde and protein carbonyl content. The results suggested that the plant extract improved spatial memory impairment induced by Aβ (1–42) by reducing oxidative stress [174].

Sharma et al. explored the variety of neuroprotective mechanism presented by *Piper nigrum* L., which makes it suitable for drug development in neurodegenerative diseases including AD, amyotrophic lateral sclerosis, Huntington’s disease, multiple sclerosis,
PD, prion disease, etc. They found that *P. nigrum* L. extracts inhibited AChE, Aβ fibrillation, and oxidative damage by reducing ROS production and also had anti-glycation activity [175].

In a review by Balakrishnan et al., the pharmacological potential of black pepper and its active constituent in the treatment of age-related neurological disorders like AD is summarized. They concluded that black pepper has antioxidant, anti-diabetic, anti-obesity, antihypertensive, anti-inflammatory, anticancer, hepatoprotective, and neuroprotective properties. They also declared that black pepper's major bioactive neuroprotective compounds, i.e. piperine, significantly prevent age-related neurological disorders [2].

**Stroke.** It has been proved that using *Piper nigrum* L. and *Piper longum* L. is widely influential in stroke treatment. Hua et al. investigated the impacts of a dichloromethane fraction (100 and 200 mg/kg) of *Piper longum* L. and *Piper nigrum* L. on neuron injury after apoplexy in rats, using a persistent middle cerebral artery blockage model for 14 days. Dichloromethane fraction reduced neurological deficits and noticeably averted ischemia-prompted cell damage. The immunohistochemistry results indicate that Postsynaptic density protein 95 and synapsin I proteins are elevated, but the α-syn expression was significantly reduced in the brain sample from the sham group. According to western blot analysis, calmodulin, phospho-calmodulin kinases II, postsynaptic density protein 95, and N-methyl-d-aspartate receptor subunit 2B levels were significantly reduced in the model group. In model groups treated with dichloromethane fraction, calmodulin, phospho-calmodulin kinases II, postsynaptic density protein 95, and N-methyl-d-aspartate receptor subunit 2B were increased. Ultra-high-performance liquid chromatography-mass spectroscopy analysis revealed eight main components of dichloromethane fraction, of which piperine accounted for the largest proportion [176].

In the studies by da Cruz et al., piperine, an alkaloid found in the *Piper* genus, was proven to have anticonvulsant activity, assessed via way of means of the pilocarpine-induced models in mice. Pilocarpine-induced convulsions are decreased by piperine through gamma-aminobutyric acid mechanisms. Increased striatal concentrations of gamma-aminobutyric acid, taurine, and glycine occurred with piperine, and nitrite concentrations in the brain and sera were reversed with piperine. Consequently, the anticonvulsant effects of piperine are because of its anti-oxidant and anti-inflammatory properties. Piperine also may contribute to the anticonvulsant effects of the drug by inhibiting amino acids and gamma-aminobutyric acid system function [177].

**Differences and advantages of Kadha and its individual ingredients.**

While the individual components of Kadha like ginger, basil, black pepper, cinnamon, and raisins demonstrate promising neuroprotective, anti-inflammatory, and antioxidant properties in various studies, it's crucial to acknowledge the potential differences and advantages associated with consuming Kadha as a whole compared to its separate components. The first one is the synergistic effects between its ingredients, potentially amplifying their individual benefits or leading to the emergence of additional effects not observed with each element alone. The second one is their dosage and bioavailability which might differ from individual consumption of these components, potentially impacting their bioavailability and effectiveness. The third one is their delivery method as consuming Kadha as a beverage offers a convenient and potentially more palatable method of ingesting these ingredients compared to taking them individually as supplements or consuming larger quantities of raw ingredients. Finally, their complexity and compliance since managing and adhering to a regimen involving multiple individual ingredients might be more complex compared to consuming a single, pre-prepared formulation like Kadha. This could influence long-term compliance and potentially affect the overall effectiveness of the intervention [178].

Table 1 summarizes the data in the study.

