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REVIEW ARTICLE

Neuroprotective Potential of Caffeic Acid Phenethyl Ester (CAPE) in CNS Disorders: Mechanistic and Therapeutic Insights

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Abstract: Neurological disorders like Alzheimer's disease (AD), Parkinson's disease (PD), stroke, amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), epilepsy, traumatic brain injury (TBI), depression, and anxiety are responsible for thousands of deaths worldwide every year. With the increase in life expectancy, there has been a rise in the prevalence of these disorders. Age is one of the major risk factors for these neurological disorders, and with the aged population set to rise to 1.25 billion by 2050, there is a growing concern to look for new therapeutic molecules to treat age-related diseases. Caffeic acid phenethyl ester (CAPE) is a molecule obtained from a number of botanical sources, such as the bark of conifer trees as well as propolis which is extracted from beehives. Though CAPE remains relatively unexplored in human trials, it possesses antioxidant, anti-inflammatory, antimitogenic, and anti-cancer activities, as shown by preclinical studies. Apart from this, it also exhibits tremendous potential for the treatment of neurological disorders through the modulation of multiple molecular pathways and attenuation of behavioural deficits. In the present article, we have reviewed the therapeutic potential of CAPE and its mechanisms in the treatment of neurological disorders.

Keywords: Alzheimer's disease, Parkinson's disease, stroke, caffeic acid phenethyl ester, neurological disorders, epilepsy.

1. INTRODUCTION

With the increase in life expectancy, there has been a surge in the prevalence of neurological diseases like Alzheimer's disease (AD), Parkinson's disease (PD), stroke, amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), epilepsy, traumatic brain injury (TBI), depression and anxiety. Aging is a major risk factor for most of these diseases [1]. Aging contributes to a progressive impairment in the mitochondrial function apart from altering the activities of antioxidant defense enzymes that lead to free radical-induced oxidative damage [2]. Also, it leads to a decrease in autophagy, causing the accumulation of misfolded protein aggregates that affect neuronal homeostasis and are associated with many neurodegenerative disorders [3].

AD is one of the most prevalent neurological disorders, which contributes to 60-80% of the total cases of dementia around the world. Vulnerability towards AD increases with age, almost doubling in frequency of occurrence every five years after the age of 65 years [4-6]. Currently, approximately 47 million people worldwide suffer from AD [7]. After AD, PD is the second most common neurological disorder, which will affect more than 10 million people worldwide by the year 2030 [8]. Of the total cases of PD, only an estimated 4% of the cases are attributed to early-onset PD (before 50 years), whereas the remaining 96% belong to the late-onset category emphasizing the importance of age as one of the risk factors for it [9]. Alternatively, age is also one of the most robust factors contributing to stroke deaths among the elderly, with the risk of incidence doubling every 10 years after the age of 55 and only a third of the cases occurring before 65 years of age [10, 11]. Also, 25-30 % of the people suffer from cognitive impairment or vascular dementia following ischemic stroke [12]. Therefore, emerging evidence suggests the role of aging in neurodegenerative disorders [13]. Moreover, some of the other neurological diseases like ALS, HD, epilepsy, TBI, depression, anxiety and neuropathic pain also bear a direct or indirect correlation with aging and senescence [14, 15]. This has caused a significant decrease in the quality of life apart from contributing to deaths around the world [16]. Despite efforts, treatment options to treat neurological diseases remain limited, and most drugs available in the market suffer from side effects, and have poor efficacy, and provide only symptomatic relief. Since these neurological diseases are mostly progressive in nature, there is a need to find drugs that can help maintain the quality of life of the patients. As the pathology of these neurological conditions involves numerous pathways, it demands drugs that can modulate multiple targets simultaneously and provide relief [17-22]. With the aged population set to rise to 1.25 billion by the year 2050,

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which will account for 22% of the total world population, there is an emerging need to find new therapeutic molecules to prevent or treat these diseases [23, 24]. There are several natural products that are known to be effective against neurological disorders like flavonoids, astragalosides, and polyphenols [25-27].

Caffeic acid phenethyl ester (CAPE) is a naturally occurring hydrophobic, polyphenolic compound obtained from propolis which is extracted from the bark of conifer trees and from honeybee hives [28]. Apart from this, CAPE is also a constituent of the resinous exudates from the buds and leaves of various species of *Populus*. It has been found in the exudates of *P. nigra, P. ungustifolia, P. ciliata, P. deltoides, P. tristis, P. cathayana, P. szechuanica, P. koreana, P. maxomowiczii, P. suaveolens, P. simonii, P. yunnanensis, P. violascens, P. canadensis*. Also, it is found in *Citrullus colosynthis* which is a medicinal plant from Arab countries. Recently, it was also shown to be a part of the twigs of *Cinnamomum cassia* [29]. CAPE has been shown to exhibit antioxidant, anti-inflammatory, antimitogenic, and anticarcinogenic activity [30, 31]. CAPE has also been investigated in clinical trials for its inhibitory activity on matrix metalloproteinases (MMPs) [32]. Apart from this, various preclinical studies have demonstrated the neuroprotective effects of CAPE in different neurological disorders like AD, PD, stroke, neuropathic pain, ALS, HD, epilepsy, TBI, depression, and anxiety [17-19, 22, 33-36]. The present review highlights the pharmacotherapeutic targets and mechanistic contributions of CAPE in the treatment of these neurological disorders, which are closely linked to the process of senescence and aging.

2. THERAPEUTIC POTENTIAL OF CAPE IN ALZHEIMER'S DISEASE AND COGNITIVE IMPAIRMENTS

AD is the most common neurodegenerative condition, which primarily consists of symptoms of memory loss, difficulty in completing familiar tasks, poor judgment, and confusion with time [37]. There is a combination of age, genetic and environmental factors that predispose individuals towards the onset and prognosis of AD. Hence, a number of transgenic and toxin models are in place for the understanding of AD pathophysiology and screening of the pharmacological agents for its treatment [38-40]. A study by Jiang Qian reported that oxidative stress is a major factor involved in AD pathogenesis primarily through its damaging effects on deoxyribose nucleic acid (DNA), proteins, lipids, and other macromolecules [41]. Another study showed that neurotoxicity of the amyloid-beta 42 ($A\beta_{42}$) was associated with oxidative stress [42]. Also, it has been observed that $A\beta_{42}$ accumulation leads to an increase in the NOX2 expression in microglia, further enhancing the production of superoxide ions and leading to AD through its deleterious effects on mitochondrial function apart from contributing to nucleic acid cleavage and proteolysis [42, 43]. Increased oxidative stress along with inflammation and apoptosis are some of the converging pathways which have been extensively studied for their involvement in AD using these model systems. CAPE offers the advantage of having multiple mechanisms of action which could offer therapeutic benefits in AD by targeting these pathways (Fig. **1**). There are several studies clearly indicating the beneficial effects of CAPE therapy in the AD models. These have been listed in Table **1**.

