Caffeic Acid Phenethyl Ester

Subjects: Biochemistry & Molecular Biology

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Caffeic acid phenethyl ester (CAPE), is one of the most extensively investigated active components of propolis and it is considered responsible for most of its beneficial effects. Among the others, CAPE exerts protection towards many neurological disorders. This review summarizes the protective effects of CAPE towards oxidative stress, inflammation, apoptosis, neurotoxic substances, neurodegenerative diseases, brain tumors and neuronal injuries as well. A paragrah on derivatives of CAPE is also included.

Caffeic Acid Phenethyl Ester | neuroprotection | neurodegenerative disease | propolis | CNS injury | CNS ischemia | CNS cancer | neuroinflammation | CAPE derivatives | neurotoxic substance(s)

1. Introduction

Propolis, a honeybee product, is a resinous product obtained from different plant parts mixed with beeswax and bee salivary enzymes and represents a multimillion dollar market [1][2]. It has been used in traditional medicine for many years due to its anti-microbial, anti-inflammatory, anti-oxidant, immunomodulator, anti-mutagenic, and carcinostatic effects [3]. Propolis consists of a large number of different compounds according to the ingredients the bees collect from the plants. Its main components are phenols and related compounds. Investigations have been conducted to purify and determine which substances are responsible for these effects. The results of these investigations have suggested that caffeic acid phenethyl ester (CAPE, phenethyl 3-(3-4 dihydroxyphenyl) acrylate) is the main component that mediates most of the beneficial effects ascribed to propolis [4]. As a consequence, CAPE has become one of the most studied natural product research topics in recent years. Grunberger and co-workers extracted and described CAPE in 1988 [5], and later Sigma-Aldrich produced commercial preparations for the market [6]. CAPE is a polyphenol with hydroxyl groups within the catechol ring which provide strong antioxidant properties to the molecule and can affect many biological activities. It has a lipophilic property because of its long carbon groups in an aromatic and aliphatic structure, which leads to adequate blood concentration after intraperitoneal administration [7]. Celli et al. [8] investigated the stability of CAPE in rats and human plasma. It was found that CAPE undergoes hydrolysis to caffeic acid after 6 h in rat plasma in vitro and also in vivo, giving caffeic acid as the major metabolite. This type of hydrolysis does not occur in human plasma because it does not contain carboxylesterase, which is responsible for CAPE hydrolysis [9]. The broad spectrum of pharmacological activities shown by CAPE ranges from anti-oxidant/anti-inflammatory to anti-viral/anti-fungal properties, including anti-proliferative effects in various cancer models [10]. A recent in vivo study indicated that CAPE has the ability to cross

the blood–brain barrier in rats [11][12]. This entry focuses on the protective effects of CAPE in many diseases that can affect the central nervous system (CNS). CAPE was found to have a protective effect on different neurodegenerative disorders, either those occurring with age, such as Alzheimer's disease (AD) and Parkinson's disease (PD), or other neurodegenerative disorders, such as amyotrophic lateral sclerosis (ALS) and seizures. CAPE was proven to protect neurons from the main underlying causes of several human neurologic diseases—namely, oxidative stress, apoptosis dysregulation, and brain inflammation. In addition, CAPE was found to be able to protect the nervous system from the consequences of some diseases not directly affecting it, such as diabetes, septic shock, and hepatic encephalopathy (HE). A paragraph about the neuroprotective effects of CAPE against adverse reactions induced by different neurotoxic substances such as ethanol, methotrexate, acrolein, and others is also provided. The role of CAPE in the pathophysiology of CNS tumors and in neuronal injuries is carefully reviewed through the description of the modulatory activity of CAPE against biochemical and histopathological cascade mechanisms following ischemic conditions in the brain and spinal cord. Finally, a brief overview of CAPE synthetic derivatives follows. Five tables summarize the main findings on CAPE effects in different areas of neuroprotection. In the column named "Parameters measured", the effect of CAPE is reported between parentheses where applicable. In some case, the effect of CAPE is not directly deducible, but depends on the experimental model or conditions. This review provides a useful insight into the role of CAPE in the management of numerous pathological conditions affecting the CNS. The description of the molecular mechanisms and the focus on CAPE derivatives can help in discovering new promising targets for neuroprotection and in finely tailoring structural modifications of CAPE derivatives.