### Conclusion

This study explored the potential therapeutic effects of Kadha and its components in various age-related neurological diseases, including their anti-inflammatory and antioxidant properties. Recent research has yielded promising findings regarding the neuroprotective potential of these ingredients. Based on our research, Kadha contains ginger, basil, black pepper, cinnamon, and raisins. These components can be used to treat neurological ailments, including AD, stroke, parkinsonism, and other diseases caused by oxidative stress such as nerve cell destruction, neurotoxicity, and peripheral neuropathy. In the case of AD, basil, ginger, and raisin have a significant role in alleviating symptoms. Basil can increase memory retrieval and protect the hippocampus tissue from oxidative damage by removing free radicals and preventing cell death. Ginger has the same neuroprotective effects caused by generating 6-paradol metabolite as an acetylcholinesterase inhibitor. Also, 6-shaogoi, another metabolite, can inhibit both cysteinyl leukotriene receptors 1 and 5. Ginger contains vitamins E and C which can remove free radicals and improve memory retrieval progress. Raisins can eliminate symptoms seen in AD and improve cognitive memory behaviors via decreasing lipid and protein damage as well as affecting cholinergic neurotransmitters indirectly and containing polyphenolic compounds. Raisins are even capable of preventing aluminum toxicity. Basil increases levels of proinflammatory cytokines and reduces mitochondrial apoptosis. Besides, ginger lessens IL-17 and IL-23 along with astrogliosis and microglia activation as the cause of myelin destruction in MS. Regarding neurotoxicity and parkinsonism, cinnamon's effects are noteworthy. Cinnamon decreases apoptosis and re-activates oxygen species formulation while increasing glutathione levels, which result in protection against METH neurotoxicity. Additionally, cinnamon is applicable in PD because it terminates the progression of α-synuclein and inhibits the reduction of protein parkin and protein delicate levels lead to enhancement in Parkinson's symptoms. According to the study by our team, the various factors mentioned in this review article show that Kadha's ingredients can have several effects, such as neuroprotective, anti-inflammatory, antioxidant, and prevention of other neurological diseases. Ultimately, Kadha, in general, is a remarkable immune-booster and helpful in diabetic neuropathy in addition to oxidative stress. Due to the lack of exclusive studies about Kadha itself, more RCT and in vitro studies that can examine the therapeutic effects of Kadha as a coherent set-in human group assist in completing the gaps and confirming our study. Our study aids other researchers in this field by creating a scientific background and smoothing the research path for them.
**Table 1: A summary of the studies on the anti-viral potential of Kadha and its active components**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>First author</th>
<th>Country</th>
<th>Type of study</th>
<th>Study model</th>
<th>Kadha component</th>
<th>Dose</th>
<th>Duration</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>[11]</td>
<td>2012</td>
<td>Joung Hong</td>
<td>South Korea</td>
<td>In vitro and in vivo</td>
<td>Eight-week-old male BALB/c mice</td>
<td>Cinnamon water extract</td>
<td>20, 100 or 500 mg/kg of body weight</td>
<td>6 days</td>
<td>Treatment with cinnamon water extract had ability to decrease LPS-induced TNF-α in serum.</td>
</tr>
<tr>
<td>[12]</td>
<td>2002</td>
<td>M. Thomson</td>
<td>Kuwait</td>
<td>In vivo</td>
<td>Adult female Sprague-Dawley rats weighing 200-250 g</td>
<td>Ginger</td>
<td>50-500 mg/kg (orally or intraperitoneally)</td>
<td>4 weeks</td>
<td>1. High doses of ginger (500 mg/kg) could significantly be effective in lowering serum PGE2 when given either orally or intraperitoneally. 2. A significant reduction in serum cholesterol was detected while a higher dose of ginger (500 mg/kg) was given. Basil extract possesses anti-inflammatory properties, and the mechanism involved is a composed interaction between the inhibition of pro-inflammatory mediator and the stimulation of anti-inflammatory cytokines. Time lapse and higher doses of basil essential oil is able to reduce both the intensity and frequency of migraine attacks.</td>
</tr>
<tr>
<td>[14]</td>
<td>2017</td>
<td>Camila Martins Gúez</td>
<td>Brazil</td>
<td>In vitro</td>
<td>Human leukocytes cultures</td>
<td>Basil extract (Ocimum basilicum L.)</td>
<td>0.001–0.2 mg/mL</td>
<td>–</td>
<td>Extract of green Ocimum basilicum significantly had the ability to increase memory retention because of antioxidant activity of flavonoids, tannins and terpenoids. In hypercholesterolemic rats administration of Dill tablet and basil extract significantly started to decrease serum cholesterol thereby inhibited deposition of Aβ plaque, normalized hippocampal morphology, and restored cognitive functions. At molecular level, O. basilicum exerted neuroprotection against H₂O₂-induced cytotoxicity by decreasing oxidative damage characterized by the reduction of intracellular ROS generation and restoration of intracellular SOD levels. All the three species of Ocimum found in western Himalayan region showed significant antioxidant and antidepressant activities, however the O. kilimandscharicum was found to have highest antioxidant and antidepressant activity.</td>
</tr>
<tr>
<td>[179]</td>
<td>2020</td>
<td>Mahdieh Ahmadifard</td>
<td>Iran</td>
<td>Triple-blind clinical trial study</td>
<td>144 patients diagnosed with migraine</td>
<td>Basil essential oil</td>
<td>2, 4, 6%</td>
<td>Medications were used topically every 8 h for 3 successive months. Single dose</td>
<td></td>
</tr>
<tr>
<td>[37]</td>
<td>2012</td>
<td>Shadi Sararahoodi</td>
<td>Iran</td>
<td>In vivo</td>
<td>Male albino NMRI mice weighing 20–25 g</td>
<td>Green Ocimum basilicum (sweet basil)</td>
<td>100, 200, 400 and 800 mg/kg</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>[38]</td>
<td>2020</td>
<td>Soheila Mohammadadali</td>
<td>Iran</td>
<td>In vitro</td>
<td>Forty rats (180 ± 20 g)</td>
<td>Dill tablet and Ocimum basilicum (basil)</td>
<td>1. HCD + 300 mg/kg of Dill tablet 2. HCD + 400 mg/kg of basil aqueous extract</td>
<td>16 weeks</td>
<td></td>
</tr>
<tr>
<td>[39]</td>
<td>2018</td>
<td>Manali Haniti Mohd Zahid</td>
<td>Malaysia</td>
<td>In vitro</td>
<td>SK-N-SH neuroblastoma cells</td>
<td>Ocimum basilicum var. thyrsiflora</td>
<td>3.1–25 μg/mL</td>
<td>24 h</td>
<td></td>
</tr>
<tr>
<td>[180]</td>
<td>2015</td>
<td>Devesh Tewari</td>
<td>India</td>
<td>In vitro</td>
<td>Male albino mice between 20–30 g</td>
<td>Ocimum basilicum, O. tenuiflorum, O. kilimandscharicum</td>
<td>A single dose of 200 mg/kg/p.o.</td>
<td>21 days</td>
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Table 1 A summary of the studies on the anti viral potential of Kadha and its active (continued)