A study involving the stereotaxic intracerebroventricular injection of $A\beta_{1-42}$ oligomers induced cognitive impairment revealed that CAPE treatment (10 mg/kg, q. d. for 10 days) led to a significant improvement in memory deficits along with the reduction of oxidative stress, inflammation, and apoptosis. Besides, it also exhibited its neuroprotective effects by the modulation of glycogen synthase kinase 3 beta (GSK-3β) activity in the hippocampus accompanied with an increased expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1) [44]. This mechanism of action of CAPE and its derivatives was further confirmed in another study by *Wan et al.,* where FA-97, a CAPE analog attenuated the scopolamine-induced cognitive impairments by its positive modulatory action on Nrf2/HO-1 signaling pathways [45]. Moreover, CAPE and its 5-nitro-a-cyanocarboxamide derivatives also inhibited tau aggregation when tested using the thioflavin T-based fluorescence method [36]. These reports validated the effect of CAPE on the two major pathological hallmarks of AD *viz*. beta-amyloid plaques and aggregated tau proteins.

Streptozotocin-induced memory loss is another model, which has been extensively used in the literature for the study of progressive cognitive decline in our lab and by several other groups [39, 46-49]. When tested against the STZ-induced cognitive impairment, CAPE treatment in the doses of 6 mg/kg for 28 days led to an improvement in spatial memory and reduction in the malondialdehyde (MDA), tumour necrosis factor-alpha (TNF-α), nuclear factor-kappa B (NFκB) levels. Furthermore, an increased level of endothelial nitric oxide synthase (eNOS) mediated by the upregulation of phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signalling was also reported in the same study [50]. Similar results were obtained in another study involving STZ model where CAPE administration improved the neurobehavioral performance of the animals in the Morris Water maze test. Additionally, an increase in the expression of endogenous antioxidants like glutathione (GSH) and downregulation of Thiobarbituric acid reactive substances (TBARS) and TNF-α levels was also reported [51]. To further confirm the detailed neuroprotective mechanisms of CAPE, an *in vitro* analysis was conducted using acrolein for the induction of AD in the HT22 mouse hippocampal cell lines. At the concentration of 30 μM, CAPE rescued the neuronal death and showed a significant decrease in the reactive oxygen species levels (ROS) [52]. Moreover, positive modulation of mitogen-activated protein kinase (MAPKs) and Akt/GSK-3β signalling pathways was also seen in this study which suggested that the latter could be one of the primary targets for the beneficial effects of CAPE in AD-related neurodegeneration [53].

Other mechanisms which may contribute to its beneficial effect include the inhibition of acetylcholinesterase activity, which has also been reported by several authors [45, 54]. Additionally, neuroprotective effects of CAPE extend beyond the classical models of AD, as it has also been found to reduce cellular damage even in the brain of the aged rats

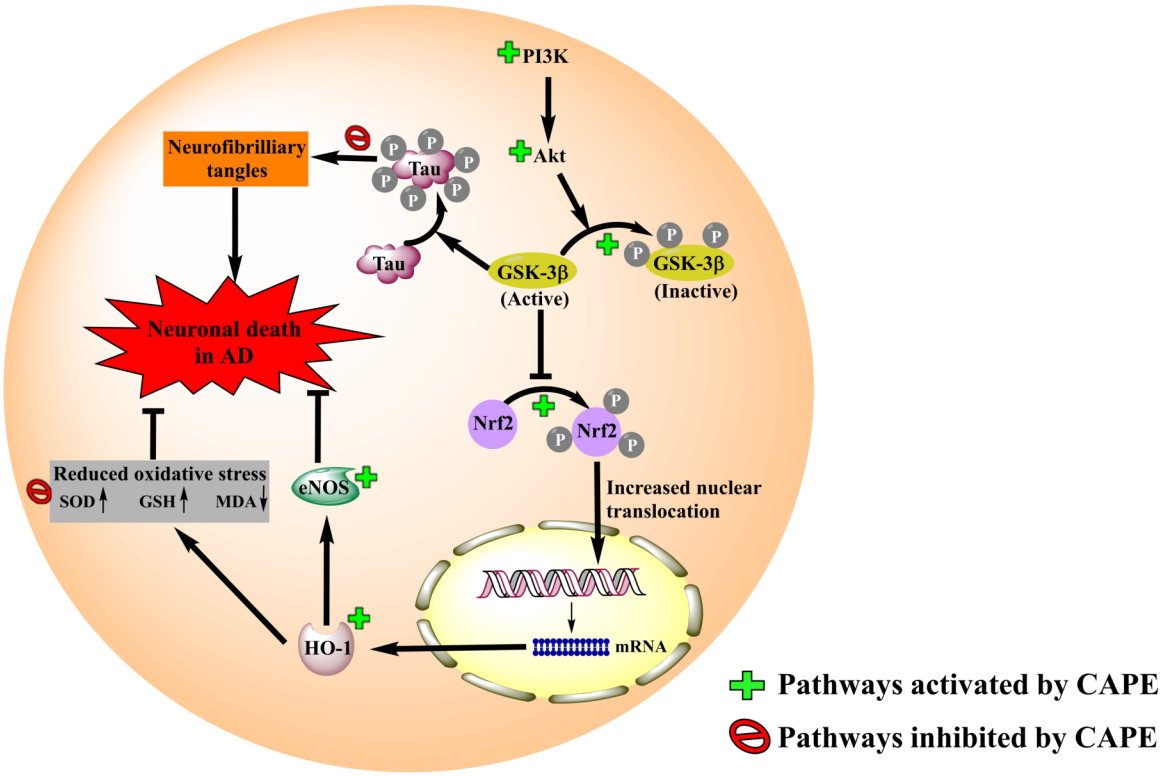

Fig. (1). Schematic diagram to represent molecular pathways, elucidating the beneficial effects of CAPE in AD. CAPE is known to accord benefits in the pathophysiology of AD through diverse mechanisms. It directly activates the PI3/Akt signaling pathway as well as leads to increased phosphorylation of GSK-3β to yield it inactive. It results in reduced hyperphosphorylation of Tau protein besides causing increased activation and nuclear translocation of Nrf2. Furthermore, this Nrf2 regulates the translation of several proteins like HO-1, which helps in the restoration of oxidative stress imbalance and activation of eNOS. These events in totality help to prevent neuronal death in AD. AD: Alzheimer's disease, PI3K: Phosphoinositide 3-kinase, Akt: Protein kinase B, GSK3β: Glycogen synthase kinase 3β, Nrf-2: Nuclear factor erythroid 2-related factor 2, eNOS: Endothelial nitric oxide synthase, SOD: Superoxide dismutase, GSH: Glutathione, MDA: Malondialdehyde, HO: Heme oxygenase. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1. Studies of neuroprotective effects of CAPE in Alzheimer's disease.

S. No.	CAPE (Dose and Duration)	AD Model	Outcomes	Refs.
1	Post-treatment with 10 mg/kg, ip for 10 days	$A\beta_{1-42}$ oligomers injection to the C57Bl/6 mice	• Improvement in spatial memory accompanied with reduction in oxidative stress, apoptosis and inflammation • Accorded neuroprotection by the modulation of Nrf2/ HO-1 pathway *via* alteration of GSK-3β signalling	[44]
2	Post-treatment with 6 mg/kg, ip for 28 days	STZ administration to the Wistar rats	• Improvement in the spatial memory • Accorded neuroprotection through increased PI3K activity and eNOS mediated nitric oxide synthesis	[50]
3	Post-treatment with 3 and 6 mg/kg, ip for 28 days	STZ administration to the Wistar rats	• Reduction of oxidative stress and levels of inflammatory markers • Reduction in the cognitive deficits	[51]
4	Pre-treatment for 30 min with 30 μM	Acroline treatment to the HT22 murine hippocampal neuronal cells	• Accorded neuroprotection by the modulation of MAPKs and Akt/GSK3β signaling pathways • Reduction in oxidative stress and restoration of α-secretase levels	[53]
5	15 mg/kg, ip for 95 days	Old Sprague Dawley rats (1.5 years)	• Reduction of oxidative stress and apoptosis	[55]

Abbreviations: STZ: Streptozotocin: eNOS: Endothelial nitric oxide synthase, PI3K: Phosphoinositide 3-kinase, Aβ- Amyloid β, Nrf-2: Nuclear factor erythroid 2-related factor 2, HO-1: Heme oxygenase-1, GSK-3β: Glycogen synthase kinase 3 beta, MAPK: Mitogen-activated protein kinase, Akt: Protein kinase B.

