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Natural products targeting mitochondria: emerging therapeutics for age-associated neurological disorders

Zhibin Liang[a,b,*], **Antonio Currais**[a], **David Soriano-Castell**[a], **David Schubert**[a,b], **Pamela Maher**[a,*]

[a]Cellular Neurobiology Laboratory, The Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, California 92037, United States

[b]The Paul F. Glenn Center for Biology of Aging Research, The Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, California 92037, United States

Abstract

Mitochondria are the primary source of energy production in the brain thereby supporting most of its activity. However, mitochondria become inefficient and dysfunctional with age and to a greater extent in neurological disorders. Thus, mitochondria represent an emerging drug target for many age-associated neurological disorders. This review summarizes recent advances (covering from 2010 to May 2020) in the use of natural products from plant, animal, and microbial sources as potential neuroprotective agents to restore mitochondrial function. Natural products from diverse classes of chemical structures are discussed and organized according to their mechanism of action on mitochondria in terms of modulation of biogenesis, dynamics, bioenergetics, calcium homeostasis, and membrane potential, as well as inhibition of the oxytosis/ferroptosis pathway. This analysis emphasizes the significant value of natural products for mitochondrial pharmacology as well as the opportunities and challenges for the discovery and development of future neurotherapeutics.

Keywords

Natural products; mitochondrial dysfunction; oxytosis/ferroptosis; aging; neurological disorders; neuropharmacology; drug discovery

1. Introduction

Neurological disorders affect nearly 50 million people worldwide (WHO, 2017). However, there are no drugs for any of these conditions that are disease modifying in the sense that

*To whom correspondence should be addressed: Cellular Neurobiology Laboratory, The Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, California 92037, United States. zliang@salk.edu (Z. Liang), pmaher@salk.edu (P. Maher).

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they slow down or revert the progression of the neuropathological process (Bellantuono, 2018; Gauthier, et al., 2016). Aging leads to progressive and detrimental changes in the brain and old age is the greatest risk factor for many neurological disorders such as Alzheimer's (AD), Parkinson's (PD), and Huntington's diseases (HD) as well as stroke. Therefore, the aging process must be taken into account in order to understand the molecular and cellular basis of neurological disorders (Hou, et al., 2019; López-Otín, Blasco, Partridge, Serrano, & Kroemer, 2013). Many have argued that deficits in cerebral bioenergetics and metabolism associated with aging are central to the development of cognitive decline (Butterfield & Halliwell, 2019; Currais, 2015; Kapogiannis & Mattson, 2011; Schubert, 2005). Mitochondria are the primary source of energy in the brain, and their impairment has been implicated in the aging process and to a greater extent in neurological disorders (Chan, 2006; Nunnari & Suomalainen, 2012). However, relatively little progress has been made towards preventing mitochondrial dysfunction to promote cognition and brain health (Lin & Beal, 2006; Murphy & Hartley, 2018). It is therefore of crucial importance to investigate the detrimental changes that take place in mitochondria with aging as well as that are exacerbated by disease or injury and, based on this knowledge, to develop therapeutic interventions for neurological disorders.

Natural products, defined as small molecule compounds from natural sources such as plants, animals, and microorganisms, have been used for the treatment of human diseases for thousands of years and they have proven to be a valuable source of new drugs. According to the latest statistics of the US-FDA approved drugs, many prescription medicines in the clinic today are derived from natural products (Newman & Cragg, 2020). Over the past decade, the identification of natural products that target mitochondrial function has become an emerging field in drug discovery. An early review by Biasutto et al. drew attention to the mitochondrial effects of selected plant dietary compounds (Biasutto, Szabo', & Zoratti, 2011). These natural products include potential therapeutics to stimulate mitochondrial biogenesis, modulate mitochondrial dynamics, improve mitochondrial bioenergetics and metabolism, sustain mitochondrial membrane potential and calcium homeostasis, and resolve imbalances in the mitochondrial redox status with aging. In the present review, we cover up-to-date research articles published within the last ten years on neuroprotective natural products from plant, animal, and microbial sources, with a specific focus on their reported bioactivities on mitochondria. In addition, some examples from our own research focused on natural product-based drug discovery for AD therapies are highlighted.

The literature search was performed with the SciFinder (Chemical Abstracts Service) and PubMed (National Institutes of Health) databases from January 2010 to May 2020, resulting in a total of 127 natural products spanning over 240 references on relevant topics. For clarity, the neuroprotective natural products are categorized into groups based on their structural classes and modes of action on mitochondria. Anticancer natural products that induce mitochondrial toxicity and apoptosis, as well as natural products that have no published reports for their positive effects on the nervous system were excluded from this review. In addition, biochemical/pharmacological investigations on natural product extracts whose bioactive chemical identities were not described were also excluded. Finally, we discuss our views on the potential use of these natural products in mitochondrial pharmacology and future drug development for the treatment of age-associated neurological disorders.

1.1. A key role for mitochondria in brain health

The human brain is a unique organ in that it consumes about 20% of the total oxygen and up to 25% of the total energy required by the body, yet it represents only 2% of the body mass (Bélanger, Allaman, & Magistretti, 2011; Schubert, 2005). The brain comprises a heterogeneous mixture of cell types including neurons, the main cell type responsible for neurotransmission, and glial cells (i.e., astrocytes, oligodendrocytes, and microglia), mostly involved in supporting brain functions. To fulfill the high energy demand required for synaptic transmission and other vital neuronal activities in the brain, neurons and glia rely on mitochondria, the “powerhouse” of the cell (Bélanger, et al., 2011; Harris, Jolivet, & Attwell, 2012).

Mitochondria are the primary source of adenosine triphosphate (ATP) which fuels energy-dependent biochemical reactions in the whole body, particularly in the brain. A majority of the ATP is produced by consuming glucose and oxygen via the Krebs cycle and oxidative phosphorylation (OXPHOS) within the brain mitochondria. Along with ATP biosynthesis, mitochondria play an essential role in numerous neuronal functions such as the maintenance of neuronal redox homeostasis, membrane potential and ion balance for synaptic signaling, exchange of neurotransmitters, as well as neuronal survival and death (Grimm & Eckert, 2017).

Owing to the multiple and crucial tasks that mitochondria execute in the central nervous system (CNS) to keep the brain functioning properly, mitochondrial dysfunction has been associated with almost every neurological disorder as well as with the aging process (Cunnane, et al., 2020; Lin & Beal, 2006). Although the underlying mechanisms by which mitochondrial dysfunction participates in such a wide range of age-related neurological disorders remain elusive, energy deficits with aging may contribute to neurodegeneration (Hou, et al., 2019; Lin & Beal, 2006) and ischemic stroke (Yousufuddin & Young, 2019), along with other neuropathological conditions, by disrupting neuronal activities in affected areas of the brain. Therefore, developing therapies to treat mitochondrial disturbances in age-associated neurological disorders is an attractive pursuit.

1.2. Mitochondrial dysfunction in age-associated neurological disorders

A growing body of preclinical and clinical evidence indicates that damage and dysregulation of mitochondrial structure and function in brain cells appear to be relevant to the pathogenesis of age-associated neurological disorders including AD, PD, HD, frontotemporal dementia (FTD), Lewy body dementia (LBD), amyotrophic lateral sclerosis (ALS), Friedreich’s ataxia (FRDA), as well as brain ischemia (Cunnane, et al., 2020; Lin & Beal, 2006; Yang, Mukda, & Chen, 2018). The high energetic activity of postmitotic neurons in the brain inevitably results in the progressive accumulation of toxic byproducts such as mitochondrial DNA (mtDNA) mutations, oxidative stress, and neurotoxic metabolites in mitochondria over time with aging (Terman, Kurz, Navratil, Arriaga, & Brunk, 2010). Therefore, neurons are believed to be more prone to mitochondrial pathologies (Grimm & Eckert, 2017). Since the incidence of many neurological disorders rises exponentially in the population above the age of 65 (WHO, 2017), it has been postulated that mitochondrial dysfunction could be one of the driving factors that contribute to the onset and progression

of these disorders (Chan, 2006; Currais, 2015). Below, we discuss four common age-associated neurological disorders (AD, PD, HD, and stroke) and their associated mitochondrial pathology.

1.2.1. Alzheimer's disease—With respect to clinical and post-mortem information in AD, it has been shown that the mitochondrial electron transport chain (ETC) complexes as well as the mitochondrial translocase of the outer membrane (TOM) and the translocase of the inner membrane (TIM) complexes show a significant reduction in activity, causing dysregulation of OXPHOS, ATP depletion, and accumulation of reactive oxygen species (ROS) in the brain tissues of AD patients (Devi, Prabhu, Galati, Avadhani, & Anandatheerthavarada, 2006; Pérez-Gracia, Torrejón-Escribano, & Ferrer, 2008; Reichmann, Fhirke, Hebenstreit, Schrubar, & Riederer, 1993). In addition, studies using *in vitro* and *in vivo* disease models have demonstrated a causative association between mitochondrial dysfunction and the disease. For instance, it has been shown that the toxic β-amyloid (Aβ) oligomers in neurons or amyloid deposits in transgenic AD mouse models can cause loss of the mitochondrial membrane potential ($\Delta\Psi m$), increase ROS, trigger influx of mitochondrial Ca^{2+}, lower ATP levels, and reduce the mitochondrial respiratory rate, which eventually results in memory loss and cognitive impairment (Behl, Davis, Lesley, & Schubert, 1994; Huang, et al., 2020; Perez Ortiz & Swerdlow, 2019).

1.2.2. Parkinson's disease—Mitochondrial defects are well-known for their clinical relevance in PD and related parkinsonism (Langston, Ballard, Tetrud, & Irwin, 1983; Subramaniam & Chesselet, 2013). In cell and rodent models mimicking the pathological features of PD, neurotoxins like 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), paraquat, and rotenone interfere with the mitochondrial ETC complexes, reduce ATP production, induce ROS production, and eventually lead to mitochondrial dysfunction and the irreversible damage of dopaminergic neurons (Blandini & Armentero, 2012; Dauer & Przedborski, 2003; Pienaar & Chinnery, 2013). These toxins achieve their neurotoxicity by distinct mechanisms due to their chemical variance, biological affinity, and cellular uptake pathways. For example, MPTP is first metabolized to 1-methyl-4-phenylpyridinium (MPP+) by monoamine oxidase B in astrocytes and then selectively transported by the dopamine transporter into dopaminergic neurons where MPP+ inhibits the mitochondrial complex I (Mizuno, Sone, & Saitoh, 1987). Rotenone targets mitochondria directly and is a systemic inhibitor of the mitochondrial complex I (Betarbet, et al., 2000). Paraquat enters the mitochondrial matrix driven by $\Delta\Psi m$ and is then reduced to monocation radicals by the mitochondrial complex I, where it subsequently triggers mitochondrial ROS production (Cochemé & Murphy, 2008). 6-OHDA is not a complex I inhibitor per se, and it primarily affects redox cycling and promotes ROS-induced neurotoxicity (Blum, et al., 2001). Regarding transgenic animal models of PD, the MitoPark mice were created by selective inactivation of mitochondrial transcription factor A (TFAM) in midbrain dopaminergic neurons (Ekstrand, et al., 2007). TFAM is a nuclear-encoded protein that translocates to mitochondria and controls vital parameters of mtDNA such as expression, copy number regulation or repair (Larsson, et al., 1998). The loss of TFAM in the MitoPark mice results in a dramatic disruption of the expression of genes encoded by mtDNA, such as cytochrome *c* oxidase, causing ETC deficiency. This model recapitulates

key features of a sporadic PD-like phenotype in humans, including the progressive, age-dependent loss of dopaminergic neurons, particularly in the substantia nigra, and decline of motor function, along with the presence of intraneuronal inclusions such as mitochondrial protein and membrane components (Ekstrand & Galter, 2009; Ekstrand, et al., 2007). These inclusions in the mice do not contain α-synuclein and hence are different from the Lewy bodies observed in PD patients. However, recent findings on post-mortem PD brains have shown that Lewy bodies containing misfolded protein aggregates (i.e., α-synuclein) also include membranes from mitochondria (Shahmoradian, et al., 2019), suggesting a role for dysfunctional mitochondria in the formation of these inclusions and the progression of the disease in PD patients.