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2. OB significantly reduced the corticosterone level and up-regulated protein and gene expressions of BDNF and glucocorticoid receptor (GR).  
3. OB reduced CUMS induced hippocampal neuron atrophy and apoptosis, and increased the number of the astrocytes and new nerve cells. OB significantly increased glial fibrillary acidic protein (GFAP)-positive cells as well as BDNF and GR immunoexpression in the hippocampus. |
| [42]      | 2019 | Elian Alegría-Herrera | Mexico | In vitro | Male ICR mice (age = 10 weeks; n = 72) | Ocimum basilicum, Ocimum selloi, and rosmarinic acid | 0.39–6.24 mg/kg | 6 weeks  | By treatment with Ocimum basilicum (Oba-EtOAc) and Ocimum selloi (Ose-EtOAc), and some doses of rosmarinic acid, the damage caused by AGII was blocked by re-establishing corticosterone serum levels and by decreasing the proinflammatory cytokines and monocyte chemoattractant protein 1 (MCP-1).  
Pre-treatment with standardized ethyl acetate extract of Ocimum basilicum (100 and 200 mg/kg, p.o.) significantly:  
1. Started to reduce cerebral infarct size and lipid peroxidation.  
2. Restored glutathione content.  
3. Attenuated impairment in short-term memory and motor coordination.  
ORB improves functional outcomes, reverses oxidative stress and cerebral damage after ischemia reperfusion. |
| [49]      | 2011 | Kundan Singh | India | In vitro | Swiss albino mice of either sex weighing 20–30 g | Ocimum basilicum | 100 and 200 mg/kg p.o. | 4 days  | Pre-treatment with standardized ethyl acetate extract of Ocimum basilicum (100 and 200 mg/kg, p.o.) significantly:  
1. Started to reduce cerebral infarct size and lipid peroxidation.  
2. Restored glutathione content.  
3. Attenuated impairment in short-term memory and motor coordination.  
ORB improves functional outcomes, reverses oxidative stress and cerebral damage after ischemia reperfusion. |
| [50]      | 2018 | Varinder Singh | India | In vitro | Swiss Albino mice weighing 25–30 g (3–4 week old) | Ocimum basilicum L. | 2,000 mg/kg | 7 days  | ORBE improves functional outcomes, reverses oxidative stress and cerebral damage after ischemia reperfusion. |
| [56]      | 2017 | Tayebeh Khodabakhshi | Iran | In vitro | 40 virgin male mice, 25 ± 5 g in weight | Ocimum basilicum hydro-alcoholic extract | PTZ group (90 mg/kg, ip), 25, 50 or 100 mg/kg of a hydro-ethanolic extract of O. basilicum before PTZ | Hydro-ethanolic extract of O. basilicum possesses significant antioxidant and anticonvulsant functions. |
| [182]     | 2004 | Qu Xun | China | In vivo | Female C57BL/6 mice, 8 weeks old | Basil polysaccharide | 1.25–5 mg/kg | 2 weeks  | 1. Basil polysaccharide of various dosages showed no effect on tumor growth.  
2. In high and middle dosage, it could significantly reduce the number or metastasis nodules (P < 0.05). |

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| [74]      | 2016 | Yuh-Fung Chen         | China   | In vivo and in vitro | Adult male CD-1 mice (weight 22–28 g) | TCA             | 10, 20, 30 mg/kg, orally administration 60 min before ischemia surgery |          | 1. TCA, an essential oil in cinnamon powder, markedly was functional to reduce infarct area in cerebral ischemia mouse model.  
           |       |                       |         |               |              |                 |        | 2. It inhibited NO production and inflammation which proposed action mechanism of TCA on neuroinflammation and neuroprotection.  
           |       |                       |         |               |              |                 |        | 3. TCA was found to reduce NO production and inflammation by decreasing the expression of genes associated with iNOS, COX-2, and TNF-α. Furthermore, it inhibited the NF-κB and p35 pathways. TCA was able to attenuate OGD/R-induced cell injury which may be related to its inhibitive effect on oxidative stress and apoptosis. |
| [75]      | 2016 | Xue Qi                | China   | In vitro | The rat adrenal pheochromocytoma cells (PC12 cells) culture | TCA             | 0.1, 1, and 10 mol/L, respectively | 24 h  | Cinnamaldehyde was functional to protect against cerebral ischaemia injury by inhibiting inflammation, partly mediated by reducing the expression of TLR-4, tumour necrosis receptor-associated factor 6 and the nuclear translocation of NF-κB. Cinnamon extract and polyphenols with procyanidin type-A polymers exhibit the potential to increase the amount of tristetraprolin (TTP), insulin receptor (IR), and glucose transporter type 4 (GLUT4) in 3T3-L1 adipocytes. |
| [76]      | 2015 | Jing-Ru Zhao          | China   | In vitro | Male CD-1 mice | Cinnamaldehyde   | 25 (CA25), 50 (CA50) and 75 mg/kg (CA75) | 24–72 h | The inclusion of water-soluble cinnamon compounds in the diet could reduce risk factors associated with diabetes and cardiovascular disease. |
| [64]      | 2007 | He-Ping Cao           | USA     | In vitro | Mouse 3T3-L1 adipocytes | Cinnamon         | 0–100 μg/mL | 120 min | Cinnamon extract and polyphenols with procyanidin type-A polymers exhibit the potential to increase the amount of tristetraprolin (TTP), insulin receptor (IR), and glucose transporter type 4 (GLUT4) in 3T3-L1 adipocytes. |
| [183]     | 2013 | Anne-Marie Roussel    | France, USA | In vivo | Twenty-two subjects, with impaired fasting blood glucose with BMI ranging from 25 to 45 | Cinnamon         | 250 mg of an aqueous extract of cinnamon (Cinnulin PF) two times per day | 12 weeks | The inclusion of water-soluble cinnamon compounds in the diet could reduce risk factors associated with diabetes and cardiovascular disease. |
| [71]      | 2016 | Li-Qing Zhang         | China   | In vitro | Nine-week-old male ICR mice (25–30 g) | TCA             | 12.5–50 mg/kg | 28 days | 1. TCA significantly decreased memory deficit.  
           |       |                       |         |               |              |                 |        | 2. It improved synaptic plasticity in LPS-challenged mice.  
           |       |                       |         |               |              |                 |        | 3. TCA suppressed microglial activation by destabilizing iNOS mRNA, which leads to improved memory impairment in mice suffering.  
           |       |                       |         |               |              |                 |        | 1. Cinnamon treatment upregulated Tregs through reduction of NO production.  
           |       |                       |         |               |              |                 |        | 2. Blocking of Tregs by neutralizing antibodies against CD25 abrogates cinnamon-mediated protection of EAE. |
| [184]     | 2015 | Susanta Mondal        | USA     | In vivo | 4–5 weeks old female SJL/J mice | Cinnamon         | 50 mg/kg | 40 days | 1. Cinnamon treatment upregulated Tregs through reduction of NO production.  
           |       |                       |         |               |              |                 |        | 2. Blocking of Tregs by neutralizing antibodies against CD25 abrogates cinnamon-mediated protection of EAE. |

