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OVERVIEW

Protective Role of Capsaicin in Neurological Disorders: An Overview

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Abstract

Different pathological conditions that begin with slow and progressive deformations, cause irreversible affliction by producing loss of neurons and synapses. Commonly it is referred to as 'protein misfolding' diseases or proteinopathies and comprises the latest definition of neurological disorders (ND). Protein misfolding dynamics, proteasomal dysfunction, aggregation, defective degradation, oxidative stress, free radical formation, mitochondrial dysfunctions, impaired bioenergetics, DNA damage, neuronal Golgi apparatus fragmentation, axonal transport disruption, Neurotrophins (NTFs) dysfunction, neuroinflammatory or neuroimmune processes, and neurohumoral changes are the several mechanisms that embark the pathogenesis of ND. Capsaicin (8-Methyl-N-vanillyl-6-nonenamide) one of the major phenolic components in chili peppers (Capsicum) distinctively triggers the unmyelinated C-fiber and acts on Transient Receptor Potential Vanilloid-1, which is a Ca^{2+} permeable, non-selective cation channel. Several studies have shown the neuroprotective role of capsaicin against oxidative damage, behavioral impairment, with 6-hydroxydopamine (6-OHDA) induced Parkinson's disease, pentylenetetrazol-induced seizures, global cerebral ischemia, and streptozotocin-induced Alzheimer's disease. Based on these lines of evidence, capsaicin can be considered as a potential constituent to develop suitable neuro-pharmacotherapeutics for the management and treatment of ND. Furthermore, exploring newer horizons and carrying out proper clinical trials would help to bring out the promising effects of capsaicin to be recommended as a neuroprotectant.

Keywords Neurological disorder · Capsaicin · Neuroprotection · Excitotoxicity · Neurochemicals · Neuronal dysfunction/death · Oxidative stress

Introduction

Neurological disorders (ND) are defined as a combination of pathological conditions which precede slow and progressive deformations and induce irreversible dysfunction along with loss of neurons and synapses in certain areas of the nervous system. Even though the basic molecular mechanism of ND remains unclear, a combination of several factors including endogenous, genetic, and environmental elements related to aging, contribute to the generation of the disease [1, 2]. Currently, ND are classified based on genetic mechanisms and the nature of the compound that is found in the protein deposits. Accumulation of mitochondrial DNA mutations may provoke reactive oxygen species (ROS) production and cause oxidative injury in aged tissues [1]. Age-related ROS production and decreased levels of adenosine triphosphate (ATP) might be responsible for Amyloid beta (Aβ) peptides production. The Aβ peptides enter the mitochondria, prompt free radicals, decline cytochrome oxidase activity, and finally inhibit the generation of ATP molecules in Alzheimer's disease (AD) patients. In AD brains, amyloid precursor protein (APP) is transported to the outer mitochondrial membranes, which initiates the transport of nuclear cytochrome oxidase proteins to mitochondria and may contribute to reduced cytochrome oxidase activity in the AD brain. Aβ is present in the mitochondrial matrix and binds to Aβ-binding alcohol dehydrogenase in the neurons of AD patients, produces reactive oxygen species (ROS), and leads to mitochondrial dysfunction. The N-terminal portion of ApoE4 is associated with mitochondria, produces free radicals, and causes oxidative injury. Gamma secretase complex proteins (presenilins, anterior pharynx-defective, and nicastrin) were present in the mitochondria and may contribute to the production of Aβ and the generation of free radicals.

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Mutant proteins of a-synuclein, Parkin, PINK1, and DJ1 are related to mitochondria and cause mitochondrial dysfunction, and the Complex-I activity is inhibited in Parkinson's disease (PD).

Due to conformational changes in proteins, these disorders are generally referred to as 'protein misfolding' diseases or proteinopathies [2–4]. Various studies have explored the function of molecular chaperones in neurological disorders which are characterized by the aggregated protein accumulation in AD [5–7], PD [8, 9], Familial Amyotrophic lateral sclerosis (FALS) [10–13], and related poly-Q expansion diseases [14–17].

Usually, the classification of neurological disorders is based upon their major clinical features, lesion topography, or a blend of both. Therefore, ND are grouped into diseases of the basal ganglia, brain stem, cerebral cortex, cerebellum, and spinal cord, which are further categorized according to their main clinical aspects (Fig. 1). The disease, which mainly influences the cerebral cortex, may be partitioned into dementia (e.g., AD) and non-dementia. The impact on basal ganglia is significantly defined by abnormal movements and hence is categorized as the hypokinetic or hyperkinetic condition. PD comes under the hypokinetic basal ganglia disorders; depending on the amplitude and velocity falloff of voluntary movements, the person becomes completely immovable. Whereas hyperkinetic basal ganglia disorders, which are described by Huntington's disease (HD) and critical tremors. Diseases that affect the cerebellum can be categorized as dentatorubral degeneration, in which the most particular lesions appear in the dentate and red nuclei. Degeneration mostly alters the lower and upper motor neurons, the substantia nigra, and the dentate system in the Machado-Joseph disease. When the disease affects the spinal cord, it shows either as ALS or spinal muscular atrophy, in which the most severe lesions occur in the (anterior part) spinal cord, and in Friedreich ataxia, lesions are found in the (posterior part) spinal cord [18].

The common pathogenic mechanisms responsible for ND involve protein misfolding dynamics, proteasomal dysfunction, aggregation, faulty degradation, oxidative stress, ROS formation, mitochondrial dysfunctions, weakened bioenergetics, DNA injury, neuronal Golgi apparatus fragmentation, cellular or axonal transport commotion, neurofibrillary tangles (NTFs) dysfunction, neuroinflammatory or neuroimmune processes, and neurohumoral changes [19]. A summary of the mechanisms of the neurological disorder is depicted in Fig. 2. These mechanisms are interconnected in complex vicious circles which eventually lead to neuronal cell dysfunction and death [19].

Age is one of the most consonant risk factors that contribute to a significant role in the progression of ND, mainly in AD or PD [20]. It generally occurs in elderly people as they show mild cognitive or motor alterations and hence this proves that aging can be deemed as a 'benign' form of