[55]. Though studies illustrate that the evidence for CAPE's neuroprotection in AD and cognitive impairment is rather convincing, more detailed investigations using electrophysiology and imaging studies are still warranted for its claim as a drug candidate in clinical trials.

3. THERAPEUTIC POTENTIAL OF CAPE IN PARKINSON'S DISEASE

PD is a neurodegenerative condition characterized by the loss of dopaminergic neurons in the nigrostriatal pathway. It is associated with the typical symptoms of motor dysfunction, such as tremors, rigidity, akinesia, and bradykinesia [56]. There are several pathways involved in the pathophysiology of PD, which tend to converge on oxidative stress and inflammation [57, 58]. These pathways have been studied in detail by our group and several others, but with little translational success [59, 60]. Also, Levodopa which is the first-line treatment for PD is associated with multiple side effects [61]. Hence, there is a need to look for new strategies that could be used for PD treatment. A few other treatments like chronic spinal cord stimulation, metformin, and astragaloside supplementation have shown some protective effects [61]. Because of the antioxidant and anti-inflammatory properties of CAPE, it could be a promising therapeutic option for the management of PD (Fig. **2**). There are several *in vitro* and *in vivo* studies, indicating the beneficial effects of CAPE in PD models (Table **2**).

CAPE exhibited a neuroprotective effect in the 6-hydroxydopamine (6-OHDA) treated primary cultures of cerebellar granule neurons and rostral mesencephalic neurons isolated from Sprague–Dawley (SD) rat pups. It was observed to increase cell viability and reduce the generation of free radical species, such as superoxides and peroxynitrites at a concentration of 10 μM in these *in vitro* studies [62, 63]. Additionally, it also accorded neuroprotection by the inhibition of caspase 3 expression and cytochrome c (Cyt c) release from the mitochondria [63]. Similar results were obtained in the *in vivo* rodent studies, which involved CAPE treatment after the stereotaxic administration of 6-OHDA. These reports further demonstrated that CAPE exhibited a protective effect on mitochondrial function by the inhibition of the mitochondrial permeability transition pore. This, in turn, led to reduced mitochondrial swelling and prevented the release of Cyt c and apoptosis-inducing factor (APAF) into the cytoplasm [36, 64, 65]. Also, a study demonstrated that CAPE activates 5' adenosine monophosphate-activated protein kinase-Silent information regulator-1 (AMPK-SIRT-1) signalling pathway, which in turn increases the expression of Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) in the neurons. As PGC-1α is a mas-

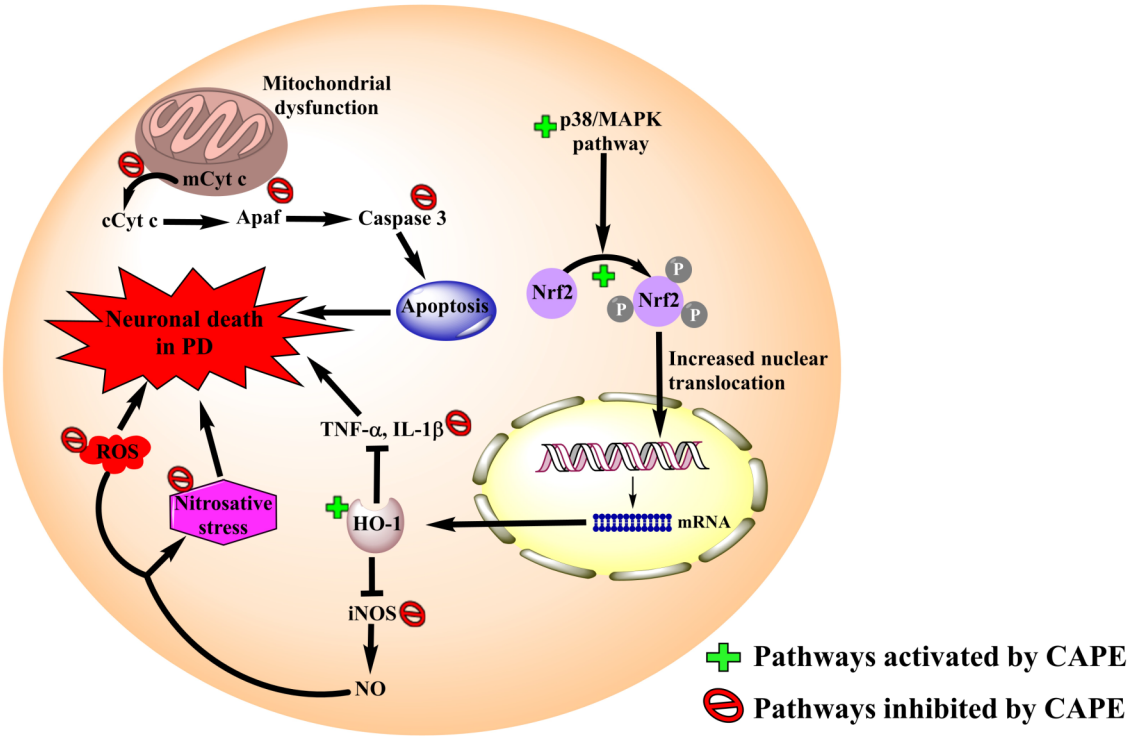

Fig. (2). Schematic diagram to represent molecular pathways, elucidating the beneficial effects of CAPE in PD. CAPE is known to modulate several intracellular targets, which are affected in PD. It directly increases the p38/MAPK signaling, which causes the increased activation and nuclear translocation of Nrf2. Furthermore, this Nrf2 regulates the translation of several proteins like HO-1, which helps in the restoration of oxidative and nitrosative stress imbalance, and inhibition of iNOS. It also leads to the inhibition of inflammatory mediators like TNF-α and IL-1β. CAPE also prevents the proapoptotic signaling by preventing the cytoplasmic release of cytochrome C, which reduces expression of APAF and caspase 3. These events in totality help to prevent neuronal death in PD. PD: Parkinson's disease, Cyt c: Cytochrome c, APAF: Apoptotic protease activating factor, ROS: Reactive oxygen species, MAPK: Mitogen-activated protein kinase, Nrf2: Nuclear factor erythroid 2-related factor 2, TNF-α: Tumour necrosis factor-alpha, IL: Interleukin, HO: Heme oxygenase, iNOS: Inducible nitric oxide synthase, NO: Nitric oxide. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 2. Studies of neuroprotective effects of CAPE in Parkinson's disease.