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</tr>
</thead>
<tbody>
<tr>
<td>[185]</td>
<td>2006</td>
<td>Sarah Mueller-Steiner</td>
<td>USA, Japan</td>
<td>In vivo and in vitro</td>
<td>Mice with neuronal expression of familial AD-mutant human amyloid precursor protein</td>
<td>CatB</td>
<td>(1–2 mg/mL)</td>
<td>7 days</td>
<td>CatB actually reduces levels of Aβ peptides, especially the aggregation-prone species Aβ1–42, through proteolytic cleavage.</td>
</tr>
<tr>
<td>[61]</td>
<td>2018</td>
<td>Burak Yulug</td>
<td>Turkey, USA</td>
<td>In vitro</td>
<td>Twenty-eight C57BL/6 male mice weighing 25–30 g</td>
<td>Cinnamon polyphenol extract</td>
<td>10 mg/kg</td>
<td>24 h</td>
<td>Cinnamon polyphenol extract effectively reduced infarct and edema formation which were associated with significant alterations in inflammatory and oxidative parameters, including NF-κB, IL-1β, IL-6, nuclear factor erythroid 2-related factor 2, glial fibrillary acidic protein, neural cell adhesion molecule, malondialdehyde, SOD, CAT and glutathione peroxidase.</td>
</tr>
<tr>
<td>[186]</td>
<td>2019</td>
<td>She-Wei Guo</td>
<td>China</td>
<td>In vitro</td>
<td>56 male C57/Bl6 mice (90–120 days old, 22–28 g)</td>
<td>Cinnamon acid (CNA)</td>
<td>100 mg/kg body weight per day</td>
<td>30 days</td>
<td>1. CNA did not affect physiological function but effectively restored neurological function and brain edema. 2. CNA alleviated the memory impairments induced by traumatic brain injury in both the Morris water maze and step-down task. CNA also recovered abnormalities in the synapses of traumatic brain injury mice by suppressing the expression of histone deacetylase 2 (HDAC2). 3. Furthermore, CNA did not alter HDAC mRNA because it promoted the expression of miR-455-3p, a miRNA that regulates HDAC2 at the posttranscriptional level.</td>
</tr>
<tr>
<td>[159]</td>
<td>2013</td>
<td>Heung Yong Jin</td>
<td>Korea</td>
<td>In vitro</td>
<td>Male 4-week-old C57BL/6J mice</td>
<td>Vitis vinifera grape seed extract (VVE)</td>
<td>100–250 mg/kg</td>
<td>12 weeks</td>
<td>VVE could play a role in the management of peripheral neuropathy, similar to other antioxidants known to be beneficial for diabetic peripheral neuropathy.</td>
</tr>
<tr>
<td>[104]</td>
<td>2021</td>
<td>Delaviz Elham</td>
<td>Iran</td>
<td>A randomized controlled trial</td>
<td>60 patients suffering from progressive-relapsing MS</td>
<td>Cinnamon</td>
<td>500 mg in each capsule: four capsules of cinnamon were taken every day</td>
<td>8 weeks</td>
<td>Cinnamon may could help improve inflammatory markers and pain in MS patients.</td>
</tr>
<tr>
<td>[108]</td>
<td>2013</td>
<td>Ji-Hi Pyo</td>
<td>China</td>
<td>In vivo</td>
<td>Male adult ICR mice (6 weeks, 20–25 g)</td>
<td>TCA</td>
<td>30 mg/kg</td>
<td>7 days</td>
<td>TCA showed anti-inflammatory efficacy to inhibit inflammation induced by both LPS-stimulated microglial activation and 6-OHDA-induced dopaminergic damages. TCA’s effects on improving memory impairment and NMDAR dysfunction is its capability to inhibit microglial activation and neuroinflammation by the blockage of the NF-κB signaling pathway in AD.</td>
</tr>
<tr>
<td>[109]</td>
<td>2019</td>
<td>Yang Zhao</td>
<td>China</td>
<td>In vivo</td>
<td>PS cDKO mice</td>
<td>TCA</td>
<td>–</td>
<td>60 days</td>
<td>Submit a manuscript: <a href="https://www.tmrjournals.com/tmr">https://www.tmrjournals.com/tmr</a></td>
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<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>[187]</td>
<td>2019</td>
<td>F. Khorash</td>
<td>Iran</td>
<td>Double-blinded randomized controlled clinical trial</td>
<td>Fifty eligible migraine patients</td>
<td>Cinnamon</td>
<td>3 capsules/day each containing 600 mg of cinnamon powder</td>
<td>2 months</td>
<td>Cinnamon considerably reduced the frequency, severity, and duration of migraine attacks in the migraine patients.</td>
</tr>
<tr>
<td>[92]</td>
<td>2020</td>
<td>Ji-Min Do</td>
<td>Korea</td>
<td>In vivo</td>
<td>Five-month-old 5XFAD mice</td>
<td>TCA</td>
<td>30 mg/kg of TCA per day</td>
<td>8 weeks</td>
<td>TCA led to an improvement in AD pathology by reducing BACE1 levels through the activation of the SIRT1-PGC1α-PPARγ pathway.</td>
</tr>
<tr>
<td>[188]</td>
<td>2020</td>
<td>Azadeh Zareie</td>
<td>Iran</td>
<td>Randomized double-blind placebo-controlled trial</td>
<td>Fifty patients with migraine</td>
<td>Cinnamon</td>
<td>3 capsules/day each containing 600 mg of cinnamon</td>
<td>2 months</td>
<td>The frequency, severity and duration of migraine attacks were significantly decreased in the cinnamon group compared with the control group. Cinnamon supplementation reduced inflammation as well as frequency, severity and duration of headache in patients with migraine.</td>
</tr>
<tr>
<td>[102]</td>
<td>2019</td>
<td>Bora Gürer</td>
<td>Turkey</td>
<td>In vitro</td>
<td>Thirty-two adult male New Zealand white rabbits</td>
<td>Cinnamaldehyde</td>
<td>50 mg/kg</td>
<td>3 days</td>
<td>1. Treatment with cinnamaldehyde was considered effective in providing neuroprotection and attenuating cerebral vasospasm after subarachnoid hemorrhage in rabbits. 2. It effectively increased the cross-sectional areas of the basilar artery and reduced the arterial wall thickness. 3. Hippocampal degeneration scores were lower in the cinnamaldehyde group.</td>
</tr>
<tr>
<td>[189]</td>
<td>2017</td>
<td>Ye Cuan</td>
<td>China</td>