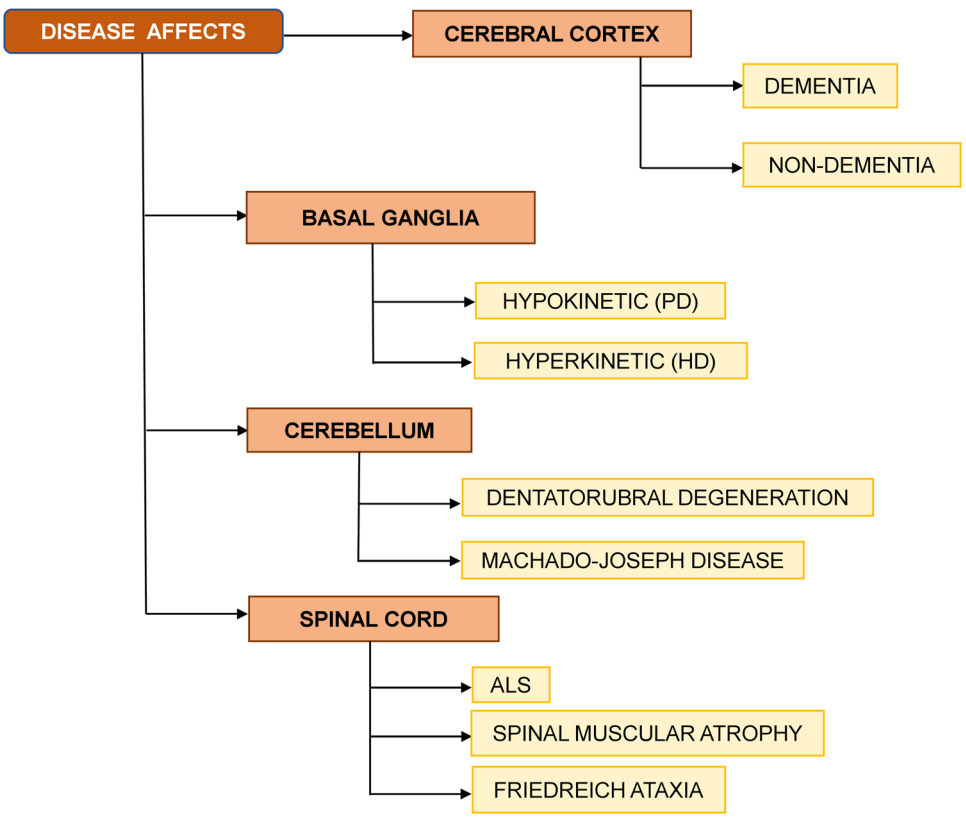

Fig. 1 Neurological disorders and the region affected in brain

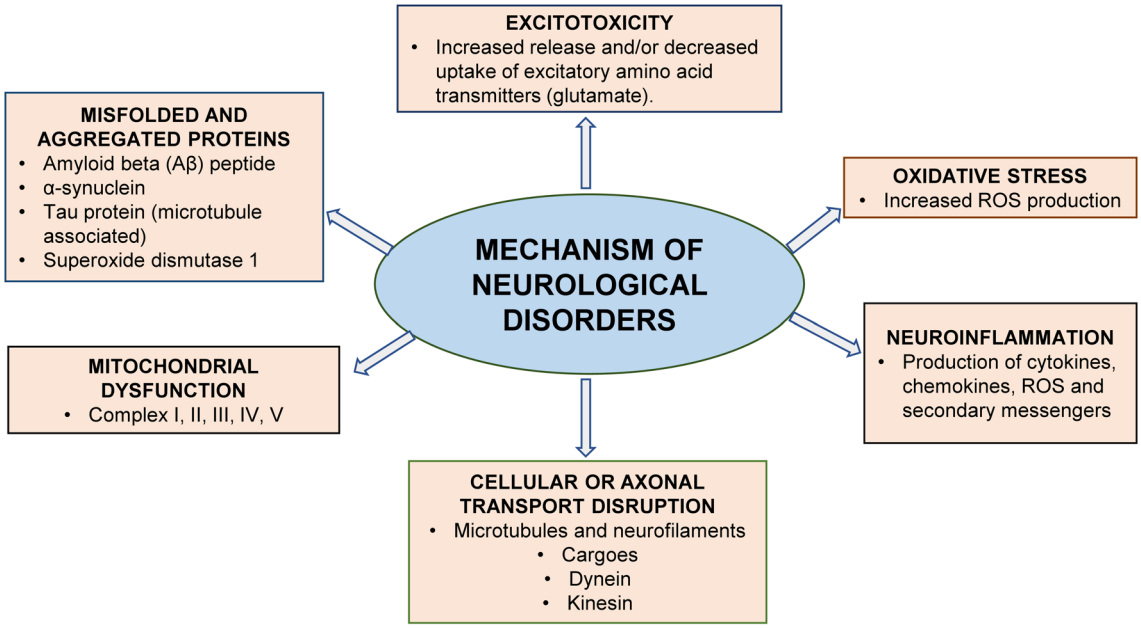

Fig. 2 Mechanism of neurological disorder and associated biomarkers

neurodegeneration. Several studies have reported that thousands of neurons are lost per day, which accounts for the cognitive fall-off and the brain size deduction which is linked with normal aging [1, 21–23]. At the same time, certain studies were reviewed by Morrison and Hof [23], and indicated that the declination in the number of neurons due to neuronal death is not particularly related to normal aging in several species including humans because other factors viz. protein misfolding dynamics, DNA injury, oxidative stress, neuroinflammatory processes and neurohumoral changes are also involved in neuronal loss [19]. This is mainly evident in the neocortex area and hippocampal subregions (entorhinal cortex and CA1) that are related to memory [23]. Other hallmarks that may be found in the brains of symptomatic individuals include the presence of Lewy bodies, senile plaques, and NFTs instead of the gradual neuronal loss [24, 25].

Conventionally, a variety of plants have been used for the cure of cognitive disorders as the phytochemicals present in these plants play a key role in keeping the major inhibitory neurotransmitters level by modifying their effect on the receptors. The phytoconstituents that exhibit a neuroprotective role and hence prove to be beneficial in neuropsychiatric and neurological disorders include fatty acids, flavonoids, phenols, saponins, and terpenes [26].

Capsaicin (8-Methyl-N-vanillyl-6-nonenamide) is one of the key phenolic components present in chili peppers (Capsicum) and is responsible for its spicy flavor. The traditional uses of capsaicin from various literature reviews include anti-bacterial [27, 28], anti-cancer [29, 30], anti-diabetic [31, 32], anti-fungal [33, 34], anti-hypertensive [35, 36], anti-inflammatory [37–39], antioxidant [40, 41], analgesic, and anti-obesity activities [42–45]. Furthermore, it can also be utilized as a treatment for cardiovascular ailments [46, 47], hepatic disorders [48, 49], and angiogenic activity [50]. A brief overview of the pharmacology of capsaicin and a summary of the important features and properties of capsaicin are summarized in Table 1. It can trigger unmyelinated C-fibre and therefore is used in the treatment of pain [51]. The multivariate functions of capsaicin include regulation of energy intake and improvement in energy expenditure, enhancement in the secretion of insulin, lessening of blood pressure, and alleviation in lipid storage and atherosclerotic lesions. Additionally, various reports suggest the anti-tumorigenic and anti-inflammatory activity of capsaicin in the allergic airway and improvement of the signs of the neurogenic bladder [52].

Indeed, capsaicin and a few capsaicin analogs have been presented in clinical research covered by several patents. Moreover, emerging data indicate its clinical significance in various clinical trials with human doses. Some of the clinical trials are summarized in Table 2.