2. Methodology

The online database PubMed was used for screening the studies for this review, with no chronological limits applied. Keywords used to search for articles included caffeic acid phenylethyl ester and neuroprotection, neurodegenerative disorders, CNS injury, CNS ischemia, CNS cancer, neuroinflammation, brain injury, spinal cord injury, and neuronal injury. The search retrieved more than 90 results, including three reviews with a section or hints about neuroprotective effect of CAPE or its protective effects against ischemia-reperfusion injury. None of these discussed the diverse signaling pathways involved. After having removed duplicates and narrowing the results according to the relevance to the core topic of the review, 77 papers were selected. A thorough analysis of the reference list of all the included studies identified additional relevant studies which, together with papers cited to introduce and clarify the various subjects, led to a total of 90 references.

3. CAPE Effects on Different Neurologic Disorders

With age, a lot of neurologic disorders become common, such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS). Common causes for the development of these diseases are oxidative stress, inflammation, and apoptosis impairment. A main goal of anti-ageing strategies is the elimination of harmful agents—in other words, free radicals—from the environment to protect organs from aging and other oxidative stress-related pathologies. One study evaluated the effects of the long-term administration of CAPE on

histological and biochemical alterations induced by ageing in the brain and cerebellum of old rats. CAPE increased the superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) activities and glutathione (GSH) levels in both cerebral and cerebellar tissues to levels similar to those in young rats. Additionally, CAPE reduced the malondialdehyde (MDA, an important marker of lipid peroxidation) level and ageing-induced ultrastructural alterations, proving to be more effective than melatonin, which is used worldwide in order to prevent ageing-related pathologies [13]. Many studies addressing the protective effects of CAPE on different neurologic disorders are described below and summarized in Table 1. Other than the above-mentioned pathological conditions, the role of CAPE in psychosis, seizures, and the side-effects of other diseases are described.

3.1. Apoptosis

Apoptosis dysregulation has been suggested to be the underlying cause of several human neurologic diseases. Transient focal or global cerebral ischemia in rodents leads to neuronal apoptosis. Reactive oxygen species (ROS) production is thought to represent a relevant mechanism in the series of biochemical events ultimately leading to apoptosis. CAPE blocks neuronal death through inhibition of inflammation and of mitochondrial cytochrome c release, and through a reduction in free radical generation [14][15]. Primary cultures of cerebellar granule neurons (CGNs) are considered a suitable in vitro model to study the mechanisms of neuronal apoptosis, which can be induced by low K^+ concentrations. CAPE exerts its anti-apoptotic effect on CGNs by blocking ROS formation and inhibiting the activity of both caspase-3 and caspase-9. Caspase-3 is the executioner caspase that is downstream of the intrinsic (mitochondrial) caspase-9 and extrinsic receptor activated (Fas) caspase-8 pathways. Interestingly, CAPE was found to completely block the activation of nuclear factor-κB (NF-κB) without interfering with the marked decrease in intracellular Ca^{2+} concentration induced by low K^+ [14][16].

Another study investigated CAPE's neuroprotective effect against apoptotic cell death in the developing rat brain after pentylenetetrazole (PTZ)-induced status epilepticus (SE). Prolonged seizures are associated with inadequate blood flow, increased excitatory amino acid release, and decreased glucose use and oxygen consumption. All these features are associated with impaired mitochondrial function and irreversible neuronal damage. CAPE showed diminished apoptosis and preservation of the number of neurons, as well as a reduced number of caspase-3-positive cells in the hippocampus and in the prefrontal cortex [17]. Another study [18] investigated the effect of CAPE on CGNs exposed to excitotoxicity by the overstimulation of glutamate receptors. Neuronal death caused by excitotoxicity plays an important role in a number of neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, and multiple sclerosis. CAPE inhibited necrosis mediated by p38 phosphorylation and apoptosis mediated by cytochrome *c* release and caspase-3 activation, while it appeared to have no effect on glutamate-induced neuronal death via the NF-κB pathway. Interestingly, CAPE proved effective in modulating neurotogenesis—i.e., the formation of new neurites—in PC12 cells challenged with the dopaminergic neurotoxin 1-methyl-4-phenylpyridinium (MPP+). CAPE induced the formation, elongation, and ramification of neurites and inhibited the shortage of neurites induced by the neurotoxin. These effects were associated with an increased expression of neuronal typical proteins responsible for axonal growth (GAP-43) and synaptogenesis (synaptophysin and synapsin I) [19].