<td>In vivo</td>
<td>Kunming mice of both sexes (25–30 g)</td>
<td>12 cinnamic acid derivatives substituted by fluorine, chlorine, bromine, and trifluoromethyl</td>
<td>100 mg/kg, 200 mg/kg and 300 mg/kg</td>
<td>–</td>
<td>Halogen-substituted cinnamic acid derivatives (compounds 1–12) have good potential anticonvulsant activities with lower toxicity. The anticonvulsant ability is closely linked to the position of the halogen substituents, and substitutions at the 4 position of the benzene ring were beneficial for antiepileptic activities.</td>
</tr>
<tr>
<td>[114]</td>
<td>2021</td>
<td>Roghayeh Rashidi</td>
<td>Iran</td>
<td>In vitro</td>
<td>PC12 cells</td>
<td>Cinnamaldehyde</td>
<td>3.75–50 μM</td>
<td>24 and 48 h</td>
<td>TCA exerted a protective effect against METH-induced neurotoxicity through mechanisms related to anti-oxidation and anti-apoptosis.</td>
</tr>
<tr>
<td>[115]</td>
<td>2019</td>
<td>Masoumeh Emamghoreishi</td>
<td>Iran</td>
<td>In vitro</td>
<td>Neuronal SH-SY5Y cell line</td>
<td>Cinnamaldehyde</td>
<td>15, 20, 23, and 25 μM</td>
<td>–</td>
<td>NMDA and adenosine receptors suppression together with ryanodine receptors stimulation may be relevant to cinnamaldehyde neuroprotective effects against Aβ neurotoxicity. Moreover, the inhibition of GSK-3β may contribute to the cinnamaldehyde neuroprotection.</td>
</tr>
<tr>
<td>[83]</td>
<td>2020</td>
<td>Sumita Raha</td>
<td>USA</td>
<td>In vivo</td>
<td>A53T mice</td>
<td>Cinnamon</td>
<td>100 mg/kg/day</td>
<td>2 months</td>
<td>Upregulation and/or normalization of DJ-1 and Parkin in the nigra of A53T mice by treatment with cinnamom and NaI was detected.</td>
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<tr>
<td>[82]</td>
<td>2020</td>
<td>Maria Medvedeva</td>
<td>Russia</td>
<td>In vitro</td>
<td>SH-SYSY cells</td>
<td>Cinnamic acid derivatives</td>
<td>IC50 of 13, 50 and 251 mM</td>
<td>48 h</td>
<td>Compounds may act by changing the structure of primary aggregates, preventing the formation of full-length fibrils. The inhibiting effect of the ligands on aggregation of alpha-synuclein was further confirmed by monitoring aggregation via turbidimetry, susceptibility to proteolytic cleavage, changes in beta-sheet content, and scanning ionconducctance microscopy.</td>
</tr>
<tr>
<td>[87]</td>
<td>2014</td>
<td>Saurabh Khasnavis Arundhati Jana</td>
<td>USA</td>
<td>In vivo</td>
<td>MPTP mouse model of PD</td>
<td>Cinnamon powder</td>
<td>100 μL cinnamon-MC mixture</td>
<td>–</td>
<td>Cinnamon therapy decreased nignal expression of GFAP and iNOS in mice poisoned with MPTP.</td>
</tr>
<tr>
<td>[88]</td>
<td>2013</td>
<td>Soumya Koppikar</td>
<td>India</td>
<td>In vitro</td>
<td>11–17-week-old fetal brains</td>
<td>Original Ceylon cinnamon and Cinnamomum cassia</td>
<td>1,000 mg capsules</td>
<td>–</td>
<td>Cinnamonum verum powder in mice incremented the amount of NaB in brain and serum of C57/BL6 mice.</td>
</tr>
<tr>
<td>[91]</td>
<td>2019</td>
<td>Dhruv Patel</td>
<td>USA</td>
<td>In vivo</td>
<td>Mouse model of PD</td>
<td>Cinnamon</td>
<td>100 mg/kg, orally</td>
<td>once daily for 7 days</td>
<td></td>
</tr>
<tr>
<td>[65]</td>
<td>2013</td>
<td>Shih-Chieh Lee, Wen-Xin Xu</td>
<td>China</td>
<td>In vivo</td>
<td>Diabetic rats induced with streptozotocin</td>
<td>6-gingerol</td>
<td>C. osmophileum (12.5, 25, or 50 mg/(kg bw)), cinnamaldehyde mg/(kg bw), 1 g daily</td>
<td>three weeks</td>
<td>C. osmophileum in low and medium doses notably ameliorated the inflammatory parameters such as IL-1β, NO, and TNF-α, in the diabetic rat’s pancreas.</td>
</tr>
<tr>
<td>[66]</td>
<td>2007</td>
<td>Steven Blevias Soumya J Koppirkar</td>
<td>USA</td>
<td>Clinical trial</td>
<td>60 individuals</td>
<td>Cinnamon</td>
<td>–</td>
<td>3 months</td>
<td>Cinnamon has different effects based on population.</td>
</tr>
<tr>
<td>[67]</td>
<td>2010</td>
<td>Jagdish V. Kamath</td>
<td>India</td>
<td>In vitro</td>
<td>Human cervical cancer cell line (SiHa)</td>
<td>The aqueous cinnamom extract</td>
<td>–</td>
<td>–</td>
<td>Cinnamon therapy decreases the human epidermal growth factor receptor 2 (Her2) oncoprotein expression.</td>
</tr>
<tr>
<td>[68]</td>
<td>2010</td>
<td>Mehmet Unlu</td>
<td>Turkey</td>
<td>In vitro</td>
<td>21 bacteria and 4 Candida species</td>
<td>Essential oil of Cinnamomum zealanicum species</td>
<td>–</td>
<td>–</td>
<td>The antimicrobial function of the necessary oil was studied on 21 bacteria and 4 Candida species, by performing MIC methods and disc diffusion.</td>
</tr>
<tr>
<td>[70]</td>
<td>2012</td>
<td>Jeong Seok Hwa</td>
<td>Korea</td>
<td>In vivo</td>
<td>Adult male Sprague-Dawley rats</td>
<td>2-methoxycinnamaldehyde from Cinnamomum cassia</td>
<td>–</td>
<td>–</td>
<td>I/R-induced myocardial dysfunction was remarkably improved by raising the amounts of the first derivative (± dp/dt) of left ventricular pressure and reduction of infarct size by the usage of 2-MCA.</td>
</tr>
<tr>
<td>[63]</td>
<td>2003</td>
<td>Jagdish V. Kamath</td>
<td>India</td>
<td>In vitro</td>
<td>Wistar rats</td>
<td>Ethanol extract of Cinnamomum zealanicum 6-gingerol</td>
<td>Oral route at a dose of 250 mg/kg and 500 mg/kg body weight</td>
<td>–</td>
<td>Strength of wound-breaking remarkably increased in the incision wound model by administration of oral ACZ extract.</td>
</tr>
<tr>
<td>[191]</td>
<td>2011</td>
<td>Juan-Juan Han</td>
<td>China</td>
<td>In vitro</td>