The following equations can be used for the conversion of animal dose to human dose for determining the amount of drug reaching the brain when humans consume chili peppers [67]. Because no studies are currently available that have applied these equations to the chili pepper case, we are planning for this purpose.

$$\text{HED (mg/kg)} = \text{Animal dose (mg/kg)} \times \left(\text{Animal } K_m / \text{Human } K_m\right)$$

Table 1 Brief overview of pharmacology of capsaicin and summary of the important features and properties of capsaicin

Feature and properties of capsaicin		References
Route of administration and half-life	Topical (24 h), Oral (25 min.)	[53, 54]
Distribution	24.4% (liver, kidney, and intestine)	[55]
Metabolism	16-hydroxycapsaicin, 17-hydroxycapsaicin, and 16,17-Dihydrocapsaicin (Liver) Vanillylamine and vanillyl acid (Skin)	[56]
Elimination	Eliminated by the kidneys with a small untransformed proportion excreted in the feces and urine	[56, 57]
Mechanism of action	Capsaicin acts on transient receptor potential vanilloid 1 (TRPV1) which is a non-selective, ligand-operated cationic channel permeable to sodium and calcium ions and located in the small fibers of nociceptive neurons	[58–63]
Clinical applications	Analgesic response Protection against ethanol and indomethacin-induced gastropathy Positive response on cognitive function	[64–66]

where: HED—Human Equivalent dose, K_m—Correction factor (ratio of average body weight of species in kg to its body surface area in m^2).

As the K_m factor for each species is constant, the K_m ratio is used to simplify calculations. Hence, equation is modified as:

$$\text{HED (mg/kg)} = \text{Animal dose (mg/kg)} \times K_m \text{ ratio}$$

Like the HED estimation, the animal equivalent dose (AED) can also be calculated on the basis of body surface area by either dividing or multiplying the human dose (mg/kg) by the K_m ratio is calculated by minor modification of Eq. 3 as:

$$\text{AED (mg/kg)} = \text{Human dose (mg/kg)} \times K_m \text{ ratio}$$

Although research developments in neuroscience, ethnopharmacology, and herbal medicine have greatly advanced our understanding of the roles of potential medicinal plants and their active constituents, there is still debate in neuropharmacology, molecular targets, and their modulation by phytocon-stituents. Therefore, the present review describes the protec-tive role of capsaicin in ND and future directions of research to develop evidence-based neuropharmacotherapeutics.

Potentials of Capsaicin in Alzheimer's Disease

AD is the highly widespread source of age-related dementia, which creates an intense social and economic burden. Currently, there is no efficient approach available for the treatment of AD or even to terminate disease progression [68, 69]. Clinically, it is characterized by a gradual and steady decline in cognitive function and pathologically it is described by the presence of deposits of Aβ microtubule tau-binding protein [70]. Previous studies have indicated that AD is related to angiogenesis [50]. Neuro-inflammation is one of the pathological characteristics of AD which is associated with overexpression of cytokines (IL-1β) that can be responsible for the induction of angiogenesis [71]. Vascular endothelial growth factor (VEGF), a strong angiogenic growth factor, is also stimulated by these cytokines and overexpressed in patients with AD [72, 73]. A previous report [74] supported the evidence that capsaicin has a vigorous anti-angiogenic effect (in-vitro and in-vivo). Capsaicin restricts the VEGF effect on the proliferation of the endothelial cell, migration, and capillary-like tube creation [74].

Streptozotocin-induced AD, one of the most prominent models, was used to determine the effect of capsaicin on the reduction of cognitive impairment. Thirty male albino rats were used in where ten rats were treated with saline *via i.c.v* and intragastric routes in a single group for forty-seven days. The disease was induced in them by a single dose of STZ (3 mg/kg, *i.c.v.*) in the left hind paw of rats. A passive avoidance test was performed to evaluate the progression of the disease which was conducted post 2 weeks of administration of the drug. After noticing the retention latency of fewer than 300 secs, rats were further divided into two groups, one with (intragastric infusion) capsaicin at a dose of 10 mg/kg whereas normal saline was injected in the second group serving the positive control. On a molecular level, Aβ1-42 tau protein levels were measured by using ELISA. The study (behavioral and biochemical parameters) showed a positive effect of capsaicin compared to normal control. It is noticed that there was a suppression of angiogenesis in the chick embryo after the administration of capsaicin. Therefore, it was demonstrated that capsaicin can enhance the behavioral and biochemical changes in STZ-induced AD [75].

Stress has been a well-known risk factor for AD, which could hasten deposition of Aβ, synaptic damage, and cognitive shortfalls in several AD paradigms [76, 77]. There is evidence that showed that capsaicin can mitigate stress-induced shortfalls in synaptic plasticity (in-vitro) [78].

Table 2 Clinical trial of capsaicin with various humans doses

NCT no of the Clinical trial phase[a]	Official title	Intervention	Condition involved	Dose	Clinical trial design
NCT02346903	Chest pain perception and capsaicin sensitivity	Single group assignment	Chest Pain	Capzasin-HP 0.1%	Open-label
NCT02346916	Chest pain perception and capsaicin sensitivity in patients with acute cardiac ischemia	Single group assignment	Chest Pain	Capzasin-HP 0.1%	Open-label
NCT00655811	Ethnic differences in response to topical capsaicin: a psychophysical study on healthy subjects	Single group assignment	Healthy	0.1%, Capzasin HP	Open-label, Randomized design
NCT01260454	The Qutenza® patch for disabling treprostinil infusion site pain	Single group assignment	Pulmonary hypertension Pulmonary arterial hypertension	Qutenza (8% capsaicin)	Open-label
NCT02493257	Double-blinded randomized prospective trial of intranasal capsaicin treatment for non-allergic irritant rhinitis	Parallel assignment	Nonallergic irritant rhinitis	intranasal capsaicin (0.1 mmol/l diluted in ethanol and 0.9%) normal saline	Randomized design with quadruple masking (Participant, Care Provider, Investigator, Outcomes Assessor)
NCT01533428	A Phase III, double-blind, randomized, placebo-controlled, multicenter study evaluating the efficacy and safety of QUTENZA® in subjects with painful diabetic peripheral neuropathy	Parallel assignment	Diabetic peripheral neuropathy Pain	Capsaicin 8% transdermal delivery system	Randomized design with quadruple masking (Participant, Care Provider, Investigator, Outcomes Assessor)
NCT02700815	A randomized, controlled multicentre parallel group study to assess the efficacy and safety of multiple doses of a topically applied combination containing diclofenac 2% + capsaicin 0.075% (2 g formulation per application; 2-times daily for 5 days) compared to placebo, as well as to diclofenac 2% and capsaicin 0.075% in patients with acute back or neck pain	Parallel assignment	Acute pain	Diclofenac and capsaicin (Fixed-dose combination)	Randomized design with double masking (Participant, Investigator)
NCT02766517	LY2951742 biomarker study in patients with migraine	Single group assignment	Migraine disorders	Single topical dose of capsaicin	Open-label
NCT03102710	Neuromodulation of Placebo and Nocebo Effects	Parallel assignment	Pain	Capsaicin cream	Randomized design with triple masking (Participant, Care Provider, Investigator)
NCT02288156	Elaboration of patient-friendly treatment strategy with capsaicin nasal spray in patients with idiopathic rhinitis	Parallel assignment	Non-allergic rhinitis	Capsaicin via nasal spray (0.1 mM, 0.01 mM, 0.001 mM)	Randomized design with quadruple masking (Participant, Care Provider, Investigator, Outcomes Assessor)

Table 2 (continued)