Table 1. CAPE protective effects in different neurological disorders. Where applicable, the effect of CAPE on the parameters measured is reported between parentheses (+, − or =).

Stimulus	Parameters Measured	CAPE Dose(s)	Experimental Model	Ref.
Aging: 18 month old rats	-Histopathological assessment -MDA (−) -SOD (+) -CAT (+) -GSH-Px (+) -GSH (+)	15 mg/kg/day, i.p., for 95 days	Male Sprague Dawley rats	[13]
Apoptosis: serum-free medium with low K^+ (5 mM KCl)	-Apoptosis (−) -ROS (−) -Ca^{2+} (=) -NF-κB (−) -Caspase-3 and -9 (−)	10 µg/mL	Primary CGNs from 8-day-old Wistar rats	[14]
SE: PTZ 40 mg/kg followed by 10 mg/kg every 10 min until SE occurrence, i.p.	-Histopathological assessment -Caspase-3 (−)	30 mg/kg /day, i.p., for 5 days starting 40 min after the SE tonic phase	Dams reared Wistar male rats	[17]
Excitotoxicity: -Cells: glutamate 30 µM/24 h -Isolated mitochondria: glutamate and maleate (both 5 mM)	-Cell viability (+) -Caspase-3 (−) -Cytochrome c (−) -Glutamate-evoked currents	0 µM–200 µM, pre- and co-treatment	-CGNs from 8-day-old Sprague Dawley rats -Mitochondria from CGNs and livers	[18]
Cytotoxicity: MPP^+ 100, 500 or 1000 µM	-Cell differentiation (+) -Cell viability (+) -Protein content (+) -Synaptophysin (+) -GAP-43 (+) -Synapsin I (+)	1, 5 or 10 µM	PC-12 cells	[19]
Neuroinflammation: IFN-γ and LPS	-NF-κB (−) -TNF-α (−) -NOS-2 (iNOS) (−) -CREB (+)	4 to 100 µM, 30 min before and during LPS exposure	Organotypic hippocampal cultures from the hippocampi of 5–7- day-old Wistar rats	[20]
Neuroinflammation: TNF-α 10 ng/mL/6 h	-CCL-2 (−) -CXCL-8 (−) -ICAM-1 (−) -Monocyte Adhesion (-) -DNA-binding activity of NF-κB and AP-1 (−) -IκBα	30 µM, pretreatment	-CRT-MG human astroglial cells -U937 human monocytic cells	[21]

Stimulus	Parameters Measured	CAPE Dose(s)	Experimental Model	Ref.
	-IKK -TRAF2 -TAK1 -MKK4 -JNKs -c-Jun			
XALD: human skin fibroblasts derived from XALD (GM04932, GM04934), and AMN (GM07531) patients	-TNF-α (−) -ROS (−) -NO (−) -Fatty acids (−)	1–5 μM	-Fibroblasts -Mouse primary mixed glia and astrocytes	[22]
EAE: 50 μg of guinea pig MBP and 7 mg/mL heat-killed Mycobacterium tuberculosis, intradermally.	-Neurological assessment -MDA (−) -NO (−) -XO -GSH-Px -ADA -SOD	25 μmol/kg/day, i.p., for 14 days after immunization	Female Wistar rats	[23]
ALS: transfection with pIRESneo and/or SOD1 mutants	-In silico analysis -DCF -Cell viability (+) -Nrf2 (+) -5- LO -NF-κB (−)	10 μM, co-treatment	NSC34 mouse motor neurons	[24]
ALS: SOD1G93A mutated mice	-CAPE level -Behavioural assessment - pp38 (−)	10 mg/kg/day, orally, for 7 days after disease onset	$SOD1^{G93A}$ mice	[25]
-Neuroinflammation, in vitro: 200 ng/mL LPS -in vivo, a single intraperitoneal injection of 20 mg/kg LPS, i.p., 2 h after the last CAPE injection	-Cell viability -ERK2 -Akt -p38, -pERK1/2 -pp38 -pAKT -pJNK -EPO (+) -HO-1 (+) -iNOS (−) -COX-2 (−) -pAMPKα (+)	-0.1 to 1.75 μM 30 min before LPS treatment, or co-treatment -1 or 5 mg/kg once daily for 3 days	-BV-2 murine microglial cell line -Eight-week-old male ICR mice	[26]
PD: 6-OHDA 70 μM for 6 h, on day 8–10	-Cell viability (+) -Cytochrome c (−)	10 to 100 μM, pre-treatment for 4 h	-Primary CGNs from 8-day-old Wistar rats	[27]