<td>Human neuroblastoma SH-SYSY cells</td>
<td>6-gingerol, a pungent ingredient of ginger</td>
<td>–</td>
<td>–</td>
<td>6-gingerol demonstrates prohibitive and/or remedial possible for the management of AD through increment of antioxidant capacity.</td>
</tr>
<tr>
<td>[192]</td>
<td>2019</td>
<td>Soumya Koppikar</td>
<td>India</td>
<td>In vivo</td>
<td>Female C57BL/6 mice</td>
<td>6-gingerol</td>
<td>–</td>
<td>–</td>
<td>6-gingerol has remarkable potential as a new anti-inflammatory factor for the cure of autoimmune illnesses such as MS through straight modifier outcomes on DCs.</td>
</tr>
</tbody>
</table>
Table 1 A summary of the studies on the anti viral potential of Kadha and its active (continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>First author</th>
<th>Country</th>
<th>Type of study</th>
<th>Study model</th>
<th>Kadha component</th>
<th>Dose</th>
<th>Duration</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>[193]</td>
<td>2015</td>
<td>Abdullah Jafarzadeh</td>
<td>Iran</td>
<td>In vivo</td>
<td>C57BL/6 mice</td>
<td>Ginger extract</td>
<td>–</td>
<td>day + 3 to + 30</td>
<td>The expression of IL-17 and IL-23 reduce by ginger in EAE mice.</td>
</tr>
<tr>
<td>[194]</td>
<td>2019</td>
<td>Arjun Sapkota</td>
<td>South Korea</td>
<td>In vivo</td>
<td>Female C57BL/6 mice</td>
<td>6-shogaol, a major constituent of ginger (Zingiber officinale), and its biological metabolite, 6-paradol</td>
<td>(5 mg/kg/day)</td>
<td>–</td>
<td>Remedial impression of 6-paradol or 6-shogaol for EAE by decreasing neuroinflammatory answers was assessed.</td>
</tr>
<tr>
<td>[121]</td>
<td>2013</td>
<td>Gao-Feng Zeng</td>
<td>China</td>
<td>In vivo</td>
<td>Female Sprague-Dawley rats</td>
<td>Ginger root extract</td>
<td>–</td>
<td>–</td>
<td>Reversal of behavioral dysfunction and prevention of AD-like symptoms were done by the usage of ginger root extract in rat model.</td>
</tr>
<tr>
<td>[123]</td>
<td>2015</td>
<td>Gao-Feng Zeng</td>
<td>China</td>
<td>In vitro</td>
<td>Rat pheochromocytoma cells (PC12 cells)</td>
<td>6 gingerol</td>
<td>–</td>
<td>–</td>
<td>6 gingerol demonstrates a guarding effect on PC12 cell apoptosis caused by Aβ 1–42.</td>
</tr>
<tr>
<td>[125]</td>
<td>2016</td>
<td>Ji-Young Na</td>
<td>Republic of Korea</td>
<td>In vitro</td>
<td>Mouse hippocampal cells (HT22 line)</td>
<td>6-shogaol</td>
<td>–</td>
<td>–</td>
<td>As a CysLT1R/cathepsin B inhibitor, 6-shogaol is a potential new therapeutic agent for the treatment of various neurodegenerative disorders, such as AD.</td>
</tr>
<tr>
<td>[127]</td>
<td>2010</td>
<td>Ganiyu Oboh</td>
<td>Nigeria</td>
<td>In vivo</td>
<td>Male Wistar strain albino rats</td>
<td>Ginger</td>
<td>–</td>
<td>–</td>
<td>Ginger extract inhibits the activity of acetylcholine and prooxidants resulting from lipid peroxidation in rat brain, which can be caused by plant chemicals such as tannins, flavonoids, terpenoids and alkaloids.</td>
</tr>
<tr>
<td>[136]</td>
<td>2011</td>
<td>Jintanaporn Wattanathorn</td>
<td>Thailand</td>
<td>In vivo</td>
<td>Male Wistar rats</td>
<td>Zingiber officinale</td>
<td>–</td>
<td>–</td>
<td>Ginger rhizome has a lucrative effect to care for focal cerebral ischemia.</td>
</tr>
<tr>
<td>[137]</td>
<td>2017</td>
<td>Ji-Young Na</td>
<td>Republic of Korea</td>
<td>In vitro</td>
<td>Female Wistar rats</td>
<td>6-gingerol-rich fraction from Zingiber officinale</td>
<td>100 mg/kg</td>
<td>35 days</td>
<td>6-gingerol-rich fraction protected against cardiac papillary fibroelastoma-induced increment in oxidative stress and malondialdehyde, inflammatory myeloperoxidase, and TNF-α, NO and apoptotic caspase-3 markers.</td>
</tr>
<tr>
<td>[138]</td>
<td>2011</td>
<td>Poonam Sharma</td>
<td>India</td>
<td>In vivo</td>
<td>The adult male and female Wistar rats</td>
<td>Ginger (Zingiber officinale) 6-shogaol</td>
<td>100 mg/kg</td>
<td>14 days</td>
<td>Ginger juice improved the tissue damage caused by lindane and dichlorovos.</td>
</tr>
<tr>
<td>[195]</td>
<td>2011</td>
<td>Sehwan Shim</td>
<td>Republic of Korea</td>
<td>In vivo</td>
<td>Sprague-Dawley rats</td>
<td>Zingiber officinale 6-shogaol</td>
<td>–</td>
<td>–</td>
<td>6-shogaol can notably reduce the diversity of neuroinflammatory answers via inducing HDAC70, and this action is done by inhibiting HDAC in cortical astrocytes.</td>
</tr>
<tr>
<td>[129]</td>
<td>2013</td>
<td>Gunhyuk Park</td>
<td>Republic of Korea</td>
<td>In vitro</td>
<td>Cultured mesencephalic cells</td>
<td>6-shogaol</td>
<td>–</td>
<td>–</td>
<td>6-shogaol usage caused protective effects on DA neurons in in vitro and in vivo PD models.</td>
</tr>
<tr>
<td>[134]</td>
<td>2019</td>
<td>Fifteen Aprila Fajrin</td>
<td>Indonesia</td>
<td>In vivo</td>
<td>5–6 months old male-Balb/C mice</td>
<td>6-shogaol</td>
<td>once daily</td>
<td>21 days</td>
<td>Pain reduction in PDN is mediated by reducing the expression of NMDAR2B and TRPV1 in the spinal cord through the limited effect of ginger extract and its compounds such as 6-shogaol on pancreatic islets.</td>
</tr>
<tr>
<td>[140]</td>
<td>2012</td>
<td>Mehdi Mehdizadeh</td>
<td>Iran</td>
<td>In vivo</td>
<td>Adult male Sprague-Dawley rats</td>
<td>Ginger extract</td>
<td>100 mg/kg</td>
<td>One week</td>
<td>MDMA-induced neurotoxicity can improve by the usage of ginger.</td>
</tr>
</tbody>
</table>
Table 1 A summary of the studies on the anti viral potential of Kadha and its active (continued)