1.2.3. Huntington's disease—Mitochondrial dysfunction also plays a role in the pathology of HD (Costa & Scorrano, 2012; Intihar, Martinez, & Gomez-Pastor, 2019). For instance, mitochondrial biogenesis has been shown to be compromised in HD. Transcriptional and protein levels of the peroxisome proliferator-activated receptor- γ coactivator 1α (PGC-1α), a key activator of mitochondrial biogenesis and respiration, are decreased in post-mortem samples from HD patients (Cui, et al., 2006; Johri, Chandra, & Flint Beal, 2013). Moreover, mutant huntingtin protein has the ability to trigger mitochondrial fission and a number of proteins controlling mitochondrial dynamics are altered in patients as well as in different models of HD (Costa, et al., 2010; Guo, et al., 2013; Shirendeb, et al., 2011; Song, et al., 2011). Finally, several studies reported impairment of mitophagy with huntingtin-induced neurotoxicity in both *in vitro* and *in vivo* models of HD (Franco-Iborra, et al., 2020; Guo, et al., 2016).

1.2.4. Brain ischemic/hemorrhagic stroke—Mitochondrial damage is one of the hallmarks in acute neurological disorders such as ischemic or hemorrhagic strokes (Campbell, et al., 2019; Yang, et al., 2018), where age is a major risk factor for the disorders (Yousufuddin & Young, 2019). Ischemic stroke deprives parts of the brain from glucose and oxygen while disturbing mitochondrial energetic and redox homeostasis and consequently leading to neuronal death (Campbell, et al., 2019; Yang, et al., 2018). In intracerebral hemorrhage, blood emerging from ruptured vessels causes immediate neuronal tissue destruction and secondary damage due to an excessive inflammatory response and an increase in ROS production (Qu, Chen, Hu, & Feng, 2016). It has been shown that exposure of neurons to hemoglobin can induce lipid peroxidation, free radical formation, and release of free iron, while causing necrotic, apoptotic and ferroptotic neuronal death (Zille, et al., 2017). In addition, defects in mitochondrial biogenesis and dynamics have been reported in rodent models of ischemic stroke associated with neuronal death (Ren, et al., 2019; Zhou, Wang, Li, Yu, & Zhao, 2018).

2. Natural product-based neurotherapeutics targeting mitochondrial dysfunction

As discussed above, extensive experimental and clinical investigations have revealed that aberrant brain alterations in mitochondria occur in neurological disorders. Thus, searching for neurotherapeutics that protect mitochondria in the CNS may be a promising approach for

developing effective treatments (Andreux, Houtkooper, & Auwerx, 2013; Murphy & Hartley, 2018; Schubert, et al., 2018). Herein, we summarize the available literature from the past ten years on natural products from plant, animal, and microbial origins that have shown promising results for their neuroprotective effects on diverse aspects of mitochondrial biology.

2.1. Modulation of mitochondrial biogenesis

Mitochondrial biogenesis is a complex process that results in the generation of new mitochondria and involves over 150 proteins including transcription factors, enzymes, and receptors. Among them, PGC-1α, AMP-activated protein kinase (AMPK), and sirtuin-1 (SIRT1) are the three major cooperating players in mitochondrial biogenesis (Figure 1) (Cantó, et al., 2009; Herzig & Shaw, 2018; Lin, Handschin, & Spiegelman, 2005). PGC-1α is a positive regulator of mitochondrial biogenesis and metabolism. In mammalian cells, PGC-1α is activated sequentially by SIRT1 (deacetylation) and AMPK (phosphorylation). PGC-1α then binds to peroxisome proliferator-activated receptor- γ (PPARγ) and activates the nuclear respiratory factors (NRF-1 and NRF-2) to induce the expression of mitochondrial genes (e.g., proteins of the Krebs cycle and OXPHOS system). PGC-1α also up-regulates multiple nuclear-encoded proteins such as TFAM, DNA polymerase γ (POLG), Twinkle helicase, and the mitochondrial single stranded binding protein (mtSSB), which are responsible for the transcription, replication, and packaging of mtDNA in mitochondria (Scheibye-Knudsen, Fang, Croteau, Wilson, & Bohr, 2015) (Figure 1). Because mitochondrial biogenesis is impaired with aging and in associated neurological disorders (Whitaker, Corum, Beeson, & Schnellmann, 2016), identifying therapeutic compounds that induce mitochondrial biogenesis through modulation of the SIRT1-AMPK-PGC-1α pathway may be beneficial towards preventing pathology.

Many natural products have been reported to modulate mitochondrial biogenesis and have shown efficacy in multiple *in vitro* and *in vivo* models of neuropathology (Table 1). One widely studied compound that has shown neuroprotection through modulation of mitochondrial biogenesis signaling is the polyphenol resveratrol from the berries of *Vaccinium* species and other plants. Resveratrol has been shown to stimulate mitochondrial biogenesis by activating the SIRT1-AMPK-PGC1-α axis in cell and animal models of AD (Porquet, et al., 2014), PD (Ferretta, et al., 2014), and Down's syndrome (Valenti, et al., 2016). Resveratrol also prevented cerebral mtDNA deletion and cognitive impairment in the brains of senescence accelerated mice prone 8 (SAMP8), a model of age-associated dementia (Liu, Zhang, Yang, & He, 2012). The resveratrol dimer, ε-viniferin from *Vitis vinifera*, attenuated the neurotoxicity of the huntingtin protein and promoted mitochondrial biogenesis in cell models of HD (Fu, et al., 2012).

Curcumin, a diarylheptanoid found in turmeric (*Curcuma longa*), has also shown promise for inducing mitochondrial biogenesis in several disease models. Curcumin stimulated the expression of the mitochondrial biogenesis genes PGC1-α, NRF-1, NRF-2, and TFAM in Aβ-treated human SH-SY5Y neuroblastoma cells (Reddy, et al., 2016). Another study showed that curcumin attenuated neuronal death and prevented cerebral ischemia/

reperfusion injury with concomitant increases in mitochondrial mass and expression of the mitochondrial biogenesis regulators NRF-1 and TFAM in rat brains (Liu, et al., 2014).

A number of flavonoids belonging to different structural classes are potential simulators of mitochondrial biogenesis. The flavonol quercetin, found in many fruits and vegetables, was able to increase mitochondrial mass and mtDNA content in mouse dopaminergic MN9D cells as well as in the MitoPark mouse model of PD, where it stimulated expression of PGC-1α, TFAM, and cytochrome B that are responsible for mitochondrial biogenesis (Ay, et al., 2017). The flavanonol dihydromyricetin from *Ampelopsis grossedentata* has been shown to protect against neurodegeneration and memory impairment in rats subjected to cerebral hypoxia-ischemia, where it increased PGC-1α and TFAM expression in hippocampal neurons (Liu, et al., 2016). The flavone baicalein from *Scutellaria baicalensis* was found to stimulate the expression of PGC-1α, NRF-1, and TFAM in the substantia nigra of rotenone-treated PD rats and to improve their motor behavior (Zhang, et al., 2017). Epigallocatechin-3-gallate (EGCG), commonly found in green tea, is an ester of epigallocatechin and gallic acid. Research showed that EGCG promoted neuronal mitochondrial biogenesis by activating SIRT1/AMPK/PGC-1α signaling in hippocampal neural progenitor cells from the Ts65Dn mouse model of Down's syndrome as well as in primary fibroblasts from Down's syndrome patients (Valenti, et al., 2013).

Observations of induced mitochondrial biogenesis were also noted for plant-derived flavonoid glycosides. Isoorientin is a 6-*C*-glycosylflavone found in corn, passion flower, and Fenugreek seed. Isoorientin and its derivatives have been shown to protect from amyloid and tau toxicities in the SH-SY5Y neuronal cells and APP/PS1 mouse model of AD, where their neuroprotective mechanisms work in part due to the promotion of mitochondrial biogenesis (Liang, Zhang, Su, Williams, & Li, 2016; Ziqubu, et al., 2020). Icariin, a prenylated flavonol glucoside from *Epimedium grandiflorum*, protected against rotenone-induced loss of dopaminergic neurons in the rat substantia nigra through up-regulation of PGC-1α expression (Zeng, Wang, et al., 2019). Salidroside, a simple phenolic glucoside from *Rhodiola rosea*, has been shown to protect from hypoxia-induced neurodegeneration and memory impairment, where it was found to increase PGC-1α, AMPK and SIRT1 expression and mtDNA content in the rat hippocampus (Barhwal, Das, Kumar, Hota, & Srivastava, 2015).

β-Lapachone is a naphthoquinone that was isolated from the bark of the lapacho tree *Tabebuia avellanedae*. This compound prevented behavioral and cognitive impairments in the R6/2 mouse model of HD and enhanced mitochondrial biogenesis through up-regulation of SIRT1 and deacetylation of PGC-1α in neuronal stem cells in the R6/2 HD brain (Lee, Ban, Chung, Im, & Kim, 2018). Embelin is a naturally occurring *p*-benzoquinone isolated from berries and other fruits. A recent study showed that embelin induced mitochondrial biogenesis via activation of SIRT1 and protected from MPTP-induced neurotoxicity in cellular and mouse models of PD (Rao, Sharma, & Kalivendi, 2020).

Studies also showed that phytocannabinoids such as Δ^9-tetrahydrocannabinol (Δ^9-THC) from *Cannabis sativa* L. prevented cell death induced by MPP+ toxicity in the SH-SY5Y cell model of PD by stimulating the expression of PGC-1α, NRF-1, and TFAM, and increasing

mtDNA content (Zeissler, et al., 2016). Δ^9-Tetahydrocannabinolic acid (Δ^9-THCA) was shown to rescue cell viability against mutant huntingtin protein induced toxicity in the ST*Hdh* and N2a neuronal cell models of HD, where it up-regulated the expression of PGC-1α and increased mitochondrial mass in cells (Nadal, et al., 2017).

In addition to phenolic compounds, plant-derived terpenoids were found to induce mitochondrial biogenesis. For example, the triterpenoid asiatic acid from *Centella asiatica* showed neuroprotective effects against glutamate, rotenone, and α-synuclein toxicities in SH-SY5Y cells, where it concomitantly stimulated the expression of PGC-1α and SIRT1 (Ding, et al., 2018; Xu, et al., 2012). The triterpenoid saponins such as ginsenosides Rb1 and Rg1 from *Panax ginseng* increased mtDNA content and mitochondrial function to protect from oxygen–glucose-deprivation/reperfusion (OGD/R)-induced injury, a stroke model, in mouse primary astrocytes (Xu, et al., 2019).

Alkaloids and related hormones were found to be potential stimulators of mitochondrial biogenesis as well. For instance, berberine, an isoquinoline alkaloid found in the plant *Berberis* species, can modulate the SIRT1/AMPK/PGC-1α pathway and improve cognitive function in aging rats (Yu, et al., 2018). Melatonin, an indole-type hormone (derived from tryptophan) mainly found in animals, has been shown to prevent amyloid neurotoxicity and memory loss in a rat AD model, where it promoted the expression of SIRT1 and TFAM in conjunction with increased mtDNA content in the hippocampus (Ansari Dezfouli, Zahmatkesh, Farahmandfar, & Khodagholi, 2019).

In summary, a large amount of evidence shows that natural products are able to promote mitochondrial biogenesis in a variety of cellular and animal models of neurological disorders (a complete compound list is found in Table 1). Most of these compounds belong to the classes of plant polyphenols, terpenoids, and alkaloids, suggesting their therapeutic potential for modulating age-associated mitochondrial disorders.

2.2. Modulation of mitochondrial fusion and fission dynamics

Mitochondria form a dynamic network with the ability to constantly elongate (fusion) and fragment (fission) within eukaryotic cells. Mitochondrial fusion/fission dynamics are crucial for the maintenance of mitochondrial homeostasis and resilience against cellular stresses. While mitochondrial fusion accelerates the exchange of mitochondrial materials (e.g., mtDNA, proteins, lipids) and assists in the repair of defective mitochondria, mitochondrial fission is important for the removal of damaged mitochondria through mitophagy (Figure 2) (Youle & van der Bliek, 2012). In mammalian cells, mitochondrial fusion is mainly controlled by proteins such as optic atrophy protein 1 (OPA1) and mitofusins (MFN1 and MFN2). In contrast, fission depends mainly on proteins like dynamin-related protein 1 (DRP1), mitochondrial fission 1 protein (FIS1), and mitochondrial fission factor (MFF). Defects in mitochondrial dynamics by disruption of either fusion or fission are known to occur with aging as well as in many neuropathological conditions. Specifically, decreased mitochondrial fusion and increased fission have been associated with the progression of neurodegenerative diseases (Itoh, Nakamura, Iijima, & Sesaki, 2013). Therefore, pharmacological interventions that maintain mitochondrial dynamics could be an approach for treating neurological disorders.