Stimulus	Parameters Measured	CAPE Dose(s)	Experimental Model	Ref.
	-Caspase-3 (−) -Ca^{2+}		-Rat liver mitochondria from 7-day-old Sprague–Dawley rats	
Dopaminergic neurodegeneration: 6-OHDA, 40 µM for RMN and 70 µM for CGN	-Free radicals (−) -Peroxynitrite (−)	10 µM, pre-treatment for 2 h	-Rat RMN -Primary CGNs	[28]
PD: 6-OHDA 8 mg/mL, s.i.	-Fe, Cu, Zn and Mn (−) -ROS (−) -Protein content -TH -Mitochondrial functions: Ca^{2+}-induced swelling, Ca^{2+} uptake and respiration	-In Vivo: 10 µmol/kg/day, i.p., 5 days -In Vitro: 0.5 or 10 µM	Wistar rats	[29]
-Dopaminergic neurodegeneration, in vitro: LPS/72 h -PD, in vivo: LPS 3 µg/µL, intranigral, or 6-hydroxydopamine 2 µg/µL, intrastriatal, 30 min after first CAPE injection.	-NO (−) -ERK -p38 MAPK -HO-1 (+) -BDNF (+) -Nrf2	-In Vitro: 3–30 µM -In Vivo: 10 or 30 mg/kg/day, i.p., for 4 days	-In Vitro: rat organotypic midbrain slice cultures -In Vivo: mouse model of dopaminergic neurodegeneration	[30]
PD: rotenone1 mg/kg, s.c., every 48 h, 9 injections	-Behavioural assessment -Histopathological assessment -CD11b -COX-2 (−) -iNOS (−) -NF-κB (−) -Dopamine level (+) -TNF-α (−) -IL-1β	2.5, 5 or 10 mg/kg/day. orally, every 48 h, 9 doses	Male Swiss albino mice	[31]
PD: CPF 80 mg/kg, s.c.	-PON1 activity (+) -Lipid profile -TSA (+) -TAC (+) -TOC (−) -Histopathological assessment	10 µmol/kg/day, i.p., 21 days	Male Swiss albino mice	[32]

Stimulus	Parameters Measured	CAPE Dose(s)	Experimental Model	Ref.
PD: MPTP–HCl 20 mg/kg, i.p., four in at 2 h intervals	-TH-positive neurons (+) -Cell viability (+) -CAPE and MPP+ levels -DA (+) -MAO (−) -i- and nNOS (−) -Caspase-1 (−) -Cytochrome c (−) -AIF (−) -Free radicals (−) -Peroxynitrite (−)	2, 5, or 10 mg/kg/day, 7days	Eight-week-old male C57BL/6 mice	[33]
Loss of memory (AD): STZ 3 mg/kg, bilaterally on day 1 and 3	-TBARS (−) -GSH (+) -SOD (+) -CAT (+) -Nitrite (−) -AChE (−) -TNF-α (−) -eNOS (+) -NF-κB (−) -Behavioural assessment -Histopathological assessment	6 mg/kg/day, i.p., 28 days	Wistar rats	[34]
Dementia (AD type): STZ; 3 mg/kg, on day 1 and 3, ICV	-MDA (−) -GSH (+) -TNF-α (−) -Behavioural tests	3, 6 mg/kg/day, i.p., 28 days	Wistar rats	[35]
Dementia (AD type): Aβ1-42O, unilateral stereotaxic, ICV	-Behavioural assessment -ROS (−) -Nrf2 (+) -GSH -pGSK3α/β -Caspase-9	10 mg/kg/day, i.p., 1 h after brain lesion, 10 days	Male C57Bl/6 mice	[36]
Seizures: 60 mg/kg PTZ, i.p., single dose	-Neurological assessment -MDA (−) -NO (−) -XO -SOD (+)	100 µmol/kg, i.p., 2 days prior to PTZ injection	Female Swiss albino mice	[15]
Psychosis: dizocilpine maleate (MK-801), 0.5	-Behavioural assessment	10 µmol/kg, 6 days, started one day	Wistar rats	[37]