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<th>Dose</th>
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<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>[142]</td>
<td>2018</td>
<td>Ebenezer</td>
<td>Nigeria</td>
<td>In vivo</td>
<td>Male Wistar rats</td>
<td>6-gingerol-rich fraction from Zingiber officinale</td>
<td>–</td>
<td>–</td>
<td>6-gingerol-rich fraction can be a possible remedial factor in the cure of acrylonitrile-induced model of cerebral damage.</td>
</tr>
<tr>
<td>[143]</td>
<td>2017</td>
<td>M. Hamzeh</td>
<td>Iran</td>
<td>In vivo</td>
<td>Adult male Wistar rats</td>
<td>Ginger</td>
<td>–</td>
<td>–</td>
<td>Ginger administration by antioxidant acting demonstrated a significant protective effect against diazinon-induced cerebral injury.</td>
</tr>
<tr>
<td>[196]</td>
<td>2021</td>
<td>Sudheer</td>
<td>India</td>
<td>In vivo</td>
<td>C57BL/6 mice</td>
<td>Dehydrozingerone, an active ingredient of Zingiber officinale</td>
<td>–</td>
<td>–</td>
<td>Dehydrozingerone showed MAO-A inhibitor effect in silico, and the enhancement of neurotransmitter amounts in the brain in vivo was related to an antidepressant-like effect.</td>
</tr>
<tr>
<td>[145]</td>
<td>2018</td>
<td>Li-Juan Ma</td>
<td>China</td>
<td>In vivo</td>
<td>Sprague-Dawley rats</td>
<td>Vitis vinifera L.</td>
<td>–</td>
<td>–</td>
<td>One of the protective mechanisms of Vitis vinifera L. in AD mice can be increased synaptic plasticity and indirect change of cholinergic neurotransmitters.</td>
</tr>
<tr>
<td>[150]</td>
<td>2017</td>
<td>Gioacchino</td>
<td>Italy</td>
<td>In vivo</td>
<td>One-hundred eleven individuals</td>
<td>V. vinifera-based dietary supplement cognigrape</td>
<td>250 mg/day</td>
<td>12 weeks</td>
<td>12 weeks of taking a cognitive supplement is safe and can improve the profile of physiological cognition and negative psycho-neurological status in healthy elderly people.</td>
</tr>
<tr>
<td>[153]</td>
<td>2012</td>
<td>G. Marzulli</td>
<td>Italy</td>
<td>In vitro</td>
<td>Human peripheral blood mononuclear cells</td>
<td>Fermented grape marc</td>
<td>–</td>
<td>–</td>
<td>The possible application of fermented grape marc can demonstrate a creditable remedial action to relieving neuroinflammation in pathologies including AD and PD.</td>
</tr>
<tr>
<td>[154]</td>
<td>2021</td>
<td>Yu-Ni Hong</td>
<td>Korea</td>
<td>In vivo</td>
<td>C57BL/6 mice</td>
<td>Ampelopsin A isolated from Vitis vinifera L.</td>
<td>10 ng/μl, three times a week</td>
<td>a month</td>
<td>The central usage of ampelopsin A helps to enhancement neuroprotective and neurocognitive effects on behaviors and intrinsic neuronal excitability.</td>
</tr>
<tr>
<td>[155]</td>
<td>2019</td>
<td>Deepthi</td>
<td>India</td>
<td>In vivo</td>
<td>Sprague-Dawley rats</td>
<td>Vitis vinifera</td>
<td>250 mg/kg and 500 mg/kg</td>
<td>16 weeks</td>
<td>Vitis vinifera does remarkable neuroprotective functions.</td>
</tr>
<tr>
<td>[163]</td>
<td>2021</td>
<td>Chatrawee</td>
<td>Thailand</td>
<td>In vitro</td>
<td>HT22 hippocampal neuronal cells</td>
<td>Vitis Vinifera leaf extract</td>
<td>–</td>
<td>–</td>
<td>Juglone-induced oxidative stress in C. elegans and glutamate-induced oxidative toxicity in HT22 hippocampal neurons are protected by VVE.</td>
</tr>
<tr>
<td>[164]</td>
<td>2021</td>
<td>Noha</td>
<td>Egypt</td>
<td>In vivo</td>
<td>CCL-4-intoxicated rats</td>
<td>Vitis vinifera polyphenols</td>
<td>–</td>
<td>10 days</td>
<td>Vitis vinifera is being suggested as a hopeful and useful natural anti-systemic toxicity factor for aiming ROS/NF-κB signaling pathways in variant rat organs, especially pulmonary tissue.</td>
</tr>
<tr>
<td>[165]</td>
<td>2009</td>
<td>Kayoko</td>
<td>Japan</td>
<td>In vitro</td>
<td>Astrocytes in the hippocampus</td>
<td>Grape seed extract</td>
<td>–</td>
<td>–</td>
<td>Grape seed extract effect on astrocytes enhanced IL-6 generation, which works as a neuroprotective paracrine, could preserve neurons from dying by oxidative stress.</td>
</tr>
<tr>
<td>Reference</td>
<td>Year</td>
<td>First author</td>
<td>Country</td>
<td>Type of study</td>
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<tr>
<td>[160]</td>
<td>2018</td>
<td>Laura Michelli</td>
<td>Italy</td>
<td>In vitro</td>
<td>HT-29 cell line</td>
<td>Vitis vinifera</td>
<td>hydroalcoholic extract</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>[161]</td>
<td>2009</td>
<td>Jian-Gang Long</td>
<td>China</td>
<td>In vivo</td>