S. No.	CAPE (Dose and Duration)	PD Model	Outcomes	Refs.
1	2.5, 5 and 10 mg/kg, orally on alternate days for 18 days	Rotenone administration to the Swiss male albino mice	• Reduction of motor deficits, microglial activation, and inflammation • Improved TH immunostaining in the substantia nigra	[1]
2	Pre-treatment with 0.01, 0.1, 1, 10 μmol/L for 30 min	Rotenone treatment to the PC12 cells	• Reduction in CysLT production and cell viability	[1, 70]
3	Treatment with 200 μL at 10 μmol/kg, ip for 5 days	6-OHDA administration to the Wistar rats	• Scavenging of ROS and chelation of metal ions • Inhibition of Mitochondrial permeability transition pore to prevent the cytoplasmic release of caspases	[36]
4	Pre-treatment with 10 μM for 2 h before 6-OHDA exposure	6-OHDA treatment to the primary cultures of cerebellar granule neurons and rostral mesencephalic neurons	• Reduced production of oxidative free radicals and increased cell viability	[62]
5	10 μM for 4 hours following the 6-OHDA exposure	6-OHDA treatment to the primary cultures of cerebellar granule neurons	• Inhibition of 6-OHDA mediated caspase-3 activation and Ca^{2+}-induced Cyt c release	[63]
6	Co-treatment with LPS with 10 μg/mL *in vitro* and 30 mg/kg, for 72 hours for 14 days	LPS treatment to the organotypic midbrain slice cultures/LPS and 6-OHDA administration to C57BL6 mice	• Accorded neuroprotection by the increased expression of HO-1 and BDNF • Reduced microglial activation and improvement in TH levels	[65]
7	Pre-treatment with 20 μM *in vitro* and 2, 5, and 10 mg/kg, orally for 2 hours/ for 7 days	MPP^+/MPTP treatment to primary cultures of cerebellar granule neurons and rostral mesencephalic neurons and in C57BL/6 mice	• Prevented the loss of striatal dopamine and TH levels • Prevented the release of Cyt c and AIF release from the mitochondria	[68]
8	Post-treatment with 10 μM for 24 h after MPP^+ treatment	MPP^+ treatment to the PC12 cells	• Increased axonal growth and synaptogenesis • Reduced cell death induced by MPP^+	[71]
9	Treatment with 10 μmol/kg, ip for 21 days	Chlorpyrifosethyl-induced Parkinson in Swiss mice	• Improvement of motor deficits • Restoration of the paraoxonase activity and increase in the antioxidant levels	[72]

Abbreviations: 6-OHDA: 6-hydroxydopamine, Cyt c: Cytochrome c, CysLT: Cysteinyl leukotrienes, ROS: Reactive oxygen species, MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, TH: Tyrosine hydroxylase, AIF: Apoptosis inducing factor, HO-1: Heme oxygenase-1, BDNF: Brain-derived neurotrophic factor.

ter regulator of mitochondrial biogenesis, CAPE could exert a positive modulatory effect on neurons in PD *via* its action on mitochondrial biogenesis [66, 67].

Besides these studies, the beneficial effect of CAPE as an antioxidant and its ability to restore tyrosine hydroxylase (TH) levels has been undisputedly testified by several authors in different PD models [1, 65, 68, 69]. Moreover, it has also been reported to exert an anti-inflammatory effect by the attenuation of 5-lipoxygenase (5-LOX) expression, inhibition of cysteinyl leukotrienes (CysLT) production, and reduction of microglial activation in both the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and rotenone models of PD [1, 69, 70]. In a study carried out using MPP^+ model in the PC12 cells, the potential of CAPE in synaptogenesis and axon growth was also evaluated. It was observed that CAPE treatment led to an increased expression of proteins, such as growth-associated protein 43 (GAP-43), synaptophysin, and synapsin I, all of which play a critical role in the increased neurite outgrowth and synapse formation. This further suggested the positive modulatory effects of CAPE on synaptic plasticity, which is otherwise disrupted in neurodegenerative diseases like PD [71].

There are reports investigating the effects of CAPE treatment on the neurobehavioral parameters in the PD models. In the Chlorpyrifos-induced parkinsonian model in mice, CAPE administration led to an improvement in motor activity of mice when tested using the pole test and the Ludolph movement analysis [72]. Similar results were observed in the rotenone model, where CAPE treated animals showed improved performance in the open field test, rotarod test, and pole test [1]. These positive modulatory changes exerted at the behavioural level confirmed the potential of CAPE for the correction of motor deficits, which form the characteristic debilitating symptoms of PD. In addition, its effects on

the modulation of inflammation by targeting extraneuronal cells, including microglia, make it an exciting prospect for cell-specific processes contributing towards PD. However, more studies are warranted before it could be taken up for the clinical trials as the detailed molecular mechanisms associated with the beneficial effects of CAPE still need elucidation.

4. THERAPEUTIC POTENTIAL OF CAPE IN STROKE

Stroke is a neurological condition that occurs due to sudden reduction or loss of blood supply to an area of the brain leading to the death of neurons and, ultimately, loss of neurological functions. It is the third leading cause of death in the developed countries and may cause deficits, including paralysis, problems with memory, language, and movement [10, 73]. Depending on the underlying pathology, stroke can be classified as either ischaemic stroke caused due to lack of blood flow or haemorrhagic stroke resulting from bleeding [10, 74].

Of the many mechanisms underlying the disease, oxidative stress and inflammation remain as the most significant contributors to the neurological damage observed in stroke patients. Various triggering factors for the onset of a stroke episode mainly include underlying disease conditions like diabetes and cardiovascular disorders [75]. These metabolic diseases are associated with the increased production of ROS through the induction of enzymes like Xanthine Oxidase (XO) and nicotinamide adenine dinucleotide phosphate hydrogen (NADPH)-oxidases. An increase in the production of ROS leads to the inactivation of nitric oxide (NO), which otherwise prevents vascular inflammation through its anti-aggregatory and anti-cell adhesive effects [76]. Apart from this, ROS also leads to inflammation through the activation of the NF-κB cascade and several other molecular pathways [77]. Different studies have demonstrated the effectiveness of CAPE in stroke models through its anti-inflammatory and antioxidant properties. They are summarised in Table **3**.

