β-Caryophyllene in Oxidative Stress and Mitochondrial Dysfunction

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Contributor: Hammad Ullah, Alessandro Di Minno, Cristina Santarcangelo, Haroon Khan, Maria Daglia

Mitochondrial dysfunction results in a series of defective cellular events, including decreased adenosine triphosphate (ATP) production, enhanced reactive oxygen species (ROS) output, and altered proteastasis and cellular quality control. An enhanced output of ROS may damage mitochondrial components, such as mitochondrial DNA and elements of the electron transport chain, resulting in the loss of proper electrochemical gradient across the mitochondrial inner membrane and an ensuing shutdown of mitochondrial energy production. Neurons have an increased demand for ATP and oxygen, and thus are more prone to damage induced by mitochondrial dysfunction. Mitochondrial dysfunction, damaged electron transport chains, altered membrane permeability and Ca^{2+} homeostasis, and impaired mitochondrial defense systems induced by oxidative stress, are pathological changes involved in neurodegenerative disorders. A growing body of evidence suggests that the use of antioxidants could stabilize mitochondria and thus may be suitable for preventing neuronal loss. Numerous natural products exhibit the potential to counter oxidative stress and mitochondrial dysfunction; however, science is still looking for a breakthrough in the treatment of neurodegenerative disorders. *β*-caryophyllene is a bicyclic sesquiterpene, and an active principle of essential oils derived from a large number of spices and food plants. As a selective cannabinoid receptor 2 (CB2) agonist, several studies have reported it as possessing numerous pharmacological activities such as antibacterial (e.g., *Helicobacter pylori*), antioxidant, anti-inflammatory, analgesic (e.g., neuropathic pain), anti-neurodegenerative and anticancer properties.

Keywords: oxidative stress ; mitochondrial dysfunction ; neurodegeneration ; β-caryophyllene ; neuroprotection

1. Introduction

Mitochondrial dysfunction refers to an impairment in mitochondrial function, resulting in a series of defective cellular events including decreased adenosine triphosphate (ATP) production, enhanced reactive oxygen species (ROS) output, altered proteostasis and cellular quality control [1]. Neurons have increased demand for ATP and oxygen, with cortical neurons being known to consume approximately 4.7 billion ATP molecules per second, and thus they are more prone to the damage induced by mitochondrial dysfunction [2]. Such critical requirements for ATP and oxygen make them susceptible to electron leakage from the electron transport chain, resulting in generation of free radicals and induced oxidative stress [3]. Furthermore, lowered levels of antioxidant defenses further increase the neuronal susceptibility to mitochondria induced oxidative damage [4]. In addition, a large ROS output not only damages the biomolecules of the neuronal cells, but also damages mitochondrial components (e.g., mitochondrial DNA) and elements of the electron transport chain, resulting in a loss of electrochemical gradient across the mitochondrial inner membrane and the ensuing shutdown of mitochondrial energy production [5].

The electron transport chain, or mitochondrial respiratory chain, consists of five complexes (complex I, II, III, IV and V) and is one of the major structural and functional components of mitochondria, catalyzing the phosphorylation of adenosine diphosphate (ADP) to ATP [6]. These complexes are comprised of over 80 proteins, 13 of which are encoded by mitochondrial DNA and are components of oxidative phosphorylation [6][7]. Complexes I–IV constitute the electron transport chain, which generates water by oxidation of hydrogen (derived from organic acids like pyruvic and fatty acids) with atomic oxygen [8]. ATP production involves two coordinated processes, including transport of electrons along the complexes to produce water and the pumping of protons across the mitochondrial inner membrane (from matrix to intermembrane space) through complexes I, III and IV. ATP is thus generated by the influx of these protons back to the matrix through complex V [9][10][11]. Under normal physiological conditions, 1.5% of the oxygen may be converted into ROS, which suggests that the majority of intracellular ROS is generated by mitochondria [12]. The production of superoxide and other reactive oxygen species occurs primarily at complexes I and III [13]. Under pathological conditions, the highly reactive hydroxyl ions could damage mitochondrial DNA, proteins, and lipids, resulting in the defective

functioning of complexes I and III, causing superoxide radical formation by increased electron reduction of oxygen, leading to metabolic oxidative stress, genomic instability, and cellular injury [14][15][16][17].