Stimulus	Parameters Measured	CAPE Dose(s)	Experimental Model	Ref.
mg/kg/day for 5 days, i.p.	-Histopathological assessment -MDA (−) -PC (−) -NO (−) -SOD -GSH-Px (−) -XO (−) -ADA (−) -CAT (=)	before MK-801, i.p.		
Diabetes: STZ 45 mg/kg, i.p., single dose	-NO (−) -SOD -GSH-Px (−) -GSH -XO (−) -CAT (−) -MDA (−) -iNOS (−) -TNF-α (−) -IFN-γ (−) -IL-10	25 µM/kg/day, two days after STZ treatment for 60 days	Male Wistar rats	[38]
Endotoxic shock: LPS, 20 mg/kg, i.p,	-TNF-α (−) -IL-1α, -1β, -6 (−) -IL-4, -10 (+) -sICAM-1 (−) -Histopathological assessment	10 µmol/kg/day, 14 days before shock induction and a single dose 30 min after induction	Male Wister rats	[39]
Hepatic encephalopathy: thioacetamide:600 mg/kg, i.p., two doses (0 and 24 h)	-Behavioural and motor assessment -Blood ammonia (=) -ALT (−) -AST (−)	10 µmol/kg/day, i.p., starting 1 day before the first dose of thioacetamide	Male Wistar rats	[40]
Optic nerve crushing, 10 s	-Apoptosis (−) -Astrocyte migration -Cell viability (+) -NF-κB (−) -IL-6 and -8 (−) -iNOS (−) -COX-2 (−) -TNF-α (−) -CCL-2 (−)	10 µmol/kg, i.p., 10 min after the surgery	Male Sprague Dawley rats [21]	[41]

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and the blood–brain barrier (BBB). CAPE maintains cell membrane integrity and function, thus preventing protein leakage and accumulation by inhibiting the peroxidation of membrane lipids. CAPE may exert its anti-inflammatory effect and ameliorate clinical symptoms by inhibiting ROS production at the transcriptional level, through the suppression of NF-κB activation, and by directly inhibiting the iNOS catalytic activity [23].

ALS is a disease that causes the death of motor neurons controlling voluntary muscles. In one study in 2009 [24], CAPE was selected from a library of 2000 small anti-oxidant molecules for the mechanism of action and the ability to be in the CNS in a concentration sufficient to give a therapeutic effect. In two experimental models of ALS, represented by mouse motor neuron cells (NSC34) expressing mutant superoxide dismutase 1 (SOD1) and motor neurons isolated from cases of familial SOD1-associated ALS, CAPE inhibited NF-κB-induced inflammation. CAPE also activated the nuclear factor erythroid 2-related factor 2 (Nrf2)–ARE pathway, which is usually down-regulated in ALS. Genes up-regulated by Nrf2 include GSH-Px, glutathione reductase, heme oxygenase 1 (HO-1); enzymes involved in GSH synthesis, and NADPH-regenerating enzymes. CAPE effects were tested also in an in vivo model of mice expressing a mutant superoxide dismutase ($SOD1^{G93A}$) linked to human ALS. CAPE increased the post-onset survival and lifespan of the mice, showing a significantly greater number of surviving motor neurons and a decreased number of activated microglia and astrocytes in the lumbar region of the spinal cord. In addition, lower levels of phosphorylated p38, a mitogen-activated protein kinase that is involved in both inflammation and neuronal death, were observed in the spinal cords of $SOD1^{G93A}$ mice [25]. Microglial activation has been widely demonstrated to mediate inflammatory processes that are crucial in several neurodegenerative disorders. CAPE was proven to inhibit cyclooxygenase-2 (COX-2) and iNOS expression and the consequent NO production both in in vitro and in vivo models of microglia activation. Anti-neuroinflammatory responses in microglial cells were mediated by 5′-adenosine monophosphate-activated protein kinase (AMPK)α, erythropoietin (EPO), and HO-1 [26].