A study carried out in rabbits using the middle cerebral artery occlusion (MCA) model showed that the post-treatment with CAPE for 7 days after the ischemic injury led to an improvement in oxidative stress parameters with a reduction in the MDA, XO, and catalase (CAT) levels. Moreover, it was accompanied by the increase in the levels of GSH, and NO, leading to vasodilation and enhanced cerebral blood flow [78]. On similar lines, prophylactic treatment with CAPE has also been shown to offer neuroprotection by an increase in the NO production in the rat MCA/bilateral common carotid artery occlusion (CCA) model [79]. However, the involvement of NO is rather controversial, and its reduced levels have also been reported by *Irmak et al.* in the CCA model of ischemia. This study confirmed the beneficial effects of CAPE on the reduction of oxidative stress through a decrease in the levels of MDA, XO, superoxide dismutase (SOD), and adenosine deaminase (ADA) [80, 81]. Furthermore, another study showed that CAPE administration at a dose of 2 mg/kg led to a decrease in the expression of proinflammatory mediators like TNF-α, Interleukin-1β (IL-1β), inducible nitric oxide synthase, NF- ΚB and Caspase 3 [52]. It also decreased the expression of intercellular adhesion molecule 1 (ICAM-1) and E–selectin, both of which are adhesion molecules involved in cell signalling and inflammation. Besides, it also reduced the levels of ectodysplasin (ED)-1, a marker of activated macrophage/microglia, and increased the expression of anti-apoptotic protein B-cell lymphoma extra-large (Bcl-xL) [35]. In line with the same, another study that assessed the effects of CAPE on neonatal hypoxic injury (HI) showed that its administration at a dose of 40 mg/kg prevented caspase 3 activation and significantly reduced the expression of inducible nitric oxide synthase [52] and caspase 1 to prevent the neuronal death. Beneficial effects of CAPE at doses of 20, 100, and 200 μmol were observed in cerebellar granule neuronal cell cultures exposed to calcium chloride ($CaCl_2$) at a concentration of 100 μM, wherein CAPE treatment prevented Ca^{2+}-mediated Cyt c release, which is a contributor towards apoptosis and excitotoxicity mediated neuronal damage [82]. Alternatively, a study also assessed its effects on the S-100 calcium-binding protein B (S-100B), a biochemical marker for stroke whose levels are highly increased in the cerebrospinal fluid (CSF) and serum of the stroke patients [83, 84]. CAPE, when administered at a dose of 10 μmol/kg/day on seven consecutive days, following ischaemic injury, showed a decrease in the level of S-100B protein [84]. In addition to its effects on oxidative stress and inflammation, it also prevented structural changes triggered by glial cell activation and vacuolization following the ischemic event [33]. Apart from these, CAPE also exhibited positive modulatory effects in ischemia-reperfusion-induced brain injury. An *in vitro* study carried out in the isolated brain mitochondria showed a decrease in the state 4 respiration, respiratory control ratio (RCR), and adenosine diphosphate/oxygen (ADP/O) ratio following re-oxygenation. It was further associated with a decrease in oxidative phosphorylation efficiency due to associated membrane damage. CAPE effectively reduced state 4 respiration besides increasing the levels of state 3 respiration, respiratory control ratio (RCR) and adenosine diphosphate/oxygen (ADP/O) ratio. A dose-dependent increase in mitochondrial protection was observed through its inhibitory effect on the decreasing membrane fluidity, lipid peroxidation, release of cardiolipin, and Cyt c [69, 85]. Similar investigations in a rat model of ischemia/reperfusion (I/R) further confirmed the beneficial effects of CAPE treatment through a decrease in the levels of MDA and elevation in GSH and NO content. Moreover, it also decreased the levels of phosphodiesterase (PDE)-4 mRNA expression, an isoenzyme in leukocytes that is involved in modulating inflammatory cell activation [86]. In addition to its effects in ischaemic stroke, one study has also elucidated the effectiveness of CAPE in treating haemorrhagic stroke. When administered at a dose of 10 μmol/kg/day for 5 consecutive days, it reduced the vasoconstriction in the basilar artery and inhibited the production of ROS [80]. These studies provide cumulative evidence that CAPE may prove to be a useful pharmacological intervention for the treatment of stroke (Fig. **3**). Hence, it can be taken up for detailed investigations on the downstream signalling pathways, which could provide new information regarding the pathophysiology of stroke and increase the chances of translational success of CAPE as a potential drug candidate. Furthermore, the beneficial effects of CAPE in improving cognition could also be utilized for complications associated with stroke, such as vascular dementia.

Table 3. Studies of neuroprotective effects of CAPE in stroke.

S. No.	CAPE (Dose and Duration)	Stroke Model	Outcomes	Refs.
1	50 µg/kg, ip, 30 mins before ischemia	MCA in Rat	• Prevention of structural changes like neuroglial cell activation and vacuolization	[33]
2	Single-dose at or after reperfusion 2 mg/kg, iv	MCA in Rat	• Reduction in oxidative stress and inflammation • Decreased expression of ICAM-1, E-selectin and ED1	[35]
3	0.1, 1 and 10 µg/kg, iv given prophylactically, 15 mins before surgery	MCA and CCA in Rat	• Increased NO levels	[79]
4	10 µmol/kg/day, ip given for 5 consecutive days, twice a day following SAH	Experimental SAH in rats	• Attenuation of vasoconstriction in basilar artery • Decreased levels of MDA and increased levels of GSH and NO	[80]
5	10 µmol/kg, ip given, 10 mins after injury	CCA in Rat	• A decrease in MDA, ADA, XO, and NO levels	[81]
6	40 mg/kg/day *in vivo*, ip given, before and after HI 20, 100, 200 µM *in vitro*	Carotid artery ligation in rat pups	• Inhibition of caspase 3 activation, iNOS expression • Direct inhibition of Ca^{2+}-induced Cyt c release from isolated brain mitochondria	[82]
7	10 µmol/kg/day, ip for 7 days after the ischemic injury	MCA in Rabbit	• A decrease in S-100B levels	[84]
8	10^{-5}, 10^{-4}, 10^{-3}, 10^{-2}, 10^{-1}, 1, 10 µM given before anoxia and just after reoxygenation	Anoxia-reoxygenation in isolated brain mitochondria	• Decreased state 4 and increased state 3 respiration, RCR, and ADP/O ratio • Protection of mitochondria by inhibiting decrease in membrane fluidity, oxidative stress, and release of CL and Cyt c	[85]
9	15 µmol/kg/day, ip given 1 hr before occlusion and 12 hrs following reperfusion	I/R model in rats	• Decreased levels of MDA and increased levels of GSH and NO • Decreased PDE4 mRNA expression	[86]

Abbreviations: MCA: Middle cerebral artery occlusion, CCA: Bilateral common carotid artery occlusion, MDA: Malondialdehyde, XO: Xanthine Oxidase, GSH: Glutathione, NO: Nitric oxide, ADA: Adenosine Deaminase, ICAM-1: Intercellular Adhesion Molecule, ED1: Ectodysplasin, iNOS: Inducible nitric oxide synthase, Cyt c: Cytochrome c, S100-B: S 100 calcium-binding protein B, RCR: Respiratory control ratio, ADP/O: Adenosine diphosphate/oxygen, CL: Cardiolipin, I/R: Ischaemia reperfusion, PDE4: Phosphodiesterase-4, SAH: Subarachnoid haemorrhage.

5. THERAPEUTIC POTENTIAL OF CAPE IN OTHER NEUROLOGICAL DISORDERS

CAPE has also been studied in the context of several other neurological disorders, which show overlapping pathophysiological hallmarks and are associated with oxidative stress and inflammation (Table **4**).

CAPE has shown potential in the treatment of ALS and HD [17, 18, 68]. ALS is known to cause degeneration of motor neurons in the primary motor cortex, corticospinal tract, brain stem, and spinal cord, which ultimately leads to progressive muscular paralysis [87]. An *in vitro* study carried out in NSC34 motor neuron cells showed that CAPE (EC_{50}: 2µM) caused the inhibition of NF-κB and promoted the activation of Nrf2 signalling cascades [18]. In line with the same, a study carried out using a transgenic ALS mice model, SOD^{G93A}, also showed that when administered orally for a period of 7 days, CAPE slowed down the disease progression of ALS significantly. It further decreased the phosphorylation of p38/MAPK and attenuated the glial cell activation in the spinal cord to increase the lifespan and post-onset survival in SOD^{G93A} mice [68]. It suggests that the neurological benefit offered by CAPE in ALS may be attributed to its ability to modulate a variety of pathways, including anti-inflammatory, antioxidant, and anti-apoptotic signalling cascades.