Damaged mitochondrial DNA may decrease the expression of critical proteins of the electron transport chain, amplifying oxidative stress which eventually triggers apoptosis [14]. The electron transport chain is also sensitive to nitrosative stress, as nitration can modify mitochondrial proteins, causing alterations in the functioning of many metabolic enzymes in the electron transport chain, such as nicotinamide adenine dinucleotide (NAD) dehydrogenase, cytochrome c oxidase, and ATP synthase [18]. Most importantly, acute exposure to ROS inactivates the iron-sulfur centers of complexes I, II and III, while chronic exposure can damage cellular and mitochondrial proteins, lipids, and genetic materials [7]. ROS also alters mitochondrial membrane permeability, as the inner membrane is located near the site of ROS production and thus is more prone to lipid peroxidation [19]. Peroxidation of mitochondrial phospholipids may increase the proton permeability of the inner membrane, which under normal physiological conditions is permeable only to tiny neutral molecules [20]. Increased membrane permeability could lead to altered fluidity, as well as impaired biochemical functions of numerous transporters and enzymes present in mitochondrial membranes [12].

Mitochondria play a critical role in regulating neuronal Ca^{2+} homeostasis, and genetic and pharmacologic manipulations enhancing mitochondrial Ca^{2+} sequestration may protect neuronal cells against excitotoxicity [21]. Excessive ROS generation alters mitochondrial Ca^{2+} homeostasis, where peroxynitrite inactivates key mitochondrial enzymes, affecting the energy status of the cell and triggering the release of Ca^{2+} from the mitochondria [22]. Elevated Ca^{2+} levels cause a shift in mitochondrial potential and result in the production of superoxide radicals which may lead to a vicious cycle. Changes in mitochondrial permeability in Ca^{2+} overloaded mitochondria result in osmotic swelling and the rupture of the outer mitochondrial membrane [23]. ROS production in mitochondria further promotes Ca^{2+} uptake and enhances membrane permeability, and eventually results in the release of cytochrome c and the initiation of apoptosis [24]. **Figure 1** depicts the links between oxidative stress and mitochondrial dysfunction, and their possible impact on aging and disease development and progression.

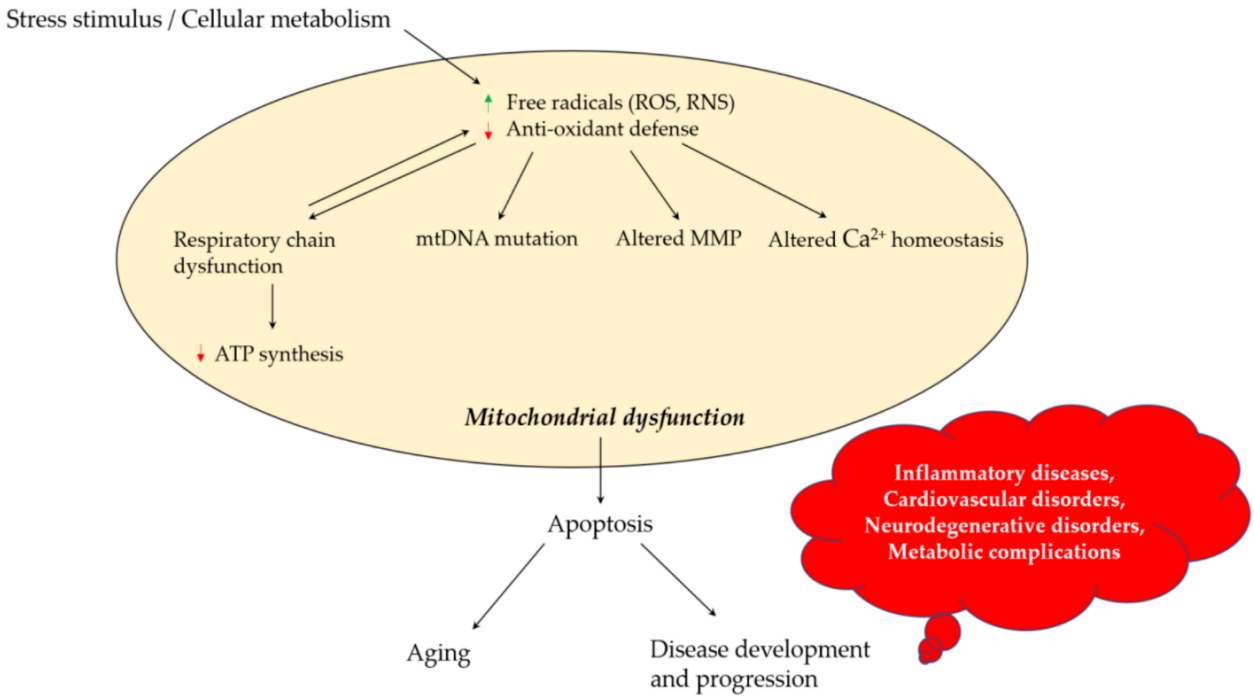

Figure 1. Mitochondrial dysfunction and its contribution towards aging and disease development and progression. Stress stimulus and irregular cellular metabolism may lead to the increased production of ROS and RNS, and decreased antioxidant defense parameters, which eventually result in mitochondrial dysfunction due to a defective mitochondrial respiratory chain, mutation in mtDNA, altered MMP and influenced Ca^{2+} homeostasis. These events could promote apoptosis, paving the road for aging and disease development and progression. ROS, reactive oxygen species; RNS, reactive nitrogen species; mtDNA, mitochondrial DNA; MMP, mitochondrial membrane potential; ATP, adenosine triphosphate.