<td>Male Sprague-Dawley rats</td>
<td>Regrapex-R® prepared from whole grape Vitis vinifera</td>
<td>–</td>
<td>–</td>
<td>Regrapex-R® is a strong free radical detergent and a mitochondrial preserver.</td>
</tr>
<tr>
<td>[162]</td>
<td>2007</td>
<td>Hyang Sook Chun</td>
<td>Korea</td>
<td>In vitro</td>
<td>The human neuroblastoma cell line SK-N-SH</td>
<td>V. vinifera</td>
<td>–</td>
<td>–</td>
<td>V. vinifera caused neuroprotective activities against ischemic injuries in both the in vitro and in vivo brain ischemia models.</td>
</tr>
<tr>
<td>[167]</td>
<td>2012</td>
<td>Pirinçcioğlu M</td>
<td>Turkey</td>
<td>In vivo</td>
<td>Male albino rats of the Wistar strain</td>
<td>Vitis vinifera L.</td>
<td>–</td>
<td>–</td>
<td>This examination shows the protective effect of Öküzgüzü grape extract and therefore scientifically defends the application of this fruit in different traditional medicines for the remedy of tissue disorders.</td>
</tr>
<tr>
<td>[169]</td>
<td>2014</td>
<td>B.V.S. Lakshmi</td>
<td>India</td>
<td>In vivo</td>
<td>Adult male Sprague-Dawley rats</td>
<td>Extract of Vitis vinifera</td>
<td>400 mg/kg</td>
<td>45 days</td>
<td>V. vinifera extract usage in a mixture with aluminium minimized its dangers.</td>
</tr>
<tr>
<td>[170]</td>
<td>2017</td>
<td>Ibrahim H. Borai</td>
<td>Egypt</td>
<td>In vivo</td>
<td>Adult male Wistar rats</td>
<td>Vitis vinifera</td>
<td>leaves polyphenolic</td>
<td>100 mg/kg body weight/day</td>
<td>–</td>
</tr>
<tr>
<td>[172]</td>
<td>2015</td>
<td>Pattamapan Lomarat</td>
<td>Thailand</td>
<td>In vitro</td>
<td>THP-1, a promonocytic cell line</td>
<td>Black pepper essential oil</td>
<td>–</td>
<td>–</td>
<td>Black pepper oil can be useful in decreasing the risk of AD by ACH inhibitor and anti-inflammatory activity through COX-2 inhibition.</td>
</tr>
<tr>
<td>[173]</td>
<td>2009</td>
<td>Pennapa Chonpathompijunlert</td>
<td>Thailand</td>
<td>In vivo</td>
<td>Adult male Wistar rats</td>
<td>Piperine, the main alkaloid of Thai black pepper</td>
<td>5, 10 and 20 mg/kg body weight</td>
<td>2 weeks</td>
<td>Piperine at all dosage ranges used in this study remarkably ameliorated neurodegeneration in hippocampus and memory impairment.</td>
</tr>
<tr>
<td>[174]</td>
<td>2014</td>
<td>Lucian Hritcu</td>
<td>Romania</td>
<td>In vivo</td>
<td>Male Wistar rats</td>
<td>Methanolic extract of Piper nigrum fruits</td>
<td>50 and 100 mg/kg, orally</td>
<td>21 days</td>
<td>The plant extract improves Aβ (1–42)-induced spatial memory disorder by decreasing the oxidative stress in the rat hippocampus.</td>
</tr>
<tr>
<td>[176]</td>
<td>2019</td>
<td>Shi-Yao Hua</td>
<td>China</td>
<td>In vivo</td>
<td>Specific pathogen-free male Sprague-Dawley rats</td>
<td>Dichloromethane extraction from Piper nigrum L. and Piper longum L.</td>
<td>100 and 200 mg/kg</td>
<td>14 days</td>
<td>DF reduced neurological deficits and notably preserved ischemic cellular injury.</td>
</tr>
<tr>
<td>[177]</td>
<td>2013</td>
<td>Giovany Michely Pinto da Cruz</td>
<td>Brazil</td>
<td>In vivo</td>
<td>Male Swiss mice</td>
<td>Piperine</td>
<td>–</td>
<td>–</td>
<td>Piperine antiepileptic effects are the outcome of its antioxidant and anti-inflammatory activities and TNF-α decrement.</td>
</tr>
<tr>
<td>[21]</td>
<td>2021</td>
<td>Amitha CM</td>
<td>India</td>
<td>Clinical trial</td>
<td>30 individuals</td>
<td>Kanjikatala Sthanika Abhyanga, Dhanyamla Parishka and Paripathan Kadha</td>
<td>–</td>
<td>–</td>
<td>The combination of Paripathadi Kadha, Dhanyamla Parishka, and Kanjika Taila Sthanika Abhyanga is found to be impressive in the handling of diabetic peripheral neuropathy.</td>
</tr>
</tbody>
</table>

Table 1 A summary of the studies on the anti viral potential of Kadha and its active (continued)
References


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89. Khasnavis S, Pahan K. Sodium benzoate, a metabolite of cinnamon and a food additive, upregulates neuroprotective Parkinson disease protein DJ-1 in astrocytes and neurons. *J


144. Kaliora AC, Kountouri AM, Karathanos VT, Koumbi L,
Papadopoulos NG, Andrikopoulos NK. Effect of Greek raisins (Vitis vinifera L.) from different origins on gastric cancer cell growth. Nutr Cancer. 2008;60(6):792–799. Available at: http://dx.doi.org/10.1080/01635380802297576


Medicine of model Cinnamon pepper L. Mueller-Steiner 2024;9(9):54

Pandey A et al. 2015:10(1):e0116566. Available at: http://doi.org/10.1371/journal.pone.0116566