Over the past few years, several natural products have been reported to modulate mitochondrial dynamics (Table 1). Resveratrol was shown to regulate mitochondrial fusion/fission dynamics through increasing the expression of MFN2 and OPA1 while decreasing the expression of DRP1 and FIS1 in the PD model of rotenone-induced dopamine neurotoxicity in rat brains (Peng, Tao, et al., 2016). Resveratrol also increased OPA1 and MFN2 expression to promote mitochondrial fusion in the hippocampus of SAMP8 mice, a model of dementia (Palomera-Avalos, et al., 2017).

Curcumin and its derivatives can also modulate mitochondrial dynamics for neuroprotection. It was found that curcumin can reduce mitochondrial fission by decreasing the expression of DRP1 and FIS1, and enhance fusion by increasing the expression of OPA1, MFN1 and MFN2 in the brains of SAMP8 mice (Eckert, et al., 2013). Tetrahydrocurcumin, a natural derivative of curcumin, was shown to regulate mitochondrial fusion/fission dynamics in mouse brain endothelial cells while protecting against homocysteine-induced oxidative stress and cell death (Vacek, et al., 2018).

Regarding flavonoids, the flavonol quercetin was found to regulate mitochondrial dynamics by inhibiting the expression of DRP1 and FIS1 and at the same time increasing the expression of MFN1 and MFN2 in the rat hippocampus, thereby improving hypoxia-induced memory deficits (Liu, et al., 2015). The flavanone liquiritigenin from *Glycyrrhiza uralensis* promoted mitochondrial fusion and prevented Aβ-induced neurotoxicity in human SK-N-MC nerve cells (Jo, et al., 2016). Xanthohumol is a prenylated chalconoid from the hop *Humulus lupulus* and a common ingredient in beers. Studies showed that xanthohumol alleviated kainic acid-induced excitotoxicity in the rat brain, a model of HD, in part by up-regulating MFN2 expression to promote mitochondrial fusion and prevent mitochondrial dysfunction (Wang, Ho, Hung, Kuo, & Wang, 2020). In a mouse model of subarachnoid hemorrhage, EGCG was found to protect mitochondrial function by down-regulating the expression of DRP1 and FIS1 in the brain (Chen, et al., 2018).

Ferulic acid, a hydroxycinnamic acid from *Ferula foetida*, was reported to reduce neuronal death in the striata of the 6-OHDA-lesioned rat model of PD, while inhibiting DRP1 and increasing MFN2 expression (Anis, et al., 2020). α-Tocopherol (vitamin E) is a terpenoid quinone rich in many vegetable oils that was found to preserve mitochondrial dynamics (increased mitochondrial OPA1) and protect against glutamate toxicity in the mouse HT22 hippocampal nerve cells (Sanderson, Raghunayakula, & Kumar, 2015).

Regarding natural products from animals, ursodeoxycholic acid, a bioactive steroid in bear bile, has been reported to modulate DRP1 and improve mitochondrial dynamics in fibroblasts from patients with sporadic and familial AD (Bell, et al., 2018). 15-Deoxy-$\Delta^{12,14}$-prostaglandin J2 is an endogenous fatty acid metabolite in humans that was found to stimulate mitochondrial remodeling against oxygen-glucose deprivation by regulation of DRP1 and OPA1 in primary neurons (Wappler, Institoris, Dutta, Katakam, & Busija, 2013). Melatonin was found to prevent DRP1-dependent mitochondrial fission induced by MPP+ in rat primary cortical neurons (Chuang, et al., 2016).

As for microbial sources, santacruzamate A, a peptide-like metabolite from the marine cyanobacterium *Symploca* sp., attenuated Aβ toxicity in PC12 cells and rescued cognitive impairment in APP/PS1 mice. Its neuroprotective mechanisms were shown to be in part due to inhibition of mitochondrial fission (decreases in DRP1, FIS1, and MFF) (Chen, et al., 2019).

Together, certain natural polyphenols, quinones, steroids, and peptidic metabolites have been shown to modulate mitochondrial fusion/fission dynamics while protecting brain cells in various models of neurological disorders (a complete compound list is found in Table 1).

2.3. Modulation of mitochondrial bioenergetics

Mitochondrial bioenergetics refers to the enzymatic and metabolic processes involved in the biochemical and molecular pathways of energy production and transformation within the mitochondrion. Bioenergetics and metabolic regulation are the primary functions of mitochondria. In mammalian cells, the metabolite pyruvate derived from glycolysis is oxidized to acetyl-coenzyme A (acetyl-CoA) that fuels the Krebs cycle in the mitochondrial matrix, powering up cellular respiration (Figure 1). NADH and $FADH_2$ from the Krebs cycle are then oxidized to NAD and FAD, respectively, which are then used as substrates of the ETC to produce ATP via OXPHOS (Figure 3). The mitochondrial OXPHOS system comprises protein complexes I to IV and ATP synthase (complex V), where the electron movement is driven by the redox potential and the proton gradient across the mitochondrial inner membrane. The ATP molecules generated from mitochondrial respiration by ATP synthase are then exported to the cytosol to fuel a variety of vital cellular functions. During mitochondrial electron transfer, oxygen consumption yields inevitable byproducts such as the ROS superoxide radical (O_2^-) that is generated predominantly at the mitochondrial complexes I and III (Sipos, Tretter, & Adam-Vizi, 2003). As such, disruptions of the finely tuned process of mitochondrial respiration can cause an abnormal production of ROS thus contributing to multiple neuropathologies (Morán, et al., 2012).

In recent years, many bioactive natural products have been reported to modulate mitochondrial bioenergetics and related pathways (Table 1). These effects were often associated with neuroprotection in multiple disease models. For example of flavonoids, fisetin, a flavonol rich in strawberries and other fruits, showed improvement of mitochondrial complex I activity in the brains of rotenone-treated rats, a model of PD (Alikatte, Palle, Rajendra Kumar, & Pathakala, 2020). The isoflavones genistein and daidzein, commonly found in soybeans, maintained mitochondrial respiration efficiency to prevent potassium deprivation-induced cell death in cerebellar granule cells (Atlante, Bobba, Paventi, Pizzuto, & Passarella, 2010). The flavone baicalein prevented rotenone-induced mitochondrial ATP deficiency in both PC12 cells and brain tissue (Li, et al., 2012). The citrus flavanone naringenin protected from H_2O_2-induced cell death in SH-SY5Y cells where it restored the activities of complexes I and V and increased ATP production (de Oliveira, Brasil, & Andrade, 2017). Silibinin, a flavonolignan from *Silybum marianum* L., modulated OXPHOS complex enzyme activity to maintain mitochondrial bioenergetics against MPP+ induced dopaminergic neurotoxicity in the rat brain (Geed, Garabadu, Ahmad, & Krishnamurthy, 2014).

Flavonoids with glycosidic groups are also known to promote mitochondrial bioenergetics under stress. Naringin, a flavanone glycoside in *Citrus* plants, showed neuroprotective effects against rotenone-induced neurotoxicity in a rat model of PD where it increased the activity of mitochondrial ETC complexes in the rat substantia nigra (Garabadu & Agrawal, 2020). The anthocyanidin glucoside chrysanthemin, from bilberry, was shown to restore the mitochondrial respiration rate in the presence of H_2O_2-induced oxidative stress in rat C6 glial cells (Ereminas, et al., 2017). Gastrodin, a simple phenolic glycoside in *Gastrodia elata* Blume, showed neuroprotection against H_2O_2-induced oxidative stress in SH-SY5Y cells where it increased mitochondrial respiration and ATP generation (de Oliveira, Brasil, & Fürstenau, 2018).

Some polyphenols like cannabidiol (CBD), derived from *Cannabis sativa* L., improved mitochondrial respiration and glucose metabolism thereby protecting against OGD/R damage in HT22 neural cells (Sun, Hu, Wu, & Zhang, 2017). 5-Heptadecylresorcinol, commonly found in cereals, was protective against H_2O_2-induced mitochondrial dysfunction in PC12 cells, where it enhanced mitochondrial respiration and ATP production (Liu, et al., 2020). Auraptene, a prenyloxycoumarin from *Citrus* spp., increased the oxygen consumption rate in response to MPP+ treatment in substantia nigra-derived SN4741 dopaminergic neuronal cells (Jang, et al., 2019). Hydroxytyrosol, a simple catechol derivative abundant in olive oil, showed beneficial effects by increasing the activities of mitochondrial OXPHOS complexes and ATP production in the brains of APP/PS1 transgenic mice (Peng, Hou, et al., 2016).

With respect to plant-derived terpenoids, the monoterpene linalool, commonly found in botanical essential oils, showed protective effects against glutamate toxicity, where it increased mitochondrial respiration in HT22 cells (Sabogal-Guáqueta, et al., 2019). Bicelaphanol A, a dimeric trinorditerpene from *Celastrus orbiculatus*, increased ATP production in mitochondria and protected from H_2O_2-induced mitochondrial stress in PC12 cells (Wang, et al., 2013). The diterpene quinones, tanshinone I and tanshinone IIa from *Salvia miltiorrhiza* Bunge (Danshen), protected mitochondrial function from paraquat and glutamate toxicity in human SH-SY5Y neural cells, where they preserved the activity of ETC complexes and ATP production (de Oliveira, Schuck, & Bosco, 2017; Li, et al., 2017).

With respect to alkaloids, huperzine A is a sesquiterpene alkaloid from *Huperzia serrata* that has been approved as a potent acetylcholinesterase (AChE) inhibitor for the treatment of AD in China. A study has shown that huperzine A, independent of its AChE inhibitory effect, ameliorated Aβ-induced impairments in ATP production and ETC complex enzyme activity in isolated cortical mitochondria from APP/PS1 transgenic mice. (Yang, Ye, Huang, Tang, & Zhang, 2012). Neferine, a bisbenzylisoquinoline alkaloid from *Nelumbo nucifera*, increased mitochondrial respiration and protected brain mitochondria in a rat model of ischemic stroke (Wu, et al., 2019). The indole hormone melatonin was shown to protect brain mitochondria from aging in SAMP8 mice by increasing the activities of ETC complexes and ATP production (Carretero, et al., 2009).

In addition to phytochemicals, animal-derived natural products, particularly steroids, were noted for their abilities to maintain mitochondrial bioenergetics in neuronal cells. Several

human endogenous neurosteroids (i.e., progesterone, estradiol, allopregnanolone, estrone, testosterone, 3α-androstanediol, and dehydroepiandrosterone) have been shown to improve mitochondrial respiration and ATP production in SH-SY5Y cells as well as in primary cortical neurons (Grimm, Schmitt, Lang, Mensah-Nyagan, & Eckert, 2014), while restoring brain bioenergetic deficits in the 3xTg mouse model of AD (Wang, Yao, Chen, Mao, & Brinton, 2020). The bile acid steroids ursodeoxycholic acid and ursocholanic acid were found to improve mitochondrial respiration and ATP generation in fibroblasts from AD and PD patients (Bell, et al., 2018; Mortiboys, Aasly, & Bandmann, 2013). α-Lipoic acid, an organosulfur compound derived from fatty acids in animals and humans, was found to increase the activities of ETC complexes in the striatum of the 3-nitropropionic acid-induced HD rat model and ameliorate HD-like behavioral deficits (Mehrotra, Kanwal, Banerjee, & Sandhir, 2015).

Taken together, as summarized in Table 1, many plant-derived polyphenols, terpenoids and alkaloids appear to be promising modulators of mitochondrial respiration thereby contributing to neuroprotection. In addition, a subset of steroids from animal sources also have shown similar beneficial effects on mitochondria.

2.4. Modulation of mitochondrial calcium (Ca^{2+}) homeostasis

Mitochondria, in coordination with the endoplasmic reticulum (ER), are crucial for the buffering and regulation of cellular calcium by sequestering and releasing the ions into the cytosol. Therefore, mitochondrial Ca^{2+} homeostasis is vital to a variety of cellular functions (Zündorf & Reiser, 2011). Driven by the mitochondrial membrane potential and transported by the mitochondrial ion channels (e.g., voltage-dependent anion channel, mitochondrial calcium uniporter, etc.) (Figure 3), Ca^{2+} ions enter the mitochondrial matrix, influencing processes such as respiration, ATP production, mitochondrial dynamics, and cell fate (Pathak & Trebak, 2018). Prolonged mitochondrial Ca^{2+} overload leads to increased ROS generation, $\Delta\Psi m$ dissipation, metabolic dysfunction, and induction of apoptosis/necrosis through the opening of the mitochondrial permeability transition pore (mPTP). It is evident that excessive mitochondrial Ca^{2+} influx is detrimental to the neuron and has been implicated in many pathophysiological processes such as those observed in neurodegeneration and ischemia (Maher, et al., 2018). As such, modulating mitochondrial Ca^{2+} uptake represents an emerging therapeutic strategy for several age-associated neurological disorders.