HD is an autosomal disorder characterized by atrophy of striatal and cortical neurons leading to physical disabilities, psychological changes and dementia [17, 88]. An *in vitro* study involving striatal neuronal culture demonstrated the neuroprotective ability of CAPE (50µM) through its radical-scavenging effects. The same study displayed that CAPE administered at a dose of 30 mg/kg in a 3-nitropropionic mice model of HD displayed significantly lower immunoreactivity towards glial fibrillary acidic protein (GFAP), a marker of astrocyte activation and CD45, a marker of microglial/macrophage activation. Therefore, its neuroprotective ability was attributed to its power to inhibit microglial activation, which seems to be perturbed in HD [17]. Alternatively, CAPE was also found to have potential in the treatment of epilepsy. CAPE administered at a dose of 100 µmol/kg in a pentylenetetrazole (PTZ) induced epilepsy showed neuroprotection mediated through its antioxidant effects, which were confirmed through a decrease in the levels of MDA and XO following administration. Besides, CAPE also perturbed NO production, which is responsible

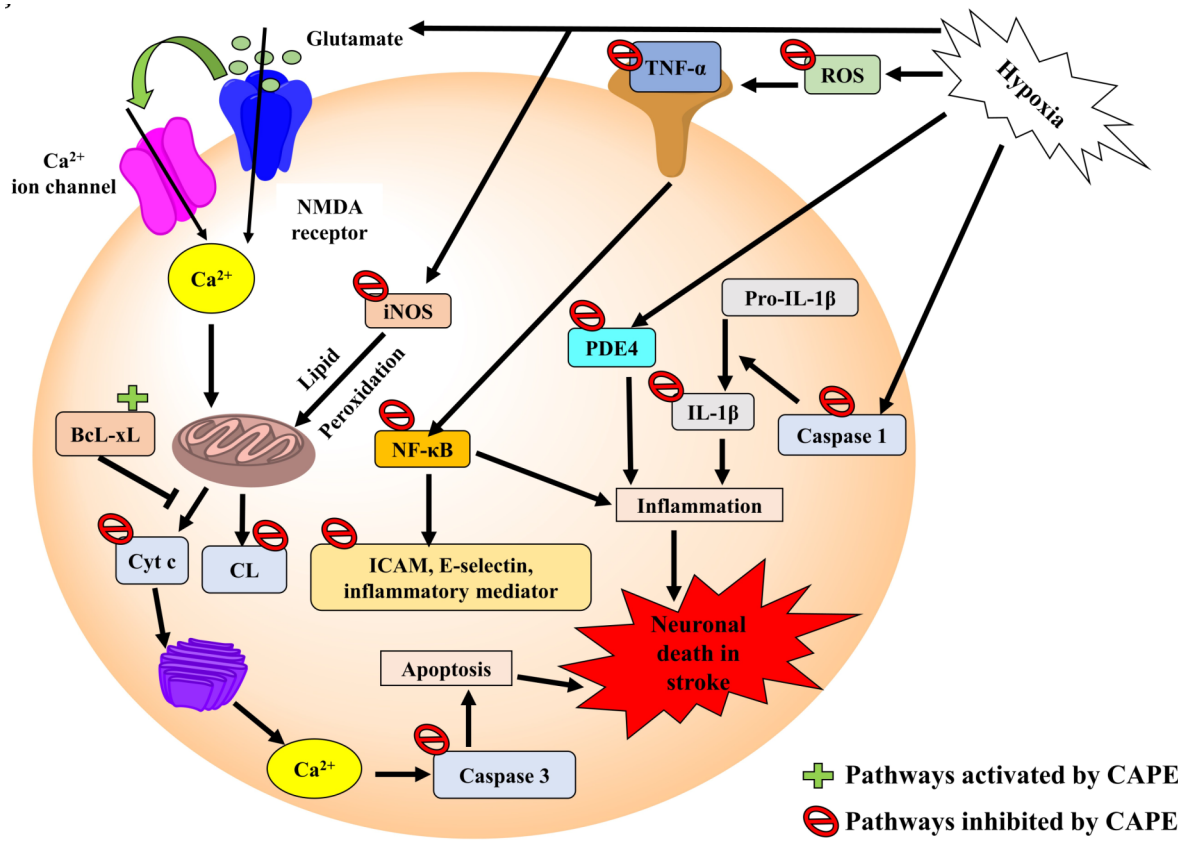

Fig. (3). Schematic diagram to represent molecular pathways, elucidating the beneficial effects of CAPE in stroke. CAPE has shown beneficial effects through the modulation of various targets involved in stroke. Hypoxia leads to the activation of various molecular pathways that ultimately culminate into neuronal death either *via* activation of inflammation or apoptosis. Hypoxia leads to an increase in the intracellular Ca^{2+} *via* the glutamate-induced opening of Ca^{2+} ion channels. This Ca^{2+} further leads to the release of CL and Cyt c, which are otherwise present in a bound form on the inner mitochondrial membrane. Release of Cyt c leads to the activation of Caspase 3, leading to apoptosis. Another activator of this pathway is iNOS which is also upregulated following hypoxia. Also, the activation of TNF-α *via* ROS and its downstream modulator NF-κB causes inflammation *via* activation of various adhesion molecules like ICAM and E-selectin. Also, hypoxia induces the production of other agents that cause inflammation like PDE4, IL-1β and Caspase 1. CAPE inhibits all these mediators apart from inducing the production of Bcl-xL, which is an anti-apoptotic molecule. These effects of CAPE in totality provide protection from neuronal death in stroke. ROS: Reactive oxygen species, TNF-α: Tumour necrosis factor-alpha, NF-κB: Nuclear factor-kappa B, ICAM-1: Intercellular Adhesion Molecule, NMDA: N-methyl-D-aspartate, iNOS: Inducible nitric oxide synthase, BcL-xL: B-cell lymphoma extra-large, Cyt c: Cytochrome c, CL: Cardiolipin, PDE4: Phosphodiesterase 4, IL: Interleukin. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

for peroxynitrite generation and contributes towards glutamate-induced neurotoxicity [34]. Likewise, another study carried out using the PTZ model in rats showed the neuroprotective ability of CAPE through the inhibition of apoptosis in the hippocampus and prefrontal cortex when administered at a dose of 30 mg/kg intraperitoneally [21].

Traumatic brain injury (TBI) is an injury caused to the brain due to mechanical stress to the brain tissue along with the other contributing factors like inflammation, excitotoxicity, and imbalance in the cerebral blood flow and brain metabolism [89]. Two reports demonstrated the effectiveness of CAPE in TBI [22, 90]. CAPE administered at a dose of 10 mg/kg in a controlled cortical injury (CCI) model helped to conserve the vascular integrity through its protective effects on the levels and cellular localization of claudin-5, a transmembrane protein involved in the maintenance of the tight junctions of the blood-brain barrier (BBB). In addition, CAPE also showed a decrease in the loss of cortical tissue and decreased contusion volume apart from decreasing the vascular dysfunction in the cortex of rats [22]. Another study that assessed the effects of CAPE in an experimental TBI in rats also demonstrated that CAPE given as a single dose, 15 mins after the trauma, was effective in treating TBI. It additionally accorded protection by decreasing lipid peroxidation and increasing the levels of internal antioxidant enzymes like SOD and Glutathione peroxidase (GPx). Moreover, it also reduced the immunoreactivity of degenerating neurons towards caspase-3, thus preventing apoptosis and promoting survival. Also, it precluded ultrastructural changes like degeneration of mitochondria, irregularly shaped nuclei, and endoplasmic reticulum (ER) dilation [90].

