



A focus on natural products for preventing and cure of mitochondrial dysfunction in Parkinson's disease

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Abstract

Mitochondria are considered the only source of energy production within cells. This organelle is vital for neural function and survival by producing energy (adenosine triphosphate (ATP)) and regulating intracellular calcium. Mitochondrial dysfunction, which significantly contributes to both idiopathic and familial types of Parkinson's disease (PD), depletes cellular energy, disrupts homeostasis, and induces oxidative stress, leading to cell death. In recent years several natural products have been discovered to be protective against mitochondrial dysfunction. This review discusses the role of mitochondria in the progression of PD to define the path for using natural products to prevent and/or cure PD.

Keywords Parkinson's disease · Molecular mechanisms · Mitochondrial dysfunction · Neuroprotection · Natural products

Introduction

PD is currently the second most common neurodegenerative disease globally and finally leads to movement disorders, including Bradykinesia, tremor and postural instability (Mohammadipour et al., 2020; Bigham et al., 2021; Heidari et al., 2019; Croese and Furlan, 2018). The mitochondrial dysfunction influences PD progression due to its connection with ATP depletion and oxidative stress elevation. Since neurons are vulnerable to oxidative stress (Shahba et al., 2021; Rastegar-Moghaddam et al. 2019; Fani et al. 2018), mitochondrial dysfunction could have a critical role in the onset and progression of neurodegenerative disorders.

The mitochondrion is a vital cell organelle enclosed by two inner and outer membranes and is considered the only energy source. This organelle is vital for neural function and survival by producing ATP and regulating intracellular calcium (Ca^{2+}) and metabolism of amino acids, fatty acids and steroids (Arun et al. 2016; Perier and Vila, 2010). Undoubtedly, one of the essential functions of mitochondria is energy production as ATP. The importance of this function in neurons is well evident because they have higher

energy demand. Although the adult brain constitutes only about 2% of the body mass, it receives 15% of cardiac output and consumes almost 20% of the total oxygen. The nervous system consumes approximately 25% of total body glucose and more than 20% of energy in ATP (Cabral-Costa and Kowaltowski, 2020; Yang et al., 2017). It has been proven that the energy demand is higher in substantia nigra (SN) dopaminergic neurons (Bolam and Pissadaki 2012). Thus, it is predictable that neurons (especially dopaminergic neurons of SN) will be highly vulnerable to mitochondrial dysfunction in PD