NCT no of the Clinical trial phase[a]	Official title	Intervention	Condition involved	Dose	Clinical trial design
NCT03074162	A single center, multiple dose, open-label, randomized, three-period crossover study to determine the relative bioavailability of diclofenac in the topical gel combination product (diclofenac 2% + capsaicin 0.075%) compared to diclofenac mono gel 2% and Voltarol® 12 h emulgel 2.32% gel in at least 42 healthy males and females	Crossover assignment	Healthy	Diclofenac and capsaicin twice daily	Open-label, randomized design
NCT03528369	A Phase 2 double-blind clinical trial to examine the comparative effects on osteoarthritic knee pain of CGS-200–1 (1% capsaicin topical liquid), CGS-200–5 (5% capsaicin topical liquid), and CGS-200–0 (vehicle, no capsaicin)	Parallel assignment	Osteoarthritis, knee pain	multi-component formulation of capsaicin at levels of 1, 5 and 0%	Randomized design with quadruple masking (Participant, Care Provider, Investigator, Outcomes Assessor)

[a]*Source* https://clinicaltrials.gov/ (access during October–November, 2021)

Furthermore, a study revealed that by promoting the amy-loidogenic route, capsaicin could interfere with APP metab-olism in the brain [79]. However, the mechanism of neu-roprotection of capsaicin in neurodegeneration caused by stress is not completely understood. In this study, capsaicin substantially ameliorated cold water stress (CWS)-induced synaptic injury and tau hyperphosphorylation, which is the well-known histopathological characteristic of AD.

The study was conducted to determine the potential of capsaicin to alleviate cognitive and pathological alterations in rats that were exposed to CWS. The animals were divided into two groups (normal and treatment) where capsaicin was given (10 mg/kg) by intragastric infusion an hour before the stress. It was concluded that administration of capsaicin decreased spatial memory loss and simultaneously subdued the PP-DG long-term potentiation. The regression induced by stress in dendritic areas was diminished and memory-associated proteins (synapsin I and PSD93) were also found to be lifted. Capsaicin also hampered CWS-induced tau hyperphosphorylation by terminating the inhibition of protein phosphatase 2A. Therefore, the study demonstrated its effect by activating the TRPV1 receptor, which could dimin-ish the CWS-induced Alzheimer's-like neuropathological changes and cognitive damage, making TRPV1 an efficient target in AD treatment [80].

Evidence suggested that capsaicin had its effects on obe-sity and enhanced glucose homeostasis in type 2 diabetes. Capsaicin plays a key role in the improvement of glucose homeostasis and insulin sensitivity. It diminished body-weight, averted inflammation of adipose tissue and liver, enhanced fatty acid oxidation in high-fat diet-fed obese mice [81], and enhanced visceral fat remodeling [82]. It accelerated GLP-1 secretion [83], and TRPV1, which is expressed in islet β cells could modify insulin secretion via an enhanced Ca^{2+} influx mechanism [84]. Brain insulin signaling impairment has been involved in the development of AD [85, 86]. Restoring brain insulin signaling is a novel approach for the treatment of AD [86]. As the study showed that the inadequacy brain-damaged insulin signaling path-way was found in type 2 diabetic rat brain, which is synony-mous with previous evidence that indicated damaged brain insulin signaling pathway in type 2 diabetes individuals [87, 88]. Involvement of proteins in the insulin signaling pathway was up-regulated in capsaicin treated diabetic type 2 rats as compared to Type 2 Diabetic rats, which is also reliable with a study that showed that red peppers extract administration facilitated to restore of insulin signaling pathway and pre-vented tau hyperphosphorylation and Aβ accumulation in Type 2 diabetic rat model united with Aβ induced dementia [89]. Other studies have indicated that Ca^{2+} influx elicited PI3K/AKT signaling pathway in numerous tissues [90–92].

Xu et al. [93] explored the role of dietary capsaicin on Alzheimer's disease in type 2 diabetic rats. The rats were provided with a capsaicin-containing high-fat (HF) diet for 10 consecutive days. To observe the effects of narrowed food intake and the resultant decrease in body weight, type 2 diabetic rats were administered with an HF diet of an average dose of capsaicin. Another group consisted of non-diabetic rats that were given a standard chow diet. Blood glucose and insulin levels were kept under check apart from the phosphorylation level of tau at individual sites, glycogen synthase kinase-3β (GSK-3β), and phosphatidylinositol 3 kinase/protein kinase B (PI3K/AKT) activities analyzed by Western blotting. It was seen that the levels of phosphorylated proteins at specific sites of Ser199, Ser202, and Ser396 in the hippocampus of type 2 diabetic rats that were administered with capsaicin had a decline compared to the pair-fed diabetic rats. Similarly, non-diabetic rats with a capsaicin diet showed insignificant changes compared to non-diabetic rats with a normal chow diet. Thus, it was concluded that capsaicin can alleviate the hyperphosphorylation of tau proteins associated with Alzheimer's disease as capsaicin increased the activity of PI3K/AKT and at the same time inhibited GSK-3β in the hippocampus of diabetic rats. This supported the protective role of capsaicin in Alzheimer's disease in diabetic patients (Fig. 3).

Previous studies have found that curcumin can inhibit the formation of Aβ oligomers and fibrils, thereby suppressing new amyloid accumulation and removing deposited amyloid [94, 95]. Curcumin and capsaicin have comparable structures and physiological effects [96]. Therefore, there may have been certain chances that capsaicin produces similar effects on amyloid, and these findings suggested that a capsaicin-rich diet may lower the chances of dementia occurrence and enhance cognitive function.

On this basis, a clinical study was conducted to explore the correlation between capsaicin consumption, cognition, and blood markers associated with AD. The study was conducted with a total of 338 volunteers of age group 40 and above from various communities. Using the Food Frequency Questionnaire (FFQ), a detailed survey of dietary habits about chili consumption was gathered. Relatively, by using the Chinese model of Mini-Mental State Examination (MMSE) cognitive function was evaluated and blood amyloid levels were measured with ELISA kits. The results achieved (univariate and multivariate analysis) based on age, educational level, alcohol consumption, gender, body mass index (BMI) and comorbidities showed a positive connection of capsaicin diet with MMSE scores and serum levels. Therefore, the study concluded that diet-rich capsaicin can have a positive effect on blood biomarkers and cognitive function related to AD in middle-aged and elderly adults [97].

Aβ Overproduction plays a crucial role in AD pathogenesis [98, 99]. Subsequent cleavage of APP through β and γ secretases is responsible for the generation of Aβ. On the