A handful of polyphenolic natural products have been reported to maintain mitochondrial Ca^{2+} homeostasis while conferring neuroprotection (Table 1). For instance, it was shown that resveratrol prevented Ca^{2+}-induced mitochondrial swelling after hypoxic injury in rat brain neurons (Kesherwani, Atif, Yousuf, & Agrawal, 2013). Curcumin prevented okadaic acid-induced memory impairment in mice, where it reduced mitochondrial Ca^{2+} uptake in the hippocampus and cerebral cortex (Rajasekar, et al., 2013). Baicalein was shown to inhibit 6-OHDA/ascorbic acid induced mitochondrial Ca^{2+} accumulation and cell death in SH-SY5Y cells (Wang, et al., 2017). The hexamethoxyflavone nobiletin from the peel of *Citrus sunki* attenuated mitochondrial Ca^{2+} overload induced by glutamate in rat primary cortical neurons (Lee, Amarsanaa, et al., 2018). Fumarprotocetraric acid from the lichen

fungus *Cetraria islandica* protected against H_2O_2-induced toxic mitochondrial Ca^{2+} uptake in both human SH-SY5Y neuroblastoma and U373-MG astrocytoma cells (Fernández-Moriano, Divakar, Crespo, & Gómez-Serranillos, 2017).

Terpenoids are also known to modulate mitochondrial Ca^{2+}. The kaurane diterpenes linearol and sidol from *Sideritis* spp. prevented both mitochondrial and cytosolic Ca^{2+} overload induced by H_2O_2 in rat PC12 cells as well as human U373-MG cells (González-Burgos, Duarte, Carretero, Moreira, & Gómez-Serranillos, 2016). The triterpenoid ginsenosides Rb1 and Rg1 protected against rotenone-induced mitochondrial Ca^{2+} influx in SH-SY5Y cells (Fernández-Moriano, González-Burgos, Iglesias, Lozano, & Gómez-Serranillos, 2017). Hyperforin and its derivative from *Hypericum perforatum* are polyketidic terpenoids and were reported to be neuroprotective in AD models. They prevented memory loss and Aβ neurotoxicity in APP/PS1 mice, and counteracted mitochondrial Ca^{2+} overload in rat hippocampal neurons exposed to Aβ (Zolezzi, et al., 2013).

Overall, a limited number of natural products (Table 1) have been reported to specifically ameliorate mitochondrial Ca^{2+} overload in neurons and/or astrocytes as well as in brain tissue of disease models. Noticeably, a majority of them are highly lipophilic compounds, which may help them penetrate the mitochondrion to buffer Ca^{2+} intake.

2.5. Modulation of mitochondrial membrane potential (ΔΨm)

The mitochondrial membrane potential (ΔΨm) is generated by the OXPHOS proton pumps (complexes I, III and IV) across the mitochondrial inner membrane, thereby powering ATP production and ion transport (i.e., Ca^{2+}) (Figure 3). Under physiological conditions, the levels of ΔΨm are relatively stable and play a critical role in mitochondrial homeostasis. However, dramatic or prolonged changes of ΔΨm are deleterious and could trigger mitochondrial damage and eventually cell death (Ward, et al., 2007; Zorova, et al., 2018). It has been observed that the ΔΨm levels decrease in many cellular and animal models of age-associated diseases (Nicholls, 2004), and researchers have identified neuroprotective natural products to counteract the loss of ΔΨm (Table 1).

Because of its mechanistic relevance, pharmacological modulation of ΔΨm usually affects other mitochondrial functions such as biogenesis, dynamics, bioenergetics, and Ca^{2+} flux, and vice versa (Figures 1–3). In many cases, changes in ΔΨm appear to be a pharmacological consequence of the compound actions and may or may not be necessarily responsible for their protective effects. Nonetheless, measurement of ΔΨm change is a useful mitochondrial parameter for characterizing the neuroprotective effects of a compound, particularly in phenotypic screening systems. To avoid redundancy in this section, we have chosen to focus on the natural products that have not been previously discussed and where the literature has shown that the restoration of ΔΨm is correlated to their protective effects. A complete summary of the natural products that were reported to modulate ΔΨm can be found in Table 1.

Flavonoids have been reported to be able to maintain ΔΨm against a variety of neuronal stressors. For example, the flavonol myricetin from many fruits and vegetables attenuated ΔΨm loss and cell death induced by MPP+ in the MES23.5 dopaminergic cell model

(Zhang, Ma, Wang, Xie, & Xie, 2011). The flavanol theaflavic acid from black tea prevented ΔΨm loss and cell damage from OGD/R in PC12 cells (Li, Shi, et al., 2020). Rutin, a flavonol glycoside, ameliorated ΔΨm loss and amylin-induced neurotoxicity in SH-SY5Y cells, which is relevant to type 2 diabetes associated with AD (Yu, Li, et al., 2015). Orientin, an 8-*C*-glycosylflavone commonly found in the bamboo *Phyllostachys nigra* attenuated ΔΨm depolarization in the hippocampus of Aβ-induced mice while improving cognitive function (Yu, Wang, et al., 2015).

Other polyphenolic compounds such as rasidasin II, a lignan from red raspberry, attenuated H_2O_2-induced ΔΨm loss in SH-SY5Y cells (Zhou, Yao, et al., 2018). α-Arbutin, a phenolic glycoside from bearberry, was found to be protective against rotenone-induced ΔΨm impairment in SH-SY5Y cells as well as in a fruit fry model of PD (Ding, et al., 2020). Coniferyl ferulate from the root of *Angelica sinensis* inhibited ΔΨm depolarization during glutamate-induced toxicity in PC12 cells (Gong, Zhou, Gong, & Qin, 2020).

A number of terpenoids have been reported to be effective modulators of ΔΨm. For example, the sesquiterpene artemisinin, a well-known antimalarial drug isolated from the sweet wormwood *Artemisia annua*, prevented H_2O_2-induced ΔΨm loss in a cellular model of age-related neurodegeneration using RGC-5 cells (Yan, Wang, Gao, Xu, & Zheng, 2017). Geniposide, an iridoid monoterpene glycoside from *Gardenia jasminoides*, prevented ΔΨm loss in isolated brain mitochondria from APP/PS1 mice (Lv, Liu, Liu, Chen, & Zhang, 2014). The triterpenoid celastrol from *Tripterygium wilfordii* was reported to alleviate ΔΨm depolarization caused by rotenone-induced mitochondrial dysfunction in SH-SY5Y cells (Deng, Shi, Liu, & Qu, 2013). Gracilin A is a unique norditerpenoid from the marine sponge *Spongionella* sp., and a study has shown that it could prevent H_2O_2-induced oxidative stress and restore ΔΨm in cortical neurons (Leirós, Sánchez, et al., 2014). Astaxanthin, a keto-carotenoid (known as a tetraterpenoid) from the freshwater microalgae *Haematococcus pluvialis*, was able to prevent MPP+-induced ΔΨm loss and cytotoxicity in SH-SY5Y cells (Lee, Kim, & Lee, 2011).

Some natural quinones and alkaloids are also known to preserve ΔΨm in neurons. For instance, the diterpenoid quinone cryptotanshinone restored ΔΨm in human-induced neuronal progenitor cells derived from fibroblasts of familial PD patients (Lee, et al., 2020). A nitrogen-containing 3-alkyl-1,4-benzoquinone from the plant *Embelia ribes* maintained ΔΨm and mitochondrial function against severe oxidative stress in primary FRDA fibroblasts (Madathil, Khdour, Jaruvangsanti, & Hecht, 2012). The naphthoquinone anhydroexfoliamycin from *Streptomyces* spp. also protected against H_2O_2-induced ΔΨm loss in mouse primary cortical neurons (Leirós, Alonso, et al., 2014). The pyrroloiminoquinone alkaloid makaluvamine J from marine *Zyzzya* sponges showed protective effects against H_2O_2-induced ΔΨm loss in SH-SY5Y cells (Alonso, et al., 2016). 3,3'-Diindolylmethane is an indole alkaloid found in many cruciferous vegetables and it has been shown to counteract the ΔΨm loss and neuronal death induced by MPP+ in SH-SY5Y cells (Ito, et al., 2017). The steroidal alkaloid tomatidine from the tomato plant *Lycopersicon esculentum* preserved ΔΨm against glutamate-induced toxicity in SH-SY5Y cells (Taveira, et al., 2014).

In summary, flavonoids, terpenoids, quinones, and alkaloids from various sources are neuroprotective and have shown their potential to maintain ΔΨm in neuronal models of disease.

2.6. Neuroprotection against mitochondrial oxidative stress in oxytosis/ferroptosis

Given the postmitotic characteristic of neurons in the adult brain, neurodegeneration with aging leads to a progressive course of neuronal cell death in a way that can hardly be regenerated. Although brain atrophy is a hallmark of many CNS disorders, it is known that many forms of neuronal death are non-apoptotic as they do not involve DNA fragmentation and activation of the caspase cascade in neurons (Berghe, Linkermann, Jouan-Lanhouet, Walczak, & Vandenabeele, 2014). The molecular mechanisms executing regulated cell death that differ from apoptosis are still poorly defined (Fricker, Tolkovsky, Borutaite, Coleman, & Brown, 2018).

Over 20 years ago, our laboratory identified oxytosis, a non-apoptotic, regulated cell death pathway that is due to glutathione (GSH) depletion triggered by inhibition of the cystine/glutamate antiporter, system X_c^-, and mediated by the dysregulated production of ROS from mitochondria that results in lethal lipid peroxidation and calcium influx (Figure 4) (Li, Maher, & Schubert, 1997; Tan, Sagara, Liu, Maher, & Schubert, 1998; Tan, Schubert, & Maher, 2001). Importantly, we have also shown that the oxytosis pathway is essentially identical to the more recently named ferroptosis pathway (Dixon, et al., 2012) that is triggered by inhibition of either system X_c^- or glutathione peroxidase 4 (GPX4) and is associated with accumulation of intracellular iron (Fe^{2+}) (Figure 4) (Lewerenz, Ates, Methner, Conrad, & Maher, 2018; Stockwell, et al., 2017). GSH is the major endogenous antioxidant, and a reduction in GSH is observed in the aging brain and is accelerated in neurodegenerative diseases including AD and PD (Currais & Maher, 2013; Mandal, Saharan, Tripathi, & Murari, 2015; Smeyne & Smeyne, 2013). GSH dysregulation in mitochondria is also observed in many metabolic and neurological disorders (Gao, et al., 2019; Ribas, García-Ruiz, & Fernández-Checa, 2014; Stockwell, et al., 2017). Therefore, oxytosis/ferroptosis is a unique regulated cell death pathway with characteristics of mitochondrial oxidative stress and dysfunction (Maher, Currais, & Schubert, 2020). In the past decade, our group has identified specific inhibitors that block the oxytosis/ferroptosis pathway, which is an evolving therapeutic strategy for age-associated neurological diseases (Maher, Currais, et al., 2020).

In early studies using glutamate-induced toxicity in mouse HT22 hippocampal neurons and primary cortical neurons as models of oxytosis/ferroptosis, we screened and identified several promising natural products including curcumin, resveratrol, α-tocopherol (vitamin E), and specific flavonoids (i.e., galangin, baicalein, kaempferol, luteolin, fisetin, quercetin, morin) that are highly neuroprotective (Ishige, Schubert, & Sagara, 2001; Schubert, Kimura, & Maher, 1992). As described above, curcumin from the curry spice turmeric is a multifunctional natural product that modulates various aspects of mitochondrial function (Table 1). Curcumin protected against glutamate-induced toxicity with an EC_{50} value of 6 μM (Liu, Dargusch, Maher, & Schubert, 2008). Further optimization of curcumin through structure-activity relationship driven medicinal chemistry led to development of J147 (EC_{50}

= 11 nM), a compound that enhances memory and is highly neuroprotective in cell and mouse models of AD (Chen, Prior, et al., 2011; Currais, et al., 2015; Prior, Dargusch, Ehren, Chiruta, & Schubert, 2013). Importantly, we have recently demonstrated that J147 targets the mitochondrial ATP synthase and modulates its activity (Goldberg, et al., 2018). J147 is currently in Phase 1 clinical trials for AD (NCT03838185). Another example is fisetin, which was identified in our screens as a protective flavonol against oxytosis/ferroptosis with an EC_{50} value of 3 μM (Ishige, et al., 2001; Maher, Akaishi, & Abe, 2006). Pharmacological studies of fisetin showed its therapeutic benefits in preclinical models of AD, PD, HD, traumatic brain injury, stroke, as well as aging (Maher, 2020). We later developed CMS121, a synthetic derivative of fisetin, with improved potency (EC_{50} = 200 nM) against oxytosis/ferroptosis as well as other improved pharmacological properties for the treatment of AD (Ates, Goldberg, Currais, & Maher, 2020; Chiruta, Schubert, Dargusch, & Maher, 2012). CMS121 is currently in Investigational New Drug (IND) studies. Interestingly, both J147 and CMS121 protect cultured nerve cells from oxytosis/ferroptosis induced by either glutamate (an inhibitor of system X_c^-) or RSL3 (an inhibitor of GPX4), and they both have an overlapping mechanism of action that is associated with strong anti-aging effects by increasing mitochondrial acetyl-CoA and activating AMPK in the brains of SAMP8 mice (Currais, et al., 2019).