3.3. Parkinson’s Disease

PD is a neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons of the substantia nigra pars compacta. 6-Hydroxydopamine (6-OHDA) is a neurotoxic synthetic organic compound used to selectively destroy dopaminergic neurons in the brain to induce PD in laboratory animals. The neurotoxicity and neuronal cell death induced by 6-OHDA are due to ROS production, cytochrome c release, and subsequent caspase-3 activation. CAPE increased the viability of cerebellar granule neurons dose dependently and markedly attenuated the 6-OHDA-induced toxicity. CAPE blocked Ca^{2+}-induced cytochrome c release and caspase-3 activation, but no interaction of CAPE with caspase-3 cleavage was found [27]. These results were confirmed in the same cellular model and in rostral mesencephalic neurons (RMNs), where CAPE pretreatment increased neuronal viability from 39% to 91% in CGNs and from 33% to 60% in RMNs. CAPE is able to block 6-OHDA-induced dopaminergic neuronal death through the blockage of O^{2-} and peroxynitrite generation, suggesting its potential use as a neuroprotective drug for PD [28]. With regard to the in vivo experimental models, CAPE inhibited mitochondrial permeability transition, a process that triggers cytochrome c release and caspase-3 activation, leading to neuronal death in rats treated with 6-OHDA to induce PD. The mechanism of protection involves the scavenging of free radicals and metal chelation without mitochondrial dysfunction [29].

CAPE can protect midbrain dopaminergic neurons in vitro and in vivo also by the induction of HO-1 and brain-derived neurotrophic factor (BDNF) expression [30]. Rotenone is commonly used to induce experimental PD because of its ability to block the complex I inhibition and to activate microglia, resulting in neuropathologic and phenotypic features of PD. In a rotenone Parkinsonian mice model, CAPE treatment raised the level of striatal dopamine and lessened the inflammatory burden by suppressing microglia cells and down-regulating the gene expression of COX-2, iNOS, and NF-κB. These effects led to an improvement in locomotor activity. CAPE exposure protected against rotenone-induced histopathological abnormalities and led to an increased number of surviving neurons as well [31]. In a model for PD induced by chlorpyrifos, CAPE showed positive effects on the paraoxonase (PON1) activity, levels of lipid profile, total sialic acid (TSA), total anti-oxidant capacity (TAC), and total oxidant capacity (TOC) in plasma and brain tissue, preventing neurodegeneration [32]. In a murine model of PD induced by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), CAPE attenuated dopaminergic neurodegeneration and dopamine loss. This effect was associated with a marked reduction in iNOS and caspase-1 expression in vivo. In Vitro, CAPE proved able to mitigate neurotoxicity by inhibiting the mitochondrial release of cytochrome c and apoptosis inducing factor (AIF) induced by MPP^+ [33].