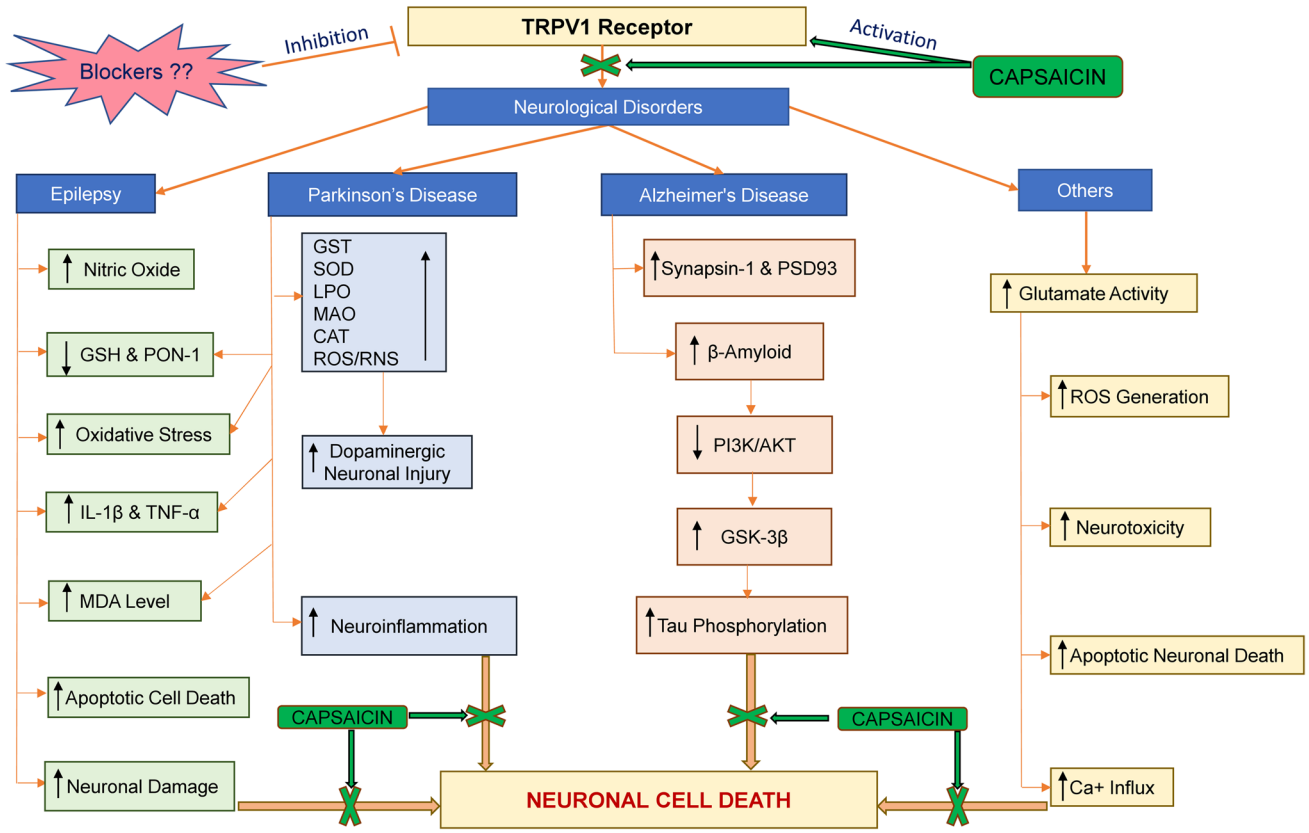

Fig. 3 Converging pathways leading to neuronal cell death in different ND through TRPV1-mediated pathways. TRPV1 activation by Capsaicin leads to modulation of biomarkers associated with neurodegeneration and beneficial effects for various neurological disorders

other hand, APP can be ripped by α-secretase, which is present in the Aβ domain, which obstructs Aβ generation. Elevated activity of α-secretase competitively diminishes β-secretase processing of the production of APP and Aβ [100]. The major α-secretase (ADAM10) is responsible for the ectodomain shedding of APP in the brain [101, 102].

Similarly, the effect of dietary capsaicin on cognition and serum Aβ levels in 40 years and overage persons was explored in APP/PS1 mice. Lines of evidence supported the role of capsaicin in Alzheimer's disease as they relocated the processing of Amyloid precursor protein (APP) to the α-cleavage side and prohibited the production of Aβ by augmenting the disintegrin and metalloproteinase 10 (ADAM10) maturation. Similarly, other Alzheimer-type pathologies including tau hyperphosphorylation, neuroinflammation, and neurodegeneration were also averted by capsaicin. Therefore, the current study demonstrated that capsaicin could act as a potential therapeutic candidate for Alzheimer's and needs further clinical trials on capsaicin to validate its efficiency as dietary supplements for the prevention and treatment of Alzheimer's disease [103].

Irrespective of the positive studies, an open cohort study was conducted by Shi et al. [104]. They tried to explore the association between chili intake and cognitive function in Chinese adults and reported a negative effect of chili on cognitive function. Home visits were conducted to assess a 3-day food record and the survey went on for 15 years. Using multivariate mixed linear regression and logistic regression, it was found that chili intake was associated with a decline in cognitive function. Including all the sociodemographic and lifestyle factors, they described self-reports of poor memory and memory decline by people with a cumulative average chili intake of more than 50 g/day [104].

Potentials of Capsaicin in Parkinson's Disease

Parkinson's disease is defined as a progressive neurodegenerative disorder which is exemplified by the loss of dopaminergic neurons in the substantia nigra (SN) pars compacta [105]. The major objective of researching this field is to uncover potential disease-modifying drugs which help slow or stop the underlying neurodegenerative progression [106]. As there are no useful neuroprotective medications or remedies have been discovered [107]. The possible mechanisms

involve neuroinflammation, protein aggregation, endoplasmic reticulum (ER) stress, mitochondrial dysfunction, and oxidative stress [108]. Earlier studies have shown that TRPV1 (capsaicin receptor), might be a therapeutic aim to improve levodopa-induced dyskinesia in an animal model of Parkinsonism [109, 110].

The study was conducted to examine the possible neuroprotective role of capsaicin in the 6-OHDA-induced Parkinson's disease paradigm in rats. The locomotor and unusual involuntary activities were found to be alleviated when capsaicin was administered intraperitoneally. Likewise, oxidative parameters such as superoxide dismutase and catalase were reduced in the brain. Western blot analysis of tyrosine hydroxylase and TRPV1 in the substantia nigra showed an improvement in the levels after the administration of capsaicin. Immunohistochemical analysis of substantia nigra further proved the potential of capsaicin against injury to dopaminergic neurons. Thus, it was observed that TRPV1 could be considered as a potential target for Parkinson's disease [111].

Increasing evidence has proven microglial activation and IL-1β upregulation in SN in PD patients [112] and LPS-lesioned SN. Other findings showed that administration of capsaicin tempered MPP^+-induced activation of microglia in the SN (in-vivo) and reduced the kainic acid-induced rise in IL-1β in the hippocampus of the rat [113], which consequently protected the neurons during the insult [114]. Various studies have shown that microglia/macrophages activation [115, 116], peripheral T lymphocytes [115], and neutrophils emigration [117] into the brain is related to the dopamine neurons death in the SN. Permeability of the Blood–Brain Barrier (BBB) was increased and blood vessel alterations were noted in the basal ganglia of PD individuals [118] and play a key role in the death of dopaminergic neurons in lipopolysaccharide (LPS) treated PD rodent models [119].