More recently, additional anti-oxytotic/ferroptotic natural products have been identified by our group. The flavanone sterubin from the plant Yerba santa (*Eriodictyon californicum*) showed effective neuroprotection against oxytosis/ferroptosis (EC_{50} = 0.8 μM) (Fischer, Currais, Liang, Pinto, & Maher, 2019; Maher, Fischer, et al., 2020). The flavonol isoquercitrin showed neuroprotection against glutamate toxicity with an EC_{50} value of 25 μM as well as anti-amyloidogenic effects (Carmona, Martín-Aragón, Goldberg, Schubert, & Bermejo-Bescós, 2020). The dimeric indole alkaloid voacamine from *Voacanga africana* protected HT22 cells against glutamate toxicity with an EC_{50} value of 0.7 μM (Currais, et al., 2014). Several phytocannabinoids such as tetrahydrocannabinol (THC), cannabidiol (CBD), cannabinol (CBN), and cannabichromene (CBC) from the *Cannabis* plant also showed promising protective effects against oxytosis, ATP depletion, and Aβ toxicity with potencies in the sub-micromolar range (EC_{50} < 1 μM) (Schubert, et al., 2019).

Other research laboratories have also reported on a number of natural products with diverse chemical structures that prevent neuronal death in cellular models using system X_c^- inhibitors (i.e., glutamate and erastin) as inducers of oxytosis/ferroptosis (Figure 4). For instance, flavonoids such as 7,8-dihydroxyflavone from *Tridax procumbens* (Chen, Chua, et al., 2011), cudraflavone B from *Cudrania tricuspidata* (Lee, Ko, Kim, Kim, & Jeong, 2014), liquiritigenin from *Glycyrrhiza uralensis* (Yang, Park, & Song, 2013), morachalcones from mulberry leaves (Wen, et al., 2020), EGCG from green tea (He, Xu, Yang, & Sun, 2019), and procyanidins from grape seeds (Song, Lee, & Kang, 2019), have all been shown to protect against glutamate/erastin-induced mitochondrial oxidative injury and nerve cell death in HT22 cells. In addition, puerarin, an 8-*C*-glycosylisoflavone from *Pueraria lobate*, protected against glutamate toxicity in SH-SY5Y cells (Zhu, et al., 2016).

Other plant-derived polyphenols with simple or complex structures have also been found to be protective against glutamate-induced oxytosis/ferroptosis in HT22 cells. These include

the stilbenoids pterostilbene (Wang, Liu, et al., 2016) and artoindonesianin O (Seo, et al., 2014), the diarylheptanoids juglanin C (Yang, Sung, Kim, & Kim, 2011) and acerogenin A (Lee, Cha, Woo, Kim, & Jang, 2015), the lignans mulberrofuran K (Xia, et al., 2019) and pinoresinol (In, et al., 2015), the neolignans obovatol and honokiol (Yang, Lee, Park, Lee, & Song, 2013), the anthraquinones emodin (Ahn, et al., 2016) and chrysophanol (Chae, et al., 2017), the prenylcinnamate artepillin C (Takashima, Ichihara, & Hirata, 2019), the xanthone γ-mangostin (Wang, Li, et al., 2016), the coumarin daphnetin (Du, et al., 2014), and the ellagitannin casuarinin (Song, Kang, & Choi, 2017).

Plant-derived terpenoids such as the monoterpenoid oleuropein (Kim, et al., 2018), the sesquiterpene artemisinin (Lin, Li, Winters, Liu, & Yang, 2018), and the diterpenoid andrographolide (Yang & Song, 2014) were reported to show neuroprotective effects against glutamate-induced oxytosis in HT22 cells. The triterpenoids protopanaxadiol (Bak, et al., 2016) and asiatic acid (Xu, et al., 2012) protected against glutamate-induced cytotoxicity in PC12 and SH-SY5Y cells.

Moreover, several plant-derived alkaloids such as huperzine A (Mao, Zhou, Li, & Liu, 2016), geissoschizine methyl ether (Sun, Ren, Qi, Yuan, & Simpkins, 2016), sanguinarine (Park, et al., 2014), and fangchinoline (Bao, Tao, & Zhang, 2019) also protected against glutamate-induced mitochondrial dysfunction in HT22 cells.

Besides, certain fungus-derived polyketidic metabolites were reported to be anti-oxytotic/ferroptotic in HT22 cells. These include polyozellin from the mushroom *Polyozellus multiplex* (Yang & Song, 2015), evariquinone from *Colletotrichum* sp. (Song, et al., 2018), and fusarubin from *Fusarium solani* (Choi, et al., 2020). In addition, the phenazine alkaloid pontemazine B from the bacterium *Streptomyces* sp. also protected from glutamate toxicity in HT22 cells (Cha, et al., 2015).

As summarized in Table 1, in recent years a growing number of natural products have been reported to prevent nerve cell death caused by oxytosis/ferroptosis, a process that is associated with mitochondrial oxidative stress and dysfunction. Most of them belong to the polyphenols, terpenoids, alkaloids, and polyketidic quinones. Impressively, some of these anti-oxytotic/ferroptotic natural products are either the same or appear to share common structural characteristics with the aforementioned neuroprotective compounds that modulate mitochondrial biogenesis, fusion/fission dynamics, bioenergetics, calcium uptake, etc.

3. Conclusions and perspectives

Human neurological disorders arise from complex and multifaceted pathological mechanisms. Although the etiology of the individual disorders may differ, there is a consensus towards mitochondrial inefficiency or dysfunction in the brain with aging as being a key pathological process shared by these disorders (Currais, 2015; Grimm & Eckert, 2017). In recent years, novel therapeutic approaches to the use of small molecule drugs to target mitochondria in the CNS have emerged (Andreux, et al., 2013; Cunnane, et al., 2020; Schubert, et al., 2018).

Natural products are a valuable source of drug candidates (Newman & Cragg, 2020). As summarized in Table 1, a total of 127 natural products covering a diverse array of structural classes have been reported over the past ten years to be efficacious in mitigating mitochondrial dysfunction and promoting cell survival in different *in vitro* and *in vivo* models of neurological disorders. More importantly, a number of these compounds, as exemplified by the cases of resveratrol, curcumin, baicalein, quercetin, EGCG and melatonin, are able to modulate at least four out of five mitochondrial functions (biogenesis, fusion/fission dynamics, bioenergetics, calcium homeostasis, and membrane potential), as well as prevent mitochondrial oxidative stress-induced nerve cell death in the form of oxytosis/ferroptosis (Figure 5). Interestingly, if one looks at the biological sources of these compounds in Figure 6A, 104 out of 127 compounds (about 82%) are derived from plants, while only 14 (11%) and 9 (7%) compounds are derived from animals and microbes, respectively, suggesting an increased potential of natural phytochemicals to target mitochondria for CNS drug discovery.

Regarding the structural classification of these natural products, the breakdown shown in the pie chart in Figure 6B indicates that flavonoids (i.e., flavone, flavonol, flavanol, flavanone, flavanonol, anthocyanidin, isoflavone, isoflavane, and chalcone as flavonoid precursor) are a predominant group, accounting for 36 compounds (28%). The second largest group is terpenoids (i.e., monoterpene, sesquiterpene, diterpene, triterpene, trinorditerpenoid, steroid, and carotenoid) that account for 31 compounds (24%). It is likely that the inherent lipophilic nature of certain flavonoids and terpenoids makes them more able to cross the cell and mitochondrial membranes and subsequently modulate mitochondrial function to achieve neuroprotection. Polyketides and alkaloids are the third and fourth groups that account for 14% and 10%, respectively. The remaining groups belong to stilbenoids (e.g., resveratrol) (3%), diarylheptanoids (e.g., curcumin) (3%), cinnamic acids (2%), lignans (5%), tannins (1%), coumarins (2%), simple phenols (3%), fatty acids (3%), and peptides (2%).

Noticeably, 90 out of the 127 natural products (71%) are polyphenolic and simple phenolic compounds (a sum of flavonoids, polyketides, stilbenoids, diarylheptanoids, cinnamic acids, lignans, tannins, coumarins, simple phenols, and certain terpenoids/alkaloids with phenolic groups). This is not surprising because phenolic natural products are well-known antioxidants for ROS scavenging and exert at least part of their function by blocking and alleviating the surge of cytotoxic byproducts from cellular respiration and ATP generation in the aging mitochondria. In addition, these natural antioxidants are effective and pleiotropic modulators of mitochondrial biogenesis and dynamics, calcium homeostasis and membrane potential, as well as inhibitors of oxytosis/ferroptosis (Table 1 and Figure 5). Notably, certain bioactivities of the phenolic compounds, such as mitochondrial biogenesis and dynamics, are not directly associated with antioxidant capacity. These modes of action could play critical roles in neuroprotection apart from antioxidant activity. Therefore, our analyses offer curated literature evidence to support the use of phenolic natural products to modulate mitochondrial pathology in age-associated neurological disorders. One point worthy of discussion is that most of the bioassays on mitochondrial function discussed in this review are based on cell culture and resulted in the identification of neuroprotective phenolic compounds. Thus, it underscores the merits of phenotypic screening that can offer an

opportunity to better realize the therapeutic value of phenolic natural products (Prior, et al., 2014).

Our observations also provide input to the controversial debate of whether polyphenolic natural products should be regarded as worthwhile for drug discovery and development, given that they are considered as pan assay interference compounds (PAINS) in single protein-based assays (Baell, 2016). With respect to the view from medicinal chemists, the main criticisms of PAINS (e.g., curcumin, resveratrol, flavonoids, quinones, and other polyphenols) are due to their reactive and promiscuous binding properties against a wide variety of proteins during high-throughput screening, thereby generating artifacts and false positives (Baell & Walters, 2014). Because one of the objectives of such target-based approaches is to achieve high specificity/selectivity of drug action against a single target of relevance, the PAINS appear to mislead, waste research efforts and increase costs for lead optimization in downstream drug discovery. However, from the standpoint of biologists, this does not apply in phenotypic drug screening using cellular and animal models that primarily focus on drug efficacy in living biological systems and deal with “unknown/uncertain protein targets” (Prior, et al., 2014; Schubert & Maher, 2012). This is particularly true for CNS drug discovery for which our knowledge of basic biology in neurosciences is still very limited. In fact, to date, all AD drug candidates based on presumed protein targets relevant to the disease (i.e., amyloid, tau, etc.) have failed in human clinical trials (Cummings, Lee, Ritter, Sabbagh, & Zhong, 2020). Paradoxically, the targets and modes of action of some commonly used CNS drugs (e.g., lithium, modafinil, and valproate) remain poorly defined (Lewis, 2016). Owing to an urgent need for effective drugs to treat neurodegenerative and other neurological disorders, the priority in CNS drug discovery should be to identify drug candidates that show pharmacological efficacy in model organisms and later to test them rigorously in human patients in clinical settings. Therefore, the antagonism towards PAINS may be unjustified. In fact, the majority of the natural products discussed throughout this review show positive effects on mitochondria and are PAINS. Moreover, the three mitochondria-targeted agents, MitoQ (NCT03514875), *S*-equol (NCT02142777) and J147 (NCT03838185) currently in clinical trials for mild cognitive impairment (MCI) and AD, are derivatives of a quinone, an isoflavonoid, and curcumin, respectively. The intrinsic biophysics and biochemistry of mitochondria such as their double membrane system, ion/proton gradients, ETC, redox cycles, etc. might actually favor therapeutic interventions with polyphenolic natural products for the treatment of neurological disorders. In principle, a balanced approach to a CNS drug pipeline that incorporates both phenotypic- and target-based strategies should be embraced (Schubert & Maher, 2012; Swinney & Anthony, 2011), and diverse chemotypes including PAINS that show neuroprotective effects in drug screening should be investigated (Rodrigues, Reker, Schneider, & Schneider, 2016).