2. Chemistry and Vegetable Sources of β-Caryophyllene

β-caryophyllene (**Figure 2**) is a bicyclic sesquiterpene, mainly occurring in the form of trans-caryophyllene in combination with small amounts of its isomers (iso-caryophyllene and α-caryophyllene or α-humulene) and its oxidative derivative β-caryophyllene oxide. β-caryophyllene and β-caryophyllene oxide are compounds with a strong wooden odor and are approved as flavorings by the Food and Drug Administration (FDA) and European Food Safety Authority (EFSA) [25]. β-caryophyllene exhibits low water solubility and thus aqueous media such as biological fluids decrease its absorption to the cell. However, the potential obstacles associated with its low water solubility can be overcome by liposomal formulation techniques, which could increase its bioavailability and ensure the desired biological cell effects [26]. β-caryophyllene is a major active principle of essential oils derived from a large number of spices and food plants (**Table 1**). As reported in the Essential Oil Database, in nature β-caryophyllene is commonly found in *Ocimum basilicum* L., *Cinnamomum* species, *Piper nigrum* L., *Syzygium aromaticum* (L.) Merr. and L.M. Perry, *Cannabis sativa* L., *Lavandula angustifolia* Mill., *Origanum vulgare* L., and *Rosmarinus officinalis* L. [27].

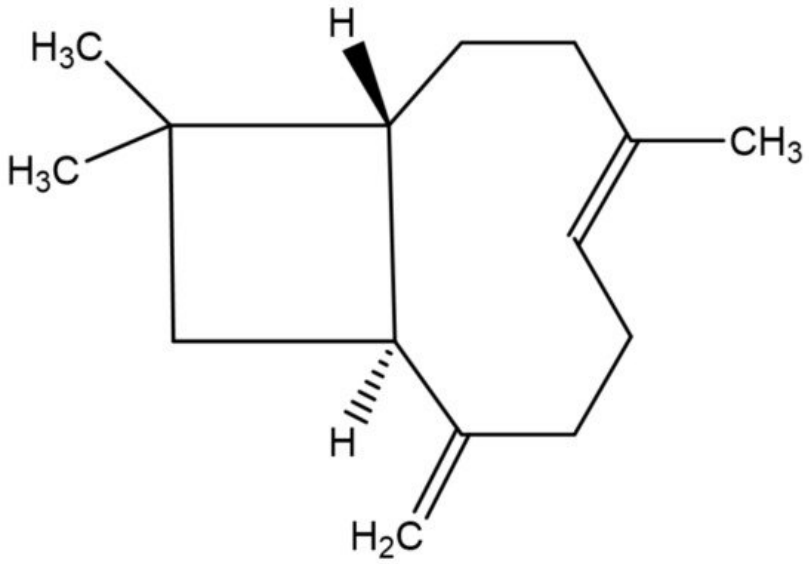

Figure 2. Chemical structure of β-caryophyllene.

Table 1. Vegetable sources of β-caryophyllene and percentage composition of their essential oils (data extracted from the Essential Oil Database) [27].

Botanical Name	Family	Active Parts	Percentage [1]
***Ocimum basilicum* L.**	**Lamiaceae**	**Leaf**	**0.3–3.1**
***Cinnamomum* species**	**Lauraceae**	**Leaf/bark [a]**	**0.2–35.9 [a]**
***Piper nigrum* L.**	**Piperaceae**	**Berries/Leaf/stem [b]**	**3.3–46 [b]**
***Syzygium aromaticum* (L.) Merr. and L.M. Perry**	**Myrtaceae**	**Floral bud**	**3.2**
***Cannabis sativa* L.**	**Cannabaceae**	**Whole plant (fresh material)**	**3–16.2**
***Lavandula angustifolia* Mill.**	**Lamiaceae/labiatae**	**Flower and stem**	**1.08**
***Lavandula angustifolia* Mill.**	**Lamiaceae/labiatae**	**Whole plant**	**0.3**
***Origanum vulgare* L.**	**Lamiaceae/labiatae**	**Leaf/Stem/Flower/Whole plant[c]**	**0.4–24.5 [c]**
***Rosmarinus officinalis* L.**	**Lamiaceae**	**Aerial parts**	**0.5–13.6**

[1] Percentage of the compound calculated by comparing the gas chromatographic peak area of the analyte with the total area of all detected peaks. [a] Depending upon different species. [b] Depending upon different cultivars. [c] Depending upon sub-species.