LPS-induced inflammatory model was used to determine the role of capsaicin in alleviating the detrimental effects of Parkinson's disease. Either of the capsaicin or TRPV1 antagonist (capsazepine) group was administered with LPS unilaterally into the SN. Subsequently, immunohistochemistry, BBB-permeability estimation, western blotting, and free radical levels were detected in the isolated tissues. It was observed that the levels of proinflammatory cytokines were leveled back to normal and there was a consistent conversion of pro-inflammatory mediators to anti-inflammatory ones. This was clear from the low expression levels of iNOS and IL-6 which are markers of the proinflammatory M1 population, whereas markers of the anti-inflammatory M2 population including arginase1 and CD206 were found to be higher. The oxidative stress-induced in the tissue due to LPS was lessened as the levels of free radicals especially peroxynitrite were low in the capsaicin-treated tissues. The beneficial effects of capsaicin in Parkinson's disease were further confirmed by the capsazepine (TRPV1 antagonist) which blocked the receptor. Hence, the role of TRPV1 in treating neurodegenerative diseases was concluded and it was suggested that capsaicin through its role on the M1/M2 population in the dopaminergic neurons help in the management of the disease by acting on the TRPV1 receptor [120]. Additionally, the study revealed that capsaicin plays a significant role in regulating neurotransmitter release from nigral slices [121] which produces hypokinesia with a reduction in the nigrostriatal dopaminergic neurons activity, [122, 123] and alters the effects of high-level of L-DOPA on motor action in reserpine treated Parkinsonism in rats, [124] implying that TRPV1 has a useful role in nigrostriatal dopaminergic neurons**.**

During inflammation, by producing NADPH oxidase-derived reactive oxygen species, reactive microglia can be responsible for the degeneration of dopaminergic neurons in the SN [125, 126]. Many experimental data have shown the presence of reactive microglia and enhanced ROS generation through stimulated NADPH oxidase deriving from reactive microglia in the SN of PD individuals [127, 128] and the SN of the MPTP model of mice [129–131].

The role of capsaicin in Parkinson's disease was evaluated through another model of MPTP through various studies [121–124]. They proved that capsaicin has the potential to reduce damage to the dopaminergic neurons in the striata and showed improved recovery in the behavioral deficits induced by MPTP. Reduction in TNF-α and IL-1β level, free radicals produced from activated microglia-derived NADPH oxidase conferred the neuroprotective role of capsaicin. This was further explored using drugs like capsazepine and iodoresiniferatoxin which are TRPV1 antagonists and hence the role of the TRPV1 receptor in neurodegenerative diseases was confirmed. The possible mechanism of action includes the alleviation of activated glial mediated oxidative stress and neuroinflammation which pave the way for the development of capsaicin and its analogs for the treatment of diseases including Parkinson's disease that is based on these mechanisms [132].

Another study [133] was conducted to investigate *Capsicum annuum* L extract effect to hinder the neuronal degeneration in rotenone-induced noxiousness in mice. Rotenone (1.5 mg/kg, *s.c.*) was administered to mice 3 times per week for 2 consecutive weeks. From the very first day of rotenone administration, mice also received a dose of *Capsicum* extract (56 or 224 mg/kg, *i.p*). After the administration of rotenone, a considerable increment was found in brain and liver MDA and nitric oxide levels, respectively. Reduced glutathione and PON1 activity diminished in both the brain and liver, respectively. The cholinesterase activity was hampered in the brain, while 5-lipoxygenase was found to be improved. Administration of *Capsicum* inhibited the increase in MDA

and nitric oxide levels in the brain tissue. It also restored GSH, PON-1 activity and reduced the upsurge in 5-lipoxygenase activity. Cholinesterase activity was restored to control value by the elevated dose of *Capsicum*. In the liver tissue, a significant decline was found in MDA, nitric oxide level, increased GSH level after the administration of capsicum extract. It also enhanced PON 1 activity. The neurotoxicity induced after the administration of rotenone was barred by *Capsicum* extract treatment which prevented the neuronal deterioration and reinstated GFAP positive cells. These findings suggested that *Capsicum* exerted a potential neuroprotective effect in rotenone-induced toxicity in mice models of Parkinson's disease [133].

The previous studies on the PD paradigm of flies confirmed that the flavonoid exposure shields the dopaminergic neuronal cell [134], and the other evidence suggested that the study with geraniol (natural plant products) on mice are sufficiently effective in shielding the dopaminergic neuronal cell and thereby outcomes in sustaining the apt dopamine levels [135]. The previous study with geraniol indicated that it does not vary α-synuclein expression and Lewy bodies formation, and that its antioxidant activity is liable for impeding the PD symptoms in the PD paradigm of flies [136], which led to the conclusion that capsaicin is having sufficient potency for the recovery of the weakened functions of PD flies.

A study [137] was conducted to investigate the effect of capsaicin on the Parkinson paradigm of flies that express alpha-synuclein. The capability of capsaicin to eradicate free radicals at doses (20, 40, 80, and 100 µM) was revealed in the study which lasted for 24 days. The flies were subjected to the diet for 24 days, after that the head homogenate was prepared from individual groups and utilized for the assessment of dopamine levels, lipid peroxidation, glutathione, Glutathione-S-transferase protein carbonyl content, and monoamine oxidase. The findings demonstrated that capsaicin at respective doses showed a vivid enhancement in the scavenging potential with a significant elevation in GSH and dopamine levels but at the same time reduced LPO, GST, and MAO activities when compared to the normal flies. Hence, it was concluded that capsaicin showed a protective part in relieving the symptoms of PD [137].

Potentials of Capsaicin in Seizures/Epilepsy

Epilepsy is a widespread neurological disorder that affects more than fifty million people all around the World [138]. It generally occurs due to the sudden and frequent occurrence of extreme and/or synchronous discharges in neurons present in the cerebral cortex. Possible pathogenetic mechanisms involve oxidative brain damage that causes hyperexcitability and ultimately leads to neurodegeneration [139–141]. By previous findings, the antiepileptic property of capsaicin was reported [114, 142] and the role of capsaicin was also found in the reduction of the number and amplitude of action potentials in pyramidal neurons from the somatosensory cortex, and the overflowing behavior induced by gabazine (GABA-A antagonist) in vitro through TRP-independent pathways [143].

To evaluate the neuroprotective role of capsaicin on epilepsy, neuronal damage, and oxidative insult, a study was conducted in which pentylenetetrazol (PTZ) induced status epilepticus [114, 142]. The administration of capsaicin to the rat (1 or 2 mg/kg, *i.p.*) thirty minutes before the first PTZ injection. Other groups were administered with vehicle or phenytoin (30 mg/kg, *i.p.*) alone or co-treated with capsaicin (2 mg/kg, *i.p.*). The study showed that after treatment with capsaicin, phenytoin, or capsaicin/phenytoin, MDA level was found to be reduced and GSH and PON-1 activity was found to be improved. Nitric oxide was reduced by capsaicin or capsaicin/phenytoin. The mean total seizure score was diminished by capsaicin only as contrasted with the admin-istration of phenytoin and capsaicin/ phenytoin co-treatment. The latency and threshold doses of PTZ were found to be improved after the administration of phenytoin. Capsaicin did not diminish the anticonvulsive effect of phenytoin but prevented the phenytoin-induced rise in latency time and threshold dose. Neuronal damage was diminished by pheny-toin or capsaicin (2 mg/kg, *i.p.*), but nearly completely pro-hibited after the co-administration of capsaicin/phenytoin. Thus, this study concluded, capsaicin reduced brain oxida-tive stress, seizures severity, and neuronal injury, as well as its co-treatment with phenytoin gave neuronal protection in the status epilepticus model.

Glutamate receptors over activation is a key risk factor for excitotoxicity that leads to neuronal cell death [144]. The mechanism responsible for which Kainic Acid-induced seizures cause neuronal injury is Glutamate receptor overac-tivation, which triggers extreme Ca influx into the neuronal cell and finally leads to neuronal cell death [145]. Contrast-ingly, capsaicin has a potent vanilloid receptor 1 (VR1) ago-nist, which is a non-selective ion channel [146]. Another study reported that some exogenous compounds (capsaicin) can rapidly desensitize the VR1 receptor and yield a neuro-protective action by diminishing the intracellular Ca^{+} influx by blocking VR1 activation.