Although much progress has been made towards identifying novel agents/drug leads from natural sources to target mitochondria, there are still significant challenges towards developing effective neurotherapeutics. Lead compounds derived from natural products usually contain a greater number of stereogenic centers, steric effects, heteroatoms, and polycyclic systems compared to synthetic molecules, which are deemed as liabilities because they are hard to modify and usually contradict the Lipinski’s “rule-of-five” dogma describing druglikeness for small molecules (Lipinski, 2004). Other major concerns

regarding polyphenolic natural products for CNS therapeutic application include their poor oral bioavailability and lower extent of blood-brain barrier (BBB) permeability *in vivo* (Hu, Wu, & Liu, 2017). It hence raises a question about whether the concentrations of polyphenolic natural products eliciting their *in vitro* effects could be achievable *in vivo*. Indeed, pharmacokinetic studies have shown that polyphenolics are metabolized easily after oral administration and the concentrations of their intact form in serum and in brain (from nanomolar to low micromolar range) often do not meet the requisite for *in vitro* effects observed in cell culture (from sub-micromolar to micromolar range). However, an apparent *in vivo* efficacy of the compounds is still observed in animal models of CNS disorders (Ines, Regina, Diana, Ines, & Claudia Nunes dos, 2017). It is known that the first-pass metabolism involving phase II conjugation (i.e., glucuronidation and sulfation) of polyphenolics with concerted actions of efflux transporters (i.e., permeability glycoprotein) causes their poor oral bioavailability and BBB penetration, and facilitates metabolic clearance (Shuai, et al., 2016; Wu, Kulkarni, Basu, Zhang, & Hu, 2011). Thus, it reduces the concentrations of polyphenolic compounds in the CNS for target engagement. However, glucuronidation and sulfation are known to be reversible *in vivo*, resulting in an equilibrium between the parent molecule and its conjugated metabolites distributed throughout the vascular and nervous systems (Andrade, Grosso, Valentao, & Bernardo, 2016). And the levels of individual conjugated metabolites (e.g., resveratrol metabolites) could be over ten times higher than those of the parent molecule in serum (Baur & Sinclair, 2006). In fact, increasing evidence indicates that metabolic conjugates along with the parent polyphenolics can be detected in the brain and that these conjugates are still bioactive (Ishisaka, Mukai, Terao, Shibata, & Kawai, 2014; Pogačnik, et al., 2016). Moreover, some glycosidic and glucuronidated phenolics bind to glucose transporters (GLUTs), sodium glucose co-transporters (SGLT1/2) and other carrier-mediated transporters, which enables their distribution across the intestinal barrier via transepithelial transport (Jesus, et al., 2017; Lies, Martens, Schmidt, Boll, & Wenzel, 2012), and across the BBB via secondary active transport (Andrade, et al., 2016; Patching, 2017). These data suggest that polyphenolic natural products in intact and/or metabolically modified forms may still be able to enter into the brain and exert therapeutic actions on mitochondria in the CNS.

Notwithstanding, future studies must emphasize lead optimization for potency/selectivity, physicochemical properties, ADME-Tox properties, bioavailability and BBB penetration of candidate neuroprotective natural compounds towards a better CNS druglikeness (Wager, Hou, Verhoest, & Villalobos, 2016). In addition, rational and strategic drug design by integrating chemical scaffolds and pharmacophores from polyphenols, terpenoids and alkaloids might add precision medicine to specifically target aspects of mitochondrial physiology in the CNS (Rodrigues, et al., 2016). This will require the collaboration of natural product/medicinal chemists, mitochondrial biologists, neuroscientists, and pharmacologists in drug discovery programs. Furthermore, a better understanding of the different molecular pathways underlying neurological disorders relevant to mitochondrial dysfunction will help scientists to develop novel classes of natural product-inspired therapeutics for healthy brain aging and other age-associated disorders.

In conclusion, over the past ten years there has been an increase in the development of new strategies based on natural products to target mitochondrial dysfunction in neurological

disorders. We hope that this review will lead readers to appreciate the importance of neuroprotective agents from Nature and offer new insights into mitochondrial pharmacology and CNS drug discovery towards the improvement of human health.

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Abbreviations:

AD	Alzheimer's disease
PD	Parkinson's disease
HD	Huntington's disease
FDA	Food and Drug Administration
CNS	central nervous system
mtDNA	mitochondrial deoxyribonucleic acid
ETC	electron transport chain
OXPHOS	oxidative phosphorylation
ROS	reactive oxygen species
ΔΨm	mitochondrial membrane potential
$[Ca^{2+}]m$	mitochondrial calcium
mPTP	mitochondrial permeability transition pore
PGC-1α	peroxisome proliferator-activated receptor- γ coactivator 1α
PPARγ	peroxisome proliferator-activated receptor- γ
AMPK	adenosine monophosphate-activated protein kinase
SIRT	sirtuin
NRF	nuclear respiratory factor
TFAM	mitochondrial transcription factor A
OPA1	optic atrophy protein 1
MFN	mitofusin
DRP1	dynamin-related protein 1

FIS1	mitochondrial fission 1 protein
MFF	mitochondrial fission factor
LOX	lipoxygenase
GSH	glutathione
GPX4	glutathione peroxidase 4
VDAC	voltage-dependent anion channel
SOCE	store-operated calcium entry
NAD	nicotinamide adenine dinucleotide
FAD	flavin adenine dinucleotide
Glu	glutamate
Cys	cysteine
AMP	adenosine monophosphate
ADP	adenosine diphosphate
ATP	adenosine triphosphate
cGMP	cyclic guanosine monophosphate
Aβ	β-amyloid
6-OHDA	6-hydroxydopamine
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MPP+	1-methyl-4-phenylpyridinium
OGD/R	oxygen–glucose-deprivation/reperfusion
EGCG	epigallocatechin-3-gallate
SAMP8	senescence accelerated mice prone 8
MOA	mode of action
PAINS	pan assay interference compounds
ADME-Tox	absorption, distribution, metabolism, excretion and toxicity
BBB	blood-brain barrier

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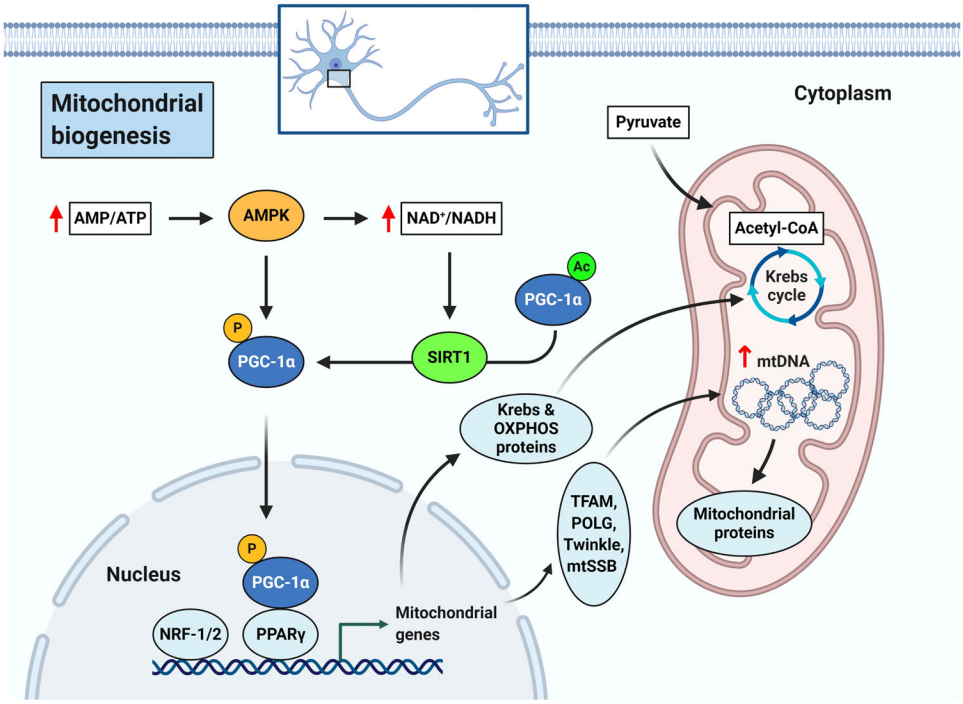

Figure 1.
Schematic representation of mitochondrial biogenesis pathway.

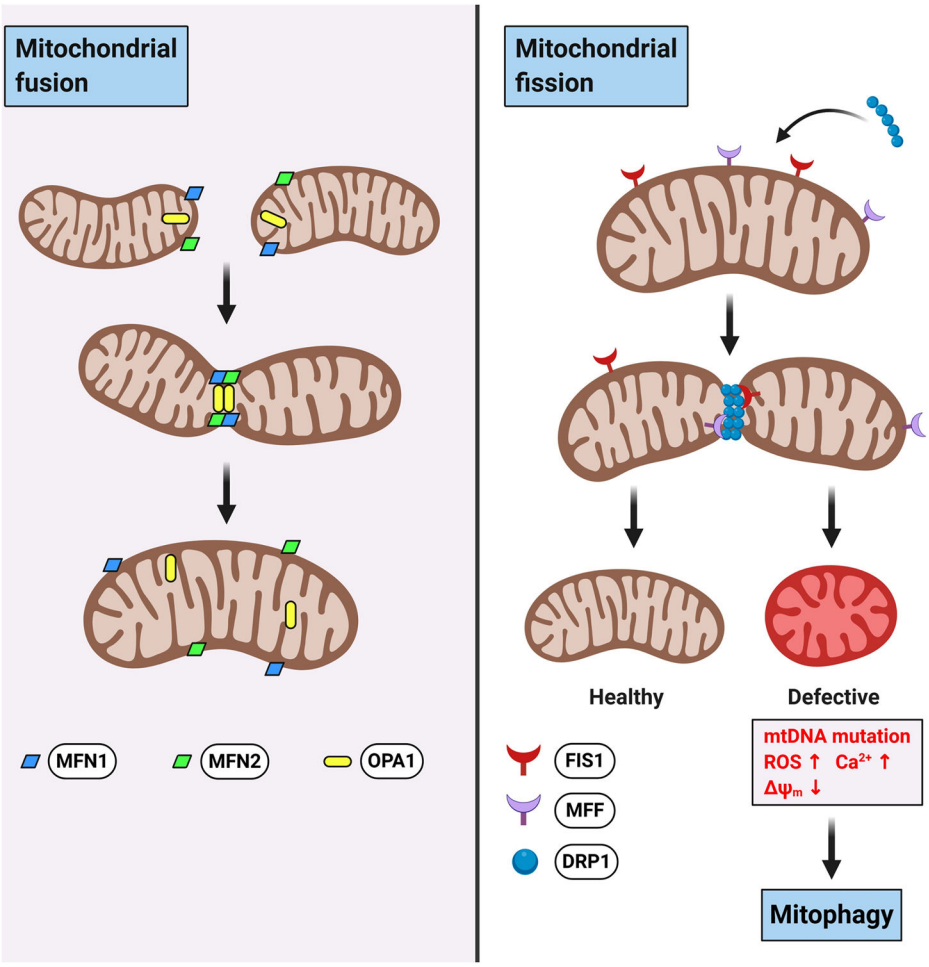

Figure 2.
Schematic representation of mitochondrial fusion and fission dynamics.