3.4. Alzheimer’s Disease

Alzheimer’s disease (AD) is an age-associated neurodegenerative disease that can be induced in rodents by the intracerebroventricular (ICV) administration of a widely used diabetogenic drug, streptozotocin (STZ). Brain PI3-kinase activity and nitric oxide production mediated by the endothelial NOS (eNOS) are involved in the memory revival function of CAPE in STZ-ICV-administered rats. The basal NF-κB activity in the rat brain was found essential for memory functions as well. The anti-apoptotic and pro-survival functions of PI3-kinase activation regulate eNOS and NFκB activity, conferring neuroprotection and improving memory [34]. A previous study by the same group showed that the CAPE down-regulation of oxidative stress and inflammation was accompanied by the amelioration of STZ-ICV-induced dementia. A great increase in the brain GSH levels and a diminution of thiobarbituric acid reactive substances (TBARS) as well as of TNF-α content were observed in the brains of rats treated with CAPE [35]. In another study, amyloid-beta oligomers were administered to mice to induce dementia and to study the AD onset and cognitive function impairment. CAPE treatment reversed cognitive deficits and improved learning and memory abilities. This action was accompanied by an induction of Nrf2 and heme oxygenase-1 via the modulation of glycogen synthase kinase 3β in the murine hippocampus [36].

3.5. Seizures and Psychosis

CAPE is useful as an adjunctive treatment of seizure disorders. Seizures induced by pentylenetetrazole (PTZ) are due to the activation of glutamate receptors and the inhibition of GABA, an inhibitory neurotransmitter. Glutamate receptors’ activation enhances the ROS level, which in turn enhances glutaminergic activity, but the administration of CAPE increased the latency and decreased the duration of seizures in PTZ-treated mice. CAPE protected the brain tissue from oxidative damage because of its ability to scavenge ROS, to decrease MDA concentration, to increase the anti-oxidant SOD level, and to significantly attenuate NO generation [15].

Psychosis has many different causes and can be experimentally induced by dizocilipine maleate (MK-801), which causes neurotoxicity inducing the intracellular generation of free radical species through the N-methyl-D-aspartate (NMDA) receptor blockage. NMDA antagonists mediate cell death triggered by ROS, which are involved in membrane pathology in CNS and play a role in neuropsychiatric disorders, including schizophrenia. In one study focusing on the rat prefrontal cortex (PFC), which is the region mainly affected in schizophrenia, CAPE modulated the brain oxidant/anti-oxidant status, stabilizing the cellular membranous structures. A CAPE therapeutic effect was exerted by decreasing the levels of malondialdehyde, protein carbonyl (PC), and nitric oxide (NO). The activity of the enzymes glutathione peroxidase (GSH-Px), xanthine oxidase (XO), and adenosine deaminase (ADA) in prefrontal tissue were decreased as well, when compared to the MK-801 groups, whereas the catalase activity was not changed. In addition, CAPE treatment decreased the number of apoptotic cells in the PFC exposed to MK-801 [37]. Figure 1 summarizes the molecules involved in the effects exerted by CAPE in different neurological conditions described in the previous paragraphs.