Owing to its widespread success preclinically and multiple mechanisms of action, CAPE was also tested in the animal models of depression and anxiety. Both depression and

Table 4. Studies of neuroprotective effects of CAPE in other neurological diseases.

S. No.	Disease	CAPE (Dose and Duration)	Model	Outcomes	Refs.
1	Huntington's disease	50 μM following the intoxication with 3-NP (5 μM)	Striatal neuronal culture	• Increased radical scavenging activity	[17]
2	ALS	Pre-treatment with EC_{50}-2 μM for 1 hour	NSC34 motor neuron cells	• Inhibition of NF-κB and activation of Nrf2 pathway	[18]
		10 mg/kg, orally for 7 consecutive days following disease onset	$SOD1^{G93A}$ mice	• Decreased phosphorylation of p38 MAPK and reduced microglial and astrocyte activation in spinal cord	[64]
3	Depression and Anxiety	5, 10, 20 μmol/kg, ip for 21 days	CUS in mice	• Enhancing GR function through downregulation of p38/MAPK signalling in hippocampus	[19]
		10, 50, 250 μmol/kg, orally for 21 days	CMS in mice	• Activation of ERK1/2-CREB • Signalling in hippocampus	[92]
4	Epilepsy	30 mg/kg, ip given after 40 minutes of tonic phase and repeated for 5 days	PTZ induced seizures in rats	Suppressed apoptosis in the hippocampusand prefrontal cortex	[21]
		100 μmol/kg, ip given 2 days prior to PTZ administration	PTZ Induced seizures in mice	• Decreased level of MDA, NO, and XO	[34]
5	Traumatic brain injury	10 mg/kg, ip given 30 mins following the injury and continued for 4 days	CCI in SD rats and C57BL/6 mice	• Prevention of claudin-5 loss • Decreased contusion volume and vascular dysfunction	[22]
		Single-injection of 10 μmol/kg, ip 15 mins following injury	TBI in SD rats	• Decreased MDA levels and increased SOD and GPx levels • Decreased caspase-3 immunoreactivity	[90]
6	Neuropathic pain	25 mg/kg, ip for 7 consecutive days following CCI	CCI in mice	• Suppressed LPS mediated activation of microglia through inhibition of phosphorylation of p38 MAPK and NF-κB • Decreased expression of TNF-α, IL-1β and IL-6	[100]
		30 mg/kg, ip given 30 mins prior to 3-NP injection and repeated for 5 days	3-NP in C57BL/6 mice	Decreased GFAP and CD45 expression	

Abbreviations: CCI: Chronic constriction injury, LPS: Lipopolysaccharide, MAPK: Mitogen-activated protein kinase, NF:κB: Nuclear factor-kappa B, TNF-α: Tumour necrosis factor-alpha, IL; Interleukin, 3-NP: 3-nitropropionate, GFAP: Glial fibrillary acidic protein, CD-45: Cluster of differentiation, PTZ: Pentylenetetrazole, MDA: Malondialdehyde, NO: Nitric oxide, XO: Xanthine oxidase, CCI: Controlled cortical injury, TBI: Traumatic brain injury, SOD: Superoxide dismutase, GPx: Glutathione peroxidase, CUS: Chronic unpredictable stress, GR: Glucocorticoid receptor, CMS: Chronic mild stress, ERK1/2: Extracellular signal-regulated kinase.

anxiety are mood disorders having high prevalence and frequently coexist [91]. In spite of their high prevalence and ability to negatively impact the quality of life, the treatment options remain limited. Two studies investigated the effects of CAPE in depression and anxiety in an attempt to investigate its potential for the treatment of these mood disorders [19, 92]. In the chronic unpredictable stress (CUS) model in mice, *Lee et al.* reported that intraperitoneal CAPE administration at doses of 5, 10, 20 μmol/kg produced an antidepressant effect in a dose-dependent manner through the enhanced function of the glucocorticoid receptors (GR) in the hippocampus. This was further modulated by the inhibition of the p38/MAPK pathway, which is known to be altered in patients with depression and anxiety [19, 93-95]. In line with the same, another study revealed that CAPE also reduced depression and anxiety-like behaviour in mice in a dose-dependent manner through the activation of extracellular signal-regulated kinase-cAMP response element-binding protein (ERK1/2-CREB) signalling pathway in the hippocampus [92].

Neuropathic pain is a disorder that occurs due to damage to the somatosensory nervous system and affects approximately 5% of the world population. It is characterized by pain that is widespread that includes sensory deficit, burning pain, pain on light stroking of skin, and attacks of pain without any apparent provocation [20, 96-98]. Despite efforts to find new therapeutic strategies, the treatment options remain limited, and those available provide only symptomatic relief [97, 99]. The neuroprotective effects of CAPE in neuropathy have been demonstrated in a study carried out in mice using

the Chronic Constriction Injury (CCI) model. CAPE administered intraperitoneally at a dose of 25 mg/kg for 7 consecutive days produced an improvement in the behavioural pain parameters through the inhibition of microglial activation and by inhibiting the phosphorylation of p38/MAPK pathway. Apart from this, CAPE also reduced the NF-κB activation and decreased the expression of proinflammatory cytokines like TNF-α, IL-1β and IL-6 [100].

These studies, in totality, point out the beneficial effects of CAPE in the modulation of various neurological disorders. These effects are exhibited through the modulation of oxidative stress, inflammation, and several other molecular pathways that are known to be affected in these neurological disorders.

6. THERAPEUTIC POTENTIAL OF CAPE IN AGING

Aging is a process that causes detrimental effects on cells, tissues, and the entire organism as a whole. Amongst the various mechanisms that result in aging, oxidative stress is a major player. The brain is one of the most vulnerable organs to oxidative stress [101]. Oxidative stress, along with other factors like mitochondrial damage, increased neuronal apoptosis, and dysregulation of autophagy, is known to cause chronic diseases like neurodegeneration which are linked to aging [2, 3]. Thus, the elderly are prone to neurodegenerative disorders [102]. The most commonly reported age-related disorders are dementias that affect cognition, followed by movement disorders, such as PD [8, 37].

The role of CAPE in delaying aging and its effects has been studied in different model systems. A study by *Shin et al*. accessed the effects of CAPE on photo-aging caused by exposure to ultraviolet (UV) radiation. CAPE was observed to be effective in preventing skin ageing through epigenetic alterations by targeting various histone acetyltransferases (HATs) like p300, CREP-binding protein (CBP), and p300/CBP-associated factor. This effect was brought about by the attenuation of UV-induced lysine acetylation. Also, CAPE was able to suppress UV-induced increase in the MMP-1 levels, and this effect was evident in the human dermal fibroblasts (HDC) as well as skin tissues [103]. Another study that accessed the protective effect of CAPE on kidneys against aging-related oxidative damage showed that CAPE administration significantly decreased the levels of malondialdehyde (MDA), a product of lipid peroxidation. On the contrary, it increased the activity of superoxide dismutase (SOD), catalase (CAT), Glutathione peroxidase (GPx), and levels of Glutathione (GSH). CAPE, in combination with melatonin, further caused a decrease in the MDA levels and protected the kidney tissue from age-related degenerative processes in the mitochondria, vacuole-related changes, changes in cristae, and oedema. The combination was also able to reverse age-related structural alterations in the tubular and glomerular structures [104]. The same combination was useful in protecting against age-related cardiovascular changes. The treatment also significantly decreased the levels of MDA and elevated the levels of antioxidant enzymes in the heart and the aorta. It was accompanied by the maintenance of nuclear irregularity and the prevention of mitochondrial damage and changes in the endothelial cells in the aorta [55]. Chronic administration of CAPE with melatonin was able to protect against age-associated microstructural changes and oxidative stress in the brain and cerebellum of aged rats [102].