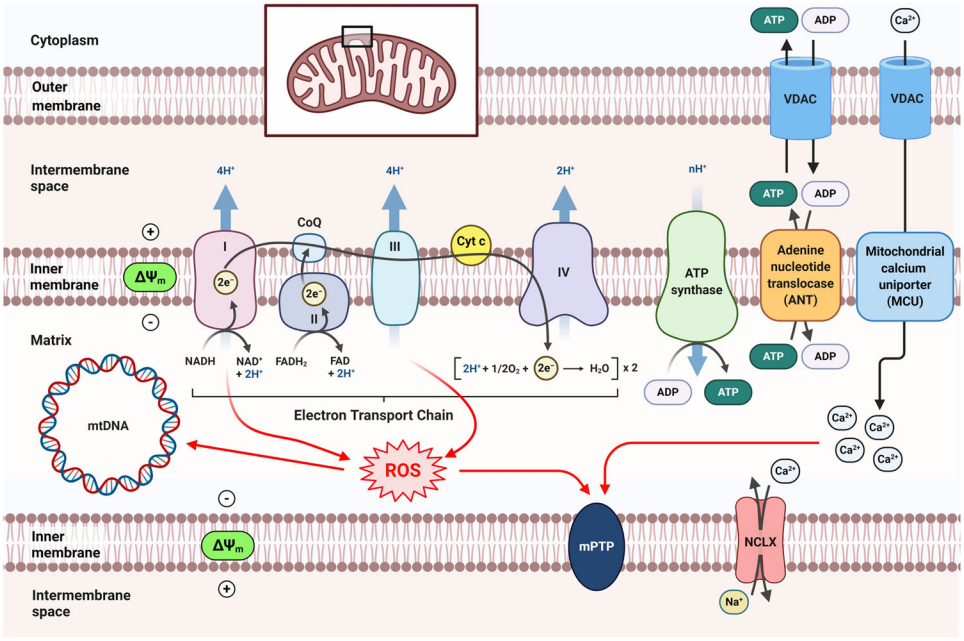

Figure 3. Schematic representation of mitochondrial respiration, mitochondrial membrane potential, calcium uptake, ROS production, and related pathological pathways.

CoQ, coenzyme Q (ubiquinone); Cyt c, cytochrome c; NCLX, Na^+/Ca^{2+} exchanger.

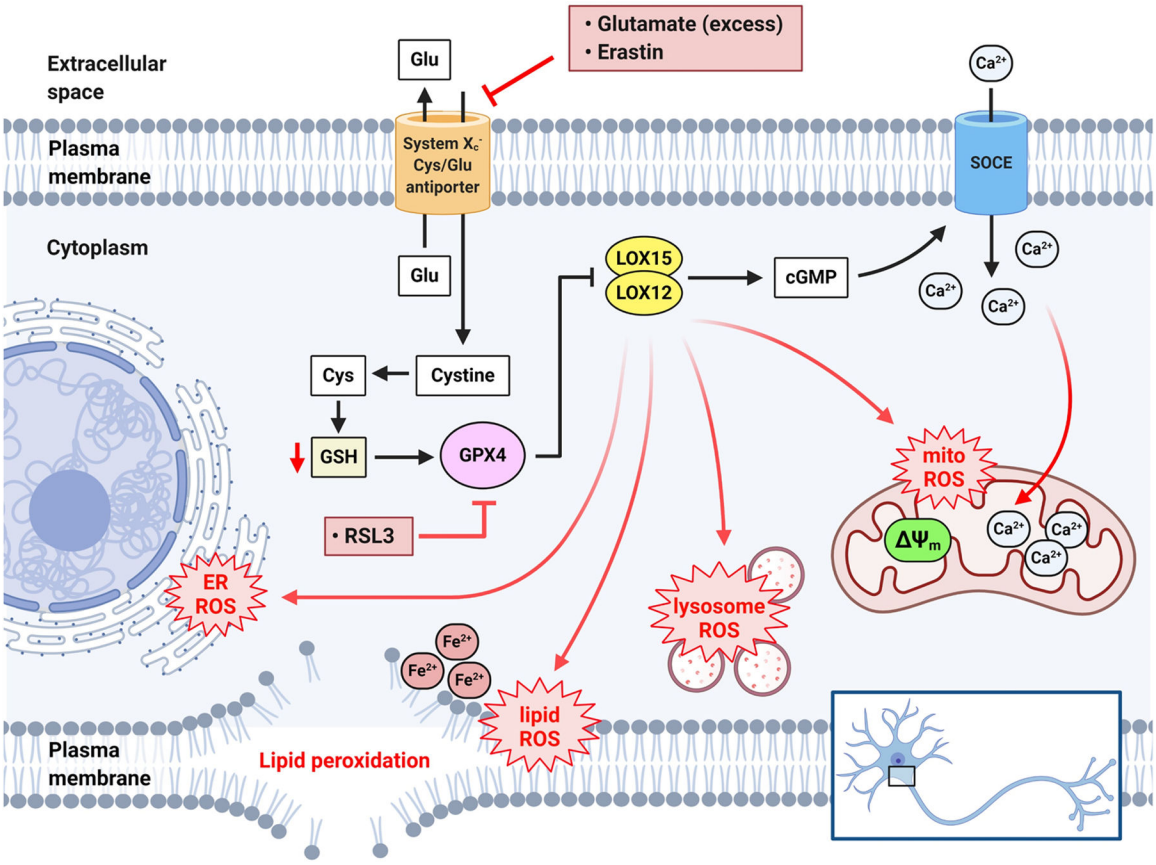

Figure 4. Schematic representation of the oxytosis/ferroptosis pathway.

Cystine uptake by system X_c^-, associated with the counter-transport of glutamate (Glu), is inhibited by excess Glu or erastin. This leads to depletion of the endogenous antioxidant GSH and subsequent inhibition of the GSH-dependent enzyme GPX4. GPX4 can also be directly inhibited by RSL3. GPX4 inhibition leads to activation of lipoxygenase (LOX) to initiate ROS production and increase cGMP. cGMP then activates SOCE on the plasma membrane allowing Ca^{2+} influx into the cytosol and subsequent accumulation in mitochondria. The additive effect of mitochondrial ROS and Ca^{2+} overload exacerbates mitochondrial oxidative stress and dysfunction. GPX4 inhibition and LOX activation, in conjunction with intracellular Fe^{2+}, also lead to lipid peroxidation (lipid ROS) in different cellular compartments such as mitochondria, ER, lysosome, and plasma membrane, thereby augmenting the overall ROS in the cell.

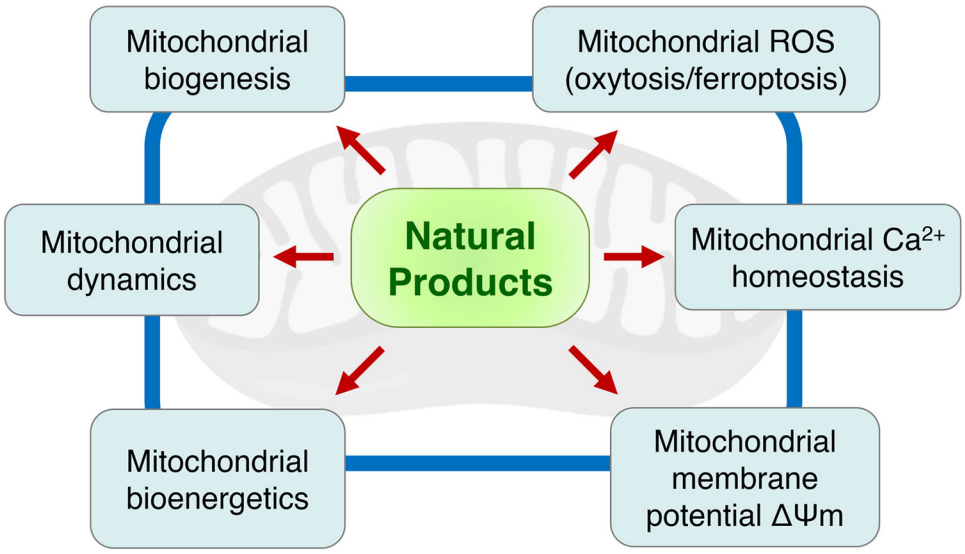

Figure 5.
The effects of natural products on multiple mitochondrial functions associated with neuroprotection.

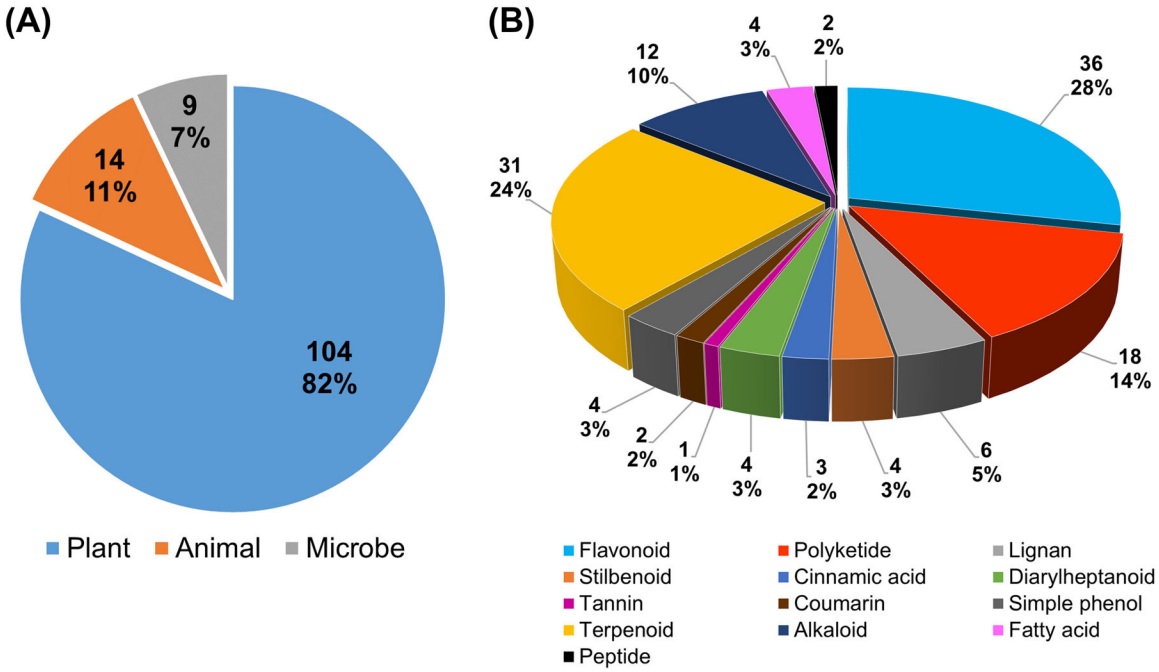

Figure 6. Natural products targeting mitochondrial dysfunction reported from January 2010 to May 2020, n = 127.

(A) Pie chart of natural products by biological source. (B) Pie chart of natural products by structural class.

Table 1.

Neuroprotective natural products targeting mitochondrial dysfunction reported from January 2010 to May 2020

[a] Mode of action (MOA) on mitochondria								
Compound name	**Structural class**	**Biogenesis**	**Dynamics**	**Bioenergetics**	**$\Delta\Psi_m$**	**$[Ca^{2+}]_m$**	**Oxytosis/ ferroptosis**	**References**
PlantSource								
Resveratrol	Stilbenoid	X	X	X	X	X	X	(Ferretta et al., 2014; Ishige et al., 2001; Kesherwani et al., 2013; Liu et al., 2012; Narayanan, Dave, Saul, & Perez-Pinzon, 2015; Peng, Tao, et al., 2016; Porquet et al., 2014; Valenti et al., 2016)
ε-Viniferin	Stilbenoid	X			X			(Fu et al., 2012)
Artoindonesianin O	Stilbenoid						X	(Seo et al., 2014)
Pterostilbene	Stilbenoid						X	(Wang, Liu et al., 2016)
Curcumin	Diarylheptanoid	X	X	X	X	X	X	(Eckert et al., 2013; Liu et al., 2008; Liu et al., 2014; Rajasekar et al., 2013; Reddy et al., 2016; Seo et al., 2010; van der Merwe et al., 2017)
Tetrahydrocurcumin	Diarylheptanoid		X					(Vacek et al., 2018)
Acerogenin A	Diarylheptanoid						X	(Lee et al., 2015)
Juglanin C	Diarylheptanoid						X	(Yang et al., 2011)
Genistein	Isoflavone	X		X	X			(Atlante et al., 2010; Rasbach & Schnellmann, 2008)
Daidzein	Isoflavone	X		X	X			(Atlante et al., 2010; Rasbach & Schnellmann, 2008)
Baicalein	Flavone	X		X	X	X	X	(Ishige et al., 2001; Li et al., 2012; Wang et al.,