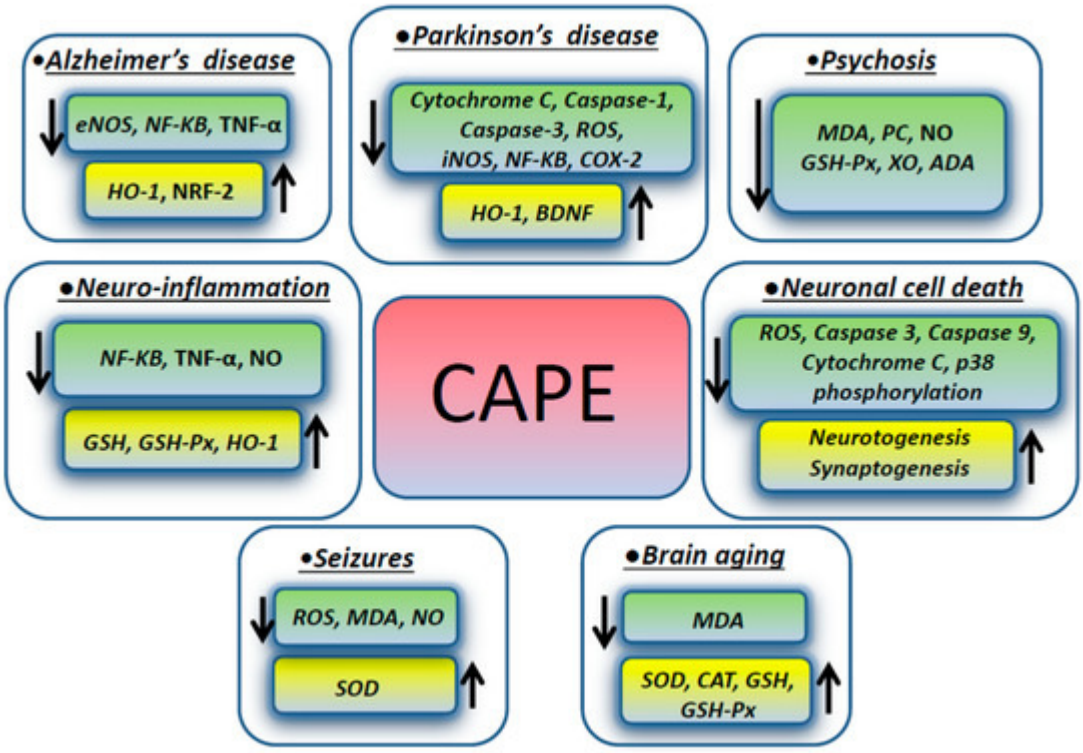

Figure 1. CAPE effects on intracellular molecules and pathways in different neurologic disorders.

3.6. Other Diseases

Some pathological conditions, different from neurodegenerative disorders, such as diabetes, septic shock, and hepatic encephalopathy (HE), can affect the health of the nervous system. Diabetes induces oxidative stress and inflammation in brain. In a murine model, CAPE significantly counteracted the effects of diabetes by decreasing the levels of nitric oxide and malondialdehyde and the activities of catalase, glutathione peroxidase, and xanthine oxidase. CAPE treatment also significantly suppressed the expression of inflammatory cytokines such as TNFα and interferon (IFN)-γ and the iNOS activity, which were remarkably enhanced in the brain by diabetes [38].

Sepsis patients suffer from severe oxidative stress, with the overproduction of reactive oxygen species and reactive nitrogen species, resulting in direct cellular injury. NF-κB plays a central role in the induction of crosstalk between cytokines and inflammatory mediators, which leads to the pathophysiology of septic shock. The effect of CAPE against lipopolysaccharide (LPS) -induced endotoxemia, neuronal damage, and the associated systemic inflammatory response was investigated in male Wistar rats. CAPE prevented neuronal damage and preserved astrocyte morphology, with no sign of inflammatory cellular infiltration, edema, or cytoplasmic swelling. CAPE decreased the levels of inflammatory cytokines (interleukin (IL)-1α, -1β, -6) and TNF-α in the plasma, increased the anti-inflammatory cytokine levels (IL-4, IL-10), and counteracted the imbalance leading to the inhibition of adhesion molecule expression (sICAM-1). This effect of CAPE on the inflammatory cellular infiltration into the brain could be directly attributed to its inhibitory effect on NF-κB activation [39].

Hepatic encephalopathy (HE) is a major neurological complication secondary to severe liver failure, causing serious neurological problems. Thioacetamide-induced HE in rats was almost fully reversed by a combination of CAPE with the laxative lactulose. The survival rates were 37.5% in the HE group, 70% in the HE + lactulose group, 80% in the HE + CAPE group, and 100% in the HE + CAPE + lactulose group. The lack of death in the animals treated with both CAPE and lactulose can be ascribed to the direct neuroprotective effect of CAPE together with the prevention of ammonia production in the body. Increased ammonia, high transaminase levels in blood, increased lipid peroxidation, and decreased antioxidant enzyme activities in most brain regions, along with impaired sensorymotor behavioral tests, were reversed to almost control values in the CAPE + lactulose-treated group [40].

Glaucoma is characterized by the death of retinal ganglion cells (RGCs) and visual field defects leading to irreversible blindness. CAPE prevented optic nerve crush-induced RGC apoptosis and neuroinflammation. These effects are mediated by the decreased expression of the inflammatory cytokines IL-8 and IL-6, inducible nitric oxide synthase, cycloooxygenase-2, tumor necrosis factor-α, and chemokine C-C ligand-2. The hypertrophy of astrocytes and Müller cells (gliosis) was modulated by CAPE through the inhibition of NF-κB signaling [41].

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