Thus, CAPE provides a lot of promise as a drug candidate to treat age-related changes in the periphery as well as CNS. Furthermore, in this review, we have mainly focused on the potential of CAPE in the treatment of various neurological disorders which are closely associated with aging.

7. CLINICAL STUDIES OF CAPE

Clinical studies of CAPE are rather limited, and very few randomized controlled trials have been performed to date [105]. A randomized control trial of its inhibitory effect on dentin MMPs was carried out on 10 patients between the ages of 12 to 18 years. It has been reported that the application of adhesive systems on dentin leads to the activation of MMPs that cause collagen degradation and loss of bond strength in adhesive restorations. The findings of the study showed that pre-treatment of CAPE (5% solution) onto dentin significantly enhanced composite resin restorations' bond strengths to dentin, resulting in the inhibition of MMPs [32]. Another randomized study evaluated its safety and tolerability profile in 18 healthy subjects between the age of 18 to 64 years. Incremental doses of CAPE were found to be safe for human consumption subjects and were deprived of any side effects [106]. The only available report of CAPE being used as an investigational drug for CNS complications includes a trial carried out by Chemigen, LLC in ALS patients. It was employed in three incremental doses of 250 mg, 500 mg, and 1000 mg q.d. for 7 days [107]. Though the trial has already been completed, its results are still awaited. Besides, several patents have also been sought for the use of CAPE and its combinations for the treatment of cancer. CAPE, in combination with other drugs, exhibited HDAC inhibitory effect and was found to be effective against breast and prostatic cancer. Also, CAPE and its analogues were found to effectively treat psoriasis through its inhibitory effect on STAT-3 [108, 109].

Although none of the studies related to the toxicity of CAPE have been reported in the literature, it must be noted that propolis, the major source of CAPE, has been shown to produce slight toxicity in mice at doses ranging from 2000-7300 g/kg [110]. Also, another hurdle to the use of CAPE as a drug candidate for treating neurological disorders is its short biological elimination half-life of 21.2 to 26.7 minutes [111]. Apart from this, propolis products, including CAPE, have been largely uncharacterized, leading to a lack of reproducibility and poor quality of clinical trials. Therefore, despite convincing evidence for its safety and efficacy, it has not yet progressed to the advanced stages of clinical trials for any of the disease conditions. However, considering the already known nutraceutical potential of propolis and the encouraging results from clinical trials for CAPE, it bears immense potential for the treatment of neurological disorders in the future.

CONCLUSION

CAPE is a polyphenolic compound present in propolis, which is characterized by its multiple biological activities. An abundance of preclinical data has demonstrated its effi-

cacy for the treatment of neurological disorders associated with aging, which otherwise pose a great threat to the quality of a patient's life. Although it is known to offer therapeutic benefits in preclinical studies, clinical investigations are still warranted to establish its claim as a drug candidate against these neurological disorders. However, before being taken up to the advanced stages of clinical trials, more studies need to be carried out using electrophysiology and advanced imaging techniques to gather enough data about its detailed mechanisms of action and potential side effects, if any. Thus, large-scale safety and toxicity studies would be helpful for the dose titration of CAPE and the design of its analogues, which could prove to be effective for the treatment of these neurological disorders associated with aging and senescence in the future.

LIST OF ABBREVIATIONS

5-LOX	=	5-lipoxygenase
6-OHDA	=	6-hydroxydopamine
AD	=	Alzheimer's disease
ADA	=	Adenosine Deaminase
ADP/O	=	Adenosine diphosphate/oxygen
AIF	=	Apoptosis inducing factor
Akt	=	Protein kinase B
ALS	=	Amyotrophic Lateral Sclerosis
AMPK	=	5' adenosine monophosphate-activated protein kinase
APAF	=	Apoptotic protease activating factor
BBB	=	Blood brain barrier
Bcl-xL	=	B-cell lymphoma extra-large
BDNF	=	Brain derived neurotrophic factor
CAPE	=	Caffeic acid phenethyl ester
CAT	=	Catalase
CBP	=	CREP-binding protein
CCA	=	Bilateral common carotid artery occlusion
CCI	=	Chronic constriction injury
CCI	=	Controlled cortical injury
CD-45	=	Cluster of differentiation
CL	=	Cardiolipin
CMS	=	Chronic mild stress
CREB	=	cAMP response element binding protein
CSF	=	Cerebrospinal fluid
CUS	=	Chronic unpredictable stress
CysLT	=	Cysteinyl leukotrienes
Cyt c	=	Cytochrome c
ED	=	Ectodysplasin
eNOS	=	Endothelial nitric oxide synthase
ER	=	Endoplasmic reticulum
ERK1/2	=	Extracellular signal-regulated kinase
GAP-43	=	Growth associated protein 43
GFAP	=	Glial fibrillary acidic protein
GPx	=	Glutathione peroxidase
GR	=	Glucocorticoid receptor
GSH	=	Glutathione
GSK-3β	=	Glycogen synthase kinase 3 beta
HAT	=	Histone acetyl transferase
HD	=	Huntington's disease
HDC	=	Human dermal fibroblasts
HI	=	Hypoxic injury
HO-1	=	Heme oxygenase-1
ICAM	=	Intercellular Adhesion Molecule
IL	=	Interleukin
iNOS	=	Inducible nitric oxide synthase
LPS	=	Lipopolysaccharide
MAPK	=	Mitogen-activated protein kinase
MCA	=	Middle cerebral artery occlusion
MDA	=	Malondialdehyde
MMP	=	Matrix metalloproteinase
MPTP	=	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NADPH	=	Nicotinamide adenine dinucleotide phosphate hydrogen
NF-κB	=	Nuclear factor kappa B
NMDA	=	N-methyl D-aspartate
NO	=	Nitric oxide
Nrf-2	=	Nuclear factor erythroid 2-related factor 2
PD	=	Parkinson's disease
PDE	=	Phosphodiesterase
PGC-1α	=	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PI3K	=	Phosphoinositide 3-kinase
PTZ	=	Pentylenetetrazole
RCR	=	Respiratory control ratio
ROS	=	Reactive oxygen species
S-100B	=	S-100 calcium-binding protein B

SAH	=	Subarachnoid haemorrhage
SD	=	Sprague-Dawley
SIRT-1	=	Silent information regulator-1
SOD	=	Superoxide dismutase
TBI	=	Traumatic brain injury
TH	=	Tyrosine hydroxylase
TNF-α	=	Tumour necrosis factor alpha
UV	=	Ultraviolet
XO	=	Xanthine Oxidase

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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