Kainic acid-induced status epilepticus model was used to investigate the anti-epileptic effect of capsaicin [114]. Male ICR mice were used in the study, which were given kainic acid at a dose of 30 mg/kg intraperitoneal before the sub-cutaneous administration of capsaicin (0.33 mg/kg or 1 mg/kg). Three days after the administration of kainic acid, ani-mals were observed for anti-ictogenic, hypothermic, antioxi-dative, anti-apoptotic, and anti-inflammatory effects of cap-saicin. The detrimental effects of kainic acid on rodents were

alleviated by capsaicin. In contrast to the kainic acid-treated group, lowered seizure activity and body temperature for three hours were found in the co-treated group, whereas in the parietal cortex intense and high-frequency seizures were also found to be diminished. The reduced levels of malondialdehyde and enhanced antioxidant levels in the blood and brain of kainic-acid-induced rats proved its antioxidant potential. On a molecular level, cytokines such as IL-1β and TNF-α that were found to be elevated were lessened significantly by capsaicin (Fig. 3). In addition, apoptotic cell death due to kainic acid in the Cornu-Ammonis portion of the hippocampus was likely diminished when capsaicin was co-administered with kainic acid. This evidence confirms the antiepileptic role of capsaicin in rodents [114].

Potentials of Capsaicin on Genes involved in Neurological Disorders

Various other studies have made it evident that other factors also play a crucial role in neurodegeneration disorders *i.e.,* mitochondrial dynamics, inflammation in neurodegenerative cascades, glutamate-induced toxicity, and the VR1 receptor. Reported studies have demonstrated the protective role of capsaicin in neurological disorders by showing their inhibitory actions on it [40, 114, 132, 133, 137, 146, 147]. Capsaicin causes activation of the TRPV1 receptor, a non-selective cation channel that thereby halts the progression of neurological diseases. Altered levels of oxidative stress markers including nitric oxide, lipid peroxidation, and endogenous antioxidants that occupied a significant place in the progression of diseases such as epilepsy and Parkinson's disease are brought back to normal levels. Similarly, elevated cytokines and mediated neuroinflammation are minimized. Due to the reduced activation of TRPV1, there is less accumulation of proteins in specific parts of the brain, thus subsequently benefiting the behavioral impairment in Alzheimer's disease. Capsaicin also has a modulatory effect on signal transduction pathways (GSK-3β and PI3/AKT), glutamate-induced apoptotic neuronal cell death, and calcium influx. Hence, all these processes that ultimately lead to neuronal cell death are modulated by capsaicin and thereby prevent the initiation and progression of neurological diseases (Fig. 3).

The study involved the importance of mitochondrial dynamics in axonal degeneration induced by capsaicin was done. It was observed that in the capsaicin-treated group, there was the inclusion of reduced mitochondrial transport, axonal swellings, or the presence of axonal degeneration in sensory axons of mice. The different variations in the mitochondrial length and transport were due to elevated levels of axoplasmic calcium. With capsaicin treatment, aversion of mutant dynamin-related protein-1 resulted in enhanced mitochondrial length, maintained mitochondrial membrane potentials, and diminished axonal loss. But at the same time, sustained mitochondrial transport did not help in lessening axonal swellings in the drug-treated group. Thus, based on these findings, it was concluded that mitochondrial stationary site size notably influences the integrity of axons, and activation of cationic channels in the axon would inhibit the Ca^{2+} dependent mitochondrial fission which promotes mitochondrial function and axonal subsistence. A study showed that capsaicin can be demonstrated as a model that releases axons upon cationic overload in neurodegenerative diseases [148].

A study was carried out to find out the role of inflammation in neurodegenerative cascades by using organotypic hippocampal slice cultures, murine primary microglia, and human primary monocytes [149]. The results demonstrated that capsaicin significantly averted the release of PGE_2, 8-iso-$PGF_{2\alpha}$, and distinctly regulated the levels of TNF-α, IL-6 & IL-1β (Fig. 3).

Some genes viz. Transient receptor potential vanilloid subfamily member 1 (*TRPV1*), Tyrosine kinase epidermal growth factor receptor (*EGFR*), and Prostaglandin-endoperoxide synthase 2 (*PTGS2*) are the key targets of capsaicin [58, 150, 151]. Pharmacological blockade via capsazepine & SB366791, and genetic deficiency of TRPV1 ($TRPV1^{-/-}$) did not prevent capsaicin-mediated suppression of PGE_2 in activated microglia and organotypic hippocampal slice cultures. Inhibition of the enzyme PGE_2 was partially due to the low levels of PGE_2 synthesizing enzymes, COX-2, and mPGES-1. Altogether, it was concluded that capsaicin lessens excessive inflammatory events by targeting the PGE_2 pathway in immune cell models (in-vitro and ex-vivo) [152]. These conclusions further confirm the new ways for disease management by TRPV1. In an independent molecular study, findings from Hwang et al. [150] suggested that capsaicin might act as a cocarcinogen in TPA-induced skin carcinogenesis through EGFR-dependent mechanisms. In a study by Wang et al. [151], they have reported that capsaicin application to mouse cultured primary sensory neurons induces *PTGS2* and *COX2* upregulation.

Similarly, the VR1 role was explored in the model of global cerebral ischemia in gerbils [146]. In ischemia-induced animals, the EEG total spectral power was narrowed, a hypothermic effect was induced for 2 h, and there was a restoration in the relative frequency band distribution when capsaicin was administered over a range of 0.01, 0.025, 0.05, 0.2, and 0.6 mg/kg, 5 min after recirculation. Soon after day 1 of ischemia, the test drug was found capable of antagonizing the effect of ischemia-induced hyperlocomotion, whereas, after 3 days, it prevented the memory impairment demonstrated through a passive avoidance task. Finally, at the end of the experiment on day 7, the drug-treated animals showed a cumulative continuity of 80% in pyramidal cells in the CA1 subfield at a concentration of

0.2 mg/kg. There was also an observation of a selective VR1 antagonist capsazepine, that diminished the protective effects induced by capsaicin over a dose of 0.01 mg/kg which concluded the neuroprotective effect of capsaicin through VR1 desensitization and present as a valuable lead in the approach for interventional pharmacology [146].

The basic mechanism of neuroprotection of capsaicin was explored [147]. It was observed that 1 or 3 nmol of capsaicin when injected into the peri-infarct area of the MCAO/reperfusion model, rats showed a reduction in the volume of infarct and demonstrated progress in the scoring of neurological behavior and motor coordination function. Following the pre-treatment with capsaicin, there was a decrease in the Calcium influx after the glutamate stimulation, whereas the expression levels of GluN1 and GluN2B, NMDA receptor subunits were found to be at a lower level. The Trpv1 knockout abolished the impact of capsaicin on glutamate-mediated calcium influx and subsequent neuronal death. Thus, these findings confirmed the neuroprotective effect of capsaicin [147].