3. β-Caryophyllene: Alteration of Oxidative Stress and Mitochondrial Dysfunction

A number of studies have suggested the alteration of oxidative stress and mitochondrial dysfunction by β-caryophyllene and β-caryophyllene-containing vegetable extracts, as one of the potential mechanisms in protecting neurons from degeneration [28]. Chávez-Hurtado et al. (2020) observed a reduction in DNA oxidation and overexpression of glial fibrillary acidic proteins with β-caryophyllene (10 mg/kg, p.o. for 4 weeks) in the prefrontal cortex and hippocampus of BALB/c mice withd-galactose induced aging [29]. In an in vivo model of PD, β-caryophyllene (50 mg/kg, i.p. for 4 weeks) ameliorated oxidative stress (restored antioxidant enzymes, increased GSH, and inhibited lipid peroxidation), neuroinflammation (decreased levels of IL-1β, IL-6, and TNF-α, and downregulated COX-2 and iNOS expression), and glial activation as well as rescuing dopaminergic neurons [30].

Javed et al. investigated the CB2 receptor mediated neuroprotective effects of β-caryophyllene in a rotenone induced animal model of PD [31]. Rotenone (2.5 mg/kg) induced a significant loss in dopaminergic neurons in the substantia nigra pars compacta and dopaminergic striatal fibers, following the activation of astrocytes and microglia when injected peritoneally once daily for 4 weeks. Moreover, rotenone downregulated antioxidant enzymes, increased nitrite levels and induced proinflammatory cytokines (IL-1β, IL-6 and TNF-α) and inflammatory mediators (NF-κB, COX-2, and iNOS). Supplementation with β-caryophyllene (50 mg/kg once daily for 4 weeks, 30 min prior to rotenone administration) attenuated the induction of pro-inflammatory cytokines and inflammatory mediators, prevented the depletion of glutathione, reduced lipid peroxidation, and augmented antioxidant enzymes (SOD and CAT). Tyrosine hydroxylase immunohistochemistry showed the rescue of dopaminergic neurons and fibers following decreased activation of glial cells.

β-caryophyllene protected C6 glioma cells from glutamate induced cytotoxicity through alteration of antioxidant responses, mainly by inhibition of ROS production and restoration of MMP via CB2 receptor dependent nuclear factor erythroid 2–related factor 2 (Nrf2) activation [32]. In a neurovascular unit model of oxygen-glucose deprivation and re-oxygenation—induced injury, β-caryophyllene significantly decreased blood–brain barrier (BBB) permeability, reduced neuronal apoptosis, relieved oxidative stress damage, decreased secretion of inflammatory cytokines, downregulated metalloproteinase-9 expression/activity and Bcl-2-associated X protein (Bax) expression, and upregulated expression of claudin-5, occludin, zonula occludens-1 (ZO-1), growth-associated protein-43 (GAP-43) and B-cell lymphoma 2 (Bcl-2) [33]. Conversely, β-caryophyllene relieved seizures in mice induced by pentylenetetrazole, but anti-convulsant doses (0, 10, 30, and 100 mg/kg i.p.) showed no benefits over pentylenetetrazole related oxidative stress i.e., thiobarbituric acid-reactive substances and nonprotein thiol content [34].

Lou et al. (2016) found an attenuation of focal cerebral ischemia-reperfusion injury in rats by treatment with β-caryophyllene through enhanced expression of Nrf2 and HO-1, and restored activity and expression of antioxidant enzymes, i.e., superoxide dismutase (SOD) and catalase (CAT) [35]. In C57BL/6 mice, β-caryophyllene ameliorated the development of experimental autoimmune encephalomyelitis through inhibiting the production of hydrogen peroxide (H2O2), IFN-γ, TNF-α, IL-17 and NO, and decreasing the number of inflammatory infiltrates and neurological damage [36]. An in vitro study demonstrated the alleviation of 1-methyl-4-phenylpyridinium induced neurotoxicity by β-caryophyllene through restoring MMP and increasing intracellular activity of GSH and glutathione peroxidase (GPx), where antioxidant effects were found to be CB2 receptor dependent [37]. Apoptosis was prevented in same study by inhibition of the up-regulation of caspase-3 and Bax, restoring Bcl-2 expression, and suppressing heme oxygenase-1 (HO-1) activation and c-Jun *N*-terminal kinase (JNK) phosphorylation.