[a] Mode of action (MOA) on mitochondria								
Compound name	**Structural class**	**Biogenesis**	**Dynamics**	**Bioenergetics**	**$\Delta\Psi_m$**	**$[Ca^{2+}]_m$**	**Oxytosis/ ferroptosis**	**References**
								2017; Zhang et al., 2017)
Luteolin	Flavone	X			X		X	(Ishige et al., 2001; Zhao, Yao-Yue, Qin, & Guo, 2012)
Nobiletin	Flavone				X	X		(Lee, Amarsanaa, et al., 2018)
7,8-Dihydroxyflavone	Flavone						X	(Chen, Chua, et al., 2011)
Cudraflavone B	Flavone						X	(Lee et al., 2014)
Quercetin	Flavonol	X	X	X	X		X	(Ay et al., 2017; Ishige et al., 2001; Liu et al., 2015)
Fisetin	Flavonol			X	X		X	(Alikatte, Palle, Rajendra Kumar, & Pathakala, 2020; Ishige et al., 2001)
Galangin	Flavonol						X	(Ishige et al., 2001)
Morin	Flavonol						X	(Ishige et al., 2001)
Kaempferol	Flavonol						X	(Ishige et al., 2001)
Myricetin	Flavonol				X			(Zhang et al., 2011)
Epigallocatechin-3-gallate (EGCG)	Flavanol	X	X	X	X	X	X	(Chen et al., 2017; Chen et al., 2018; He et al., 2019; Valenti et al., 2013; Valenti et al., 2016)
Catechin/epicatechin	Flavanol	X			X			(Moreno-Ulloa et al., 2014)
Theaflavic acid	Flavanol				X			(Li, Shi, et al., 2020)
Procyanidin B2 3”-*O*-gallate	Flavanol						X	(Song et al., 2019)
Procyanidin C1	Flavanol						X	(Song, Lee, & Kang, 2019)
Naringenin	Flavanone			X	X			(de Oliveira, Brasil, & Andrade, 2017)
Sterubin	Flavanone						X	(Fischer et al., 2019; Maher, Fischer, et al., 2020)

[a] **Mode of action (MOA) on mitochondria**

Compound name	Structural class	Biogenesis	Dynamics	Bioenergetics	$\Delta\Psi_m$	$[Ca^{2+}]_m$	Oxytosis/ ferroptosis	References
Liquiritigenin	Flavanone		X				X	(Jo et al., 2016; Yang, Park, & Song, 2013)
Dihydromyricetin	Flavanonol	X		X				(Liu et al., 2016)
Xanthohumol	Chalconoid (flavonoid)		X					(Wang, Ho, et al., 2020)
Isoliquiritigenin	Chalconoid (flavonoid)				X		X	(Yang et al., 2012)
Morachalcone A	Chalconoid (flavonoid)						X	(Wen et al., 2020)
Morachalcone D	Chalconoid (flavonoid)						X	(Wen et al., 2020)
Silibinin	Flavonolignan			X	X		X	(Geed et al., 2014; Schramm et al., 2018)
Isoorientin	Flavone glycoside	X			X			(Liang et al., 2016; Liang & Li, 2018; Ziqubu et al., 2020)
Orientin	Flavone glycoside				X			(Yu, Wang, et al., 2015)
Palhinoside D	Flavone glycoside						X	(Li et al., 2020)
Puerarin	Isoflavone glycoside				X		X	(Zhu et al., 2016)
Rutin	Flavonol glycoside				X			(Yu, Li, et al., 2015)
Icariin	Flavonol glycoside	X		X				(Zeng et al., 2019; Zeng, Wang, et al., 2019)
Isoquercitrin	Flavonol glycoside						X	(Carmona et al., 2020)
Naringin	Flavanone glycoside			X	X			(Garabadu & Agrawal, 2020)
Chrysanthemin	Anthocyanidin glycoside			X				(Ereminas et al., 2017)
Mulberrofuran K	Lignan						X	(Xia et al., 2019)
Pinoresinol	Lignan						X	(In et al., 2015)
Rasidasin II	Neolignan				X			(Zhou, Yao, et al., 2018)
Obovatol	Neolignan				X		X	(Yang, Lee, et al., 2013)
Honokiol	Neolignan				X		X	(Yang, Lee, et al., 2013)
Syringaresinol-4-O-β-D-glucopyranoside	Lignan glycoside				X			(Yang et al., 2020)

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Compound name	Structural class	Biogenesis	Dynamics	Bioenergetics	$\Delta\Psi_m$	$[Ca^{2+}]_m$	Oxytosis/ ferroptosis	References
Casuarinin	Ellagitannin						X	(Song et al., 2017)
Coniferyl ferulate	Hydroxycinnamic acid				X			(Gong et al., 2020)
Ferulic acid	Hydroxycinnamic acid		X	X	X			(Anis et al., 2020; Zafeer, Firdaus, Anis, & Mobarak Hossain, 2019)
Artepillin C	Hydroxycinnamic acid						X	(Takashima et al., 2019)
Daphnetin	Coumarin						X	(Du et al., 2014)
Auraptene	Terpenoid coumarin			X				(Jang et al., 2019)
Hydroxytyrosol	Simple phenol	X		X				(Peng, Hou, et al., 2016; Zheng et al., 2015)
Salidroside	Phenolic glycoside	X			X			(Barhwal et al., 2015)
Gastrodin	Phenolic glycoside			X	X			(de Oliveira et al., 2018)
α-Arbutin	Phenolic glycoside				X			(Ding et al., 2020)
Butylphthalide	Polyketide				X			(Xiong et al., 2012)
γ-Mangostin	Xanthonoid (polyketide)						X	(Wang, Li, et al., 2016)
β-Lapachone	Naphthoquinone (polyketide)	X						(Lee, Ban, et al., 2018)
Emodin	Anthraquinone (polyketide)						X	(Ahn et al., 2016)
Chrysophanol	Anthraquinone (polyketide)		X				X	(Chae et al., 2017)
Hyperforin	Polyketidic terpenoid					X		(Zolezzi et al., 2013)
5-Heptadecylresorcinol	Resorcinolic lipid (polyketide)			X	X			(Liu et al., 2020)
Δ^9-Tetahydrocannabinolic acid (Δ^9-THCA)	Cannabinoid (polyketidic terpenoid)	X						(Nadal et al., 2017)
Δ^9-Tetrahydrocannabinol (THC)	Cannabinoid (polyketidic terpenoid)	X			X		X	(Schubert et al., 2019; Zeissler et al., 2016)
Cannabidiol (CBD)	Cannabinoid (polyketidic terpenoid)			X			X	(Schubert et al., 2019; Sun et al., 2017)
Cannabinol (CBN)	Cannabinoid (polyketidic terpenoid)						X	(Schubert et al., 2019)

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Compound name	Structural class	Biogenesis	Dynamics	Bioenergetics	$\Delta\Psi_m$	$[Ca^{2+}]_m$	Oxytosis/ ferroptosis	References
Cannabichromene (CBC)	Cannabinoid (polyketidic terpenoid)						X	(Schubert et al., 2019)
Linalool	Monoterpenoid			X	X	X	X	(Sabogal-Guáqueta et al., 2019)
Oleuropein	Iridoid glycoside (monoterpenoid)		X				X	(Kim et al., 2018; Park et al., 2017)
Geniposide	Iridoid glycoside (monoterpenoid)				X			(Lv et al., 2014)
Artemisinin	Sesquiterpenoid				X		X	(Lin et al., 2018; Yan et al., 2017)
Daphne D	Sesquiterpenoid				X			(Wang, Liu et al., 2020)
Linearol	Diterpenoid			X	X	X		(González-Burgos et al., 2016)
Sidol	Diterpenoid			X	X	X		(González-Burgos et al., 2016)
Andrographolide	Diterpenoid						X	(Yang & Song, 2014)
Tanshinone I	Diterpenoid quinone			X	X			(de Oliveira, Schuck, & Bosco, 2017)
Tanshinone IIa	Diterpenoid quinone			X	X		X	(Li et al., 2017)
Cryptotanshinone	Diterpenoid quinone				X			(Lee et al., 2020)
Celastrol	Triterpenoid				X			(Deng et al., 2013)
Asiatic acid	Triterpenoid	X		X	X		X	(Ding et al., 2018; Lee et al., 2012; Xu et al., 2012)
Tenuigenin	Triterpenoid				X			(Liang et al., 2011)
Protopanaxadiol	Triterpenoid				X		X	(Bak et al., 2016)
Glycyrrhizic acid	Triterpenoid saponin	X			X			(Rashedinia, Saberzadeh, Khosravi Bakhtiari, Hozhabri, & Arabsolghar, 2019)
Ginsenoside Rb1	Triterpenoid saponin	X		X	X	X		(Fernández-Moriano, González-Burgos, et al., 2017; Xu et al., 2019)
Ginsenoside Rg1	Triterpenoid saponin	X		X	X	X		(Fernández-Moriano, González-

[a] Mode of action (MOA) on mitochondria								
Compound name	**Structural class**	**Biogenesis**	**Dynamics**	**Bioenergetics**	**$\Delta\Psi_m$**	**$[Ca^{2+}]_m$**	**Oxytosis/ ferroptosis**	**References**
								Burgos, et al., 2017; Xu et al., 2019)
Bicelaphanol A	Trinorditerpenoid			X				(Wang et al., 2013)
Astaxanthin	Carotenoid (tetraterpenoid)				X			(Lee et al., 2011)
α-Tocopherol (vitamin E)	Terpenoid quinone		X		X		X	(Sanderson et al., 2015; Schubert, Kimura, & Maher, 1992)
Huperzine A	Sesquiterpenoid alkaloid			X			X	(Mao et al., 2016; Yang, Ye, et al., 2012)
Tomatidine	Steroidal alkaloid (triterpenoid)				X			(Taveira et al., 2014)
Berberine	Benzylisoquinoline alkaloid	X			X			(Yu et al., 2018)
Neferine	Benzylisoquinoline alkaloid			X	X			(Wu et al., 2019)
Fangchinoline	Benzylisoquinoline alkaloid						X	(Bao et al., 2019)
Sanguinarine	Benzophenanthridine alkaloid				X		X	(Park et al., 2014)
3,3'-Diindolylmethane	Indole alkaloid				X			(Ito et al., 2017)
Voacamine	Indole alkaloid						X	(Currais et al., 2014)
Geissoschizine methyl ether	Indole alkaloid			X			X	(Sun et al., 2016)
3-Alkyl-1,4-benzoquinone	Fatty acid benzoquinone				X			(Madathil et al., 2012)
Embelin	Fatty acid benzoquinone	X		X	X			(Rao et al., 2020)
AnimalSource								
Melatonin	Indole hormone	X	X	X	X	X	X	(Ansari Dezfouli et al., 2019; Carretero et al., 2009; Chuang et al., 2016; Herrera et al., 2007; Jou et al., 2010)
α-Lipoic acid	Fatty acid	X		X	X			(Jiang, Yin, Yao, Brinton, & Cadenas, 2013; Mehrotra et al., 2015)
15-Deoxy- $\Delta^{12,14}$-prostaglandin J2	Fatty acid		X					(Wappler et al., 2013)

[a] **Mode of action (MOA) on mitochondria**

Compound name	Structural class	Biogenesis	Dynamics	Bioenergetics	$\Delta\Psi_m$	$[Ca^{2+}]_m$	Oxytosis/ ferroptosis	References
Progesterone	Steroid (triterpenoid)			X				(Grimm et al., 2014)
Estradiol	Steroid (triterpenoid)			X				(Grimm et al., 2014)
Allopregnanolone	Steroid (triterpenoid)			X				(Grimm et al., 2014; Wang, Yao, et al., 2020)
Estrone	Steroid (triterpenoid)			X				(Grimm et al., 2014)
Testosterone	Steroid (triterpenoid)			X				(Grimm et al., 2014)
3α-Androstanediol	Steroid (triterpenoid)			X				(Grimm et al., 2014)
Dehydroepiandrosterone	Steroid (triterpenoid)			X				(Grimm et al., 2014)
Ursodeoxycholic acid	Steroid (triterpenoid)		X	X	X			(Bell et al., 2018)
Ursocholanic acid	Steroid (triterpenoid)			X	X			(Mortiboys et al., 2013)
Gracilin A	Norditerpenoid				X			(Leirós, Sánchez, et al., 2014)
Makaluvamine J	Iminoquinone alkaloid				X			(Alonso et al., 2016)
MicrobialSource								
Santacruzamate A	Peptide		X		X			(Chen, et al., 2019)
Fumarprotocetraric acid	Depsidon (polyketide)				X	X		(Fernández-Moriano, Divakar, et al., 2017)
Bikaverin	Naphthoquinone (polyketide)				X			(Nirmaladevi et al., 2014)
Anhydroexfoliamycin	Naphthoquinone (polyketide)				X			(Leirós, Alonso, et al., 2014)
Fusarubin	Naphthoquinone (polyketide)						X	(Choi et al., 2020)
Evariquinone	Anthraquinone (polyketide)						X	(Song et al., 2018)
Polyozellin	Terphenylquinone						X	(Yang & Song, 2015)
Fischerin	Pyridone alkaloid						X	(Bang et al., 2019)
Pontemazine B	Phenazine alkaloid						X	(Cha et al., 2015)

[a] "X" denotes reported MOA on mitochondria.