Another study [153] was carried out to observe the role of capsaicin on the release of glutamate in the hippocampus of a rat using isolated nerve terminals and brain slices. With an approximate IC50 of 11 μM, capsaicin reduced 4-aminopyridine-induced Ca^{2+} dependent glutamate release in a dose-dependent manner in synaptosomal preparations. This effect was antagonized by capsazepine, a TRPV1 antagonist that colocalized along with the vesicle marker protein synaptophysin in double immunostaining. It was observed that capsaicin mitigated the elevated calcium concentration induced by 4-aminopyridine, whereas glutamate release due to capsaicin was prevented only by Cav2.1 (P/Q-type) and Cav2.2 (N-type) channel blocker omega-conotoxin MVIIC and not by CGP37157 and dantrolene. Furthermore, the impact of capsaicin on phosphorylation of protein phosphatase calcineurin, and its inhibitor cyclosporine A-induced by 4-aminopyridine was enhanced, whereas the inhibitory effect of capsaicin on aroused glutamate release was nullified. Parallelly, there was a decrease in the frequency of miniature excitatory postsynaptic currents devoid of its effect on amplitude in slice preparations. Hence, it was concluded that capsaicin acts through TRPV1 which are localized on the hippocampal nerve terminals and result in raised calcineurin activation that consequently shows an effect on voltage-dependent Ca^{2+} channels by inhibiting the entry of calcium and further produces a downswing in triggered glutamate release [153].

The neuroprotective role of resveratrol and capsaicin in glutamate-induced neurotoxicity was considered [154]. Cerebral cortical neurons found in the fetus of ICR mouse of embryonic day 15–16 after exposure to glutamate for 15 min, were then administered with capsaicin and resveratrol for 24 h. Glutamate-treated neurons showed minimum cell viability, which was restored by capsaicin and resveratrol treatment. But the highest effect was observed in the group of neuronal cells that were treated with both the phytochemicals. This group also reduced glutamate-induced oxidative stress and the resultant apoptotic death. On a molecular level, the up-regulated levels of cytokines such as IL-1β and TNF-α, mRNA levels of cytoplasmic glutathione peroxidase, *Bcl-xL*, and copper/zinc, and manganese superoxide dismutase was brought back to a normal level with the co-treatment in Fig. 3. The results obtained demonstrated the neuroprotective effect of capsaicin and resveratrol. Moreover, the combined effects of both phytochemicals pave the way for a valuable therapeutic option for the mitigation of neurological disorders [154].

Liu et al. [155] have performed a gene expression study to identify the effect of capsaicin on genes involved in Parkinson's disease. A molecular mechanistic study was carried out by employing a 6-OHDA- induced Parkinson's disease model, Affymetrix Gene Chip Whole Transcript Expression Arrays, where 108 genes were differentially expressed after the addition of capsaicin to the cell line. It was found that capsaicin affected two genes (*Actg1 and Gsta2*) out of seven genes selected for final analysis [155]. Actin is a cytoskeletal protein that regulates the ability of cells to divide, move and maintain shape with the help of a protein called gamma (γ)-actin [156, 157] whereas Glutathione S-transferase 2 (*Gsta2*) that belongs to the glutathione S-transferase (GST) superfamily encodes enzymes which in conjugation with glutathione plays a role in detoxification of several therapeutic drugs, carcinogens and several mutagens [158]. Capsaicin treatment resulted in down-regulation of *Actg1* (actin gamma) and up-regulation of *Gsta2* (Glutathione S-transferase alpha 2) which led to increased apoptosis in the disease cell model. Therefore, it was concluded that by regulating the expression of these two genes, capsaicin could reduce apoptosis and protect cells [155].

Adverse Effects of Capsaicin

Even though capsaicin is a widely consumed constituent, there is always confusion regarding its safety in topical use and consumption due to conflicting studies. Capsaicin, a reported mutagen [159] increases cell viability and proliferation of androgen-responsive prostate cancer LNCaP cells simultaneously with increased expression of androgen receptors [160].

It was found that when Swiss albino mice were fed with 0.03% of capsaicin in a semi-synthetic diet, neoplastic changes were seen in the liver [161] along with benign polypoid adenomas in the caecum [162]. Similar conclusions were drawn from studies where chili extract was shown to produce stomach and liver tumors in BALB/c mice [163].

Another study detailed the incidence of N-methyl-N-nitrosoguanidine–induced gastric cancer in rats administered with hot chili peppers [164]. Furthermore, significant lung and cardiac metastasis were observed in adult mice who were injected with syngeneic 4T1 mammary carcinoma cells orthotopically and treated with 125 mg/kg capsaicin due to systemic denervation of sensory neurons [165].

It has been disclosed that capsaicin has the potential to induce gall bladder and gastric cancer [166] as red chili powder has been found as a major risk factor for cancer in countries like India [167]. From several statistical analyses, there has been a strong association noticed between stomach cancer and capsaicin [168]. Even jalapeno peppers have been noted to produce non-mucosal erosions or other problems [169].

Furthermore, capsaicin administered topically in the form of creams or spray produces a condition called 'human hand' which is a type of contact dermatitis [170, 171] or other adverse events including enhancement in the pain threshold in patients who suffer from musculocutaneous or neuropathic pain [42].

Conclusion

Neurological disorders such as AD, PD, and Epilepsy consist of loss of neurons and synapses in distinct parts of the nervous system and are caused by an amalgamation of endogenous, genetic, and environmental factors which make it a slow, progressive, and irreversible disease. As the phytochemicals exert a protective nature in different neu-rological diseases, there is a huge level of exploration to determine their potency to manage these diseases. Capsaicin, a significant phytochemical obtained from chili pepper, has been shown to be effective against oxidative damage, strep-tozotocin-induced Alzheimer's model, and 6-OHDA-induced Parkinson's disease. It also possesses anticonvulsant and neuroprotective effects in pentylenetetrazol-induced seizures and global cerebral ischemia in the Mongolian gerbil. Since TRPV1 plays a dominant role in the protective action of cap-saicin, it is very important to understand its significance with relevance to the different pathways that lead to neuronal cell death. Further drug development with capsaicin as a lead compound is urgently needed in order to develop analogs that are devoid of the negative consequences as discussed in the previous section. Therefore, new drugs that target the TRPV1 (capsaicin receptor) open a promising horizon of pharmacological advances in the years to come for the man-agement of neurological disorders.

Advancing analytical techniques are widely being used to enhance the knowledge about molecular characterization and structure–activity relationship of capsaicin and their analogs that are active regarding all the positive effects (protection, anti-oxidant, anticonvulsant etc.) and devoid of the negative effects (carcinogenesis, contact dermatitis, pain threshold enhancement etc.). Capsaicin serves to be an important molecule in medicine, which often gets limited by its low production yield and pungency. To rectify these, new strategies are being explored that would improve its synthesis in plants by maneuvering the supplements or growth conditions. Similarly, other methods like in vitro cell culture techniques, chemical or enzymatic methods would lead to the production of capsaicin or its analogs, which are non-pungent, are also being analyzed for their effect. Moreover, exploring newer horizons and carrying out proper clinical trials would help to bring out the promising effects of capsaicin in the field of research, as enough knowledge about capsaicin is still lacking for it to be recommended as a neuroprotectant.

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Declarations

Conflict of interest The authors confirm that this article's content has no conflict of interest.

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