Pinus halepensis Mill. essential oil attenuated Alzheimer's toxic Aβ (1-42)-induced memory impairment and oxidative stress in rat hippocampus [38]. Inhalation of *P. halepensis* essential oil (1 and 3%) for 21 days resulted in the inhibition of hippocampal AChE activity, elevation of hippocampal antioxidant markers (SOD, CAT, GPx and GSH), and attenuation of Aβ-induced elevation of malondialdehyde (MDA) levels. Phytochemical screening of essential oils revealed the presence of 45 different compounds, with 33 of those compounds having been identified and quantified. Sesquiterpenes (β-caryophyllene) and monoterpenes (α-pinene, myrcene, terpinolene, and 2-phenylethylisovalerate) were the most abundant compounds present in the essential oil, while diterpenes (mainly cembrene) represent only 2.50% of the phytochemicals present. More importantly, β-caryophyllene was found to be the most abundant compound present with the highest percentage of 29.45%.

Essential oils extracted from the dried leaves of *Aloysia citrodora* Palau displayed significant antioxidant and protective effects against both H_2O_2 and Aβ-induced neurotoxicity in CAD neuroblastoma cell lines [39]. H_2O_2 (250 µM) and Aβ (10 µM) failed to elicit neurotoxic responses in the presence of *A. citrodora* essential oil (0.01 and 0.001 mg/mL). The in vitro antioxidant effects of *A. citrodora* essential oil was confirmed by its Fe^{2+} chelating capacity. The major chemical

components detected in this essential oil were limonene, geranial, neral, 1, 8-cineole, curcumene, spathulenol and caryophyllene oxide.

The clove oil obtained from *Syzygium aromaticum* (L.) Merr. and L.M. Perry is known to contain eugenol as its most abundant compound (87.34%), with eugenol acetate (5.18%) and *β*-caryophyllene (2.01%) being present in smaller amounts [40]. Kumar et al. reported the neuroprotective potential of clove oil in intra-cerebroventricular (ICV) colchicine-induced memory impairment in rats [41]. Treatment of colchicine challenged rats with *S. aromaticum* (0.05 mL/kg and 0.1 mL/kg, i.p.) significantly improved cognitive dysfunction, with a marked reduction of AChE activity, lipid peroxidation levels, and nitrite concentrations, and restoration of GSH and mitochondrial respiratory enzyme complex (I–IV) activities. Authors linked the attenuation of cognitive dysfunction with antioxidant and mitochondrial restoring mechanisms. *Hyptis fruticosa* Salzm. ex Benth (also known as *Eplingiella fruticosa*) leaf essential oil (containing *β*-caryophyllene, bicyclogermacrene and 1,8-cineole), complexed with *β*-cyclodextrin, showed neuroprotective effects in a mouse model of PD by decreasing membrane lipid peroxide levels in the striatum and preserving dopaminergic depletion in the striatum and substantia nigra pars compacta, when administered at a dose of 5 mg/kg, p.o. for 40 days [42].

Ocimum basilicum L. essential oil attenuated ethidium bromide-induced cognitive deficits as well as neuroinflammation, astrogliosis and mitochondrial dysfunction in the prefrontal cortex of rats, with induced MS like manifestations [43]. *O. basilicum* (100 and 200 µL/kg) significantly mitigated ethidium bromide-induced neuroinflammation by increasing the levels of proinflammatory cytokines (TNF-α and IL-6) and astrogliosis by increasing (Glial fibrillary acidic protein (GFAP) and Ionized calcium binding adaptor molecule-1 (Iba-1) levels. In addition, mitochondrial function, integrity, respiratory control rate, ATP production, and mitochondria-dependent apoptosis were positively regulated in the prefrontal cortex of rats by treatment with *O. basilicum*. Chemical analysis of the essential oil derived from *O. basilicum* L. demonstrated the presences of several phytoconstituents, with methyl chavicol, geranial, neral and caryophyllene oxide being major components [44]. *Salvia rosmarinus* Spenn. essential oil (comprised chemically of 1,8-cineole, α-pinene, camphor, and trans-caryophyllene) exhibited strong antioxidant effects evaluated by DPPH, ABTS, FRAP and *β*-carotene bleaching tests and confirmed by the relative antioxidant capacity index and significant acetylcholinesterase (AChE) inhibitory activities, suggesting neuroprotective potential in patients with AD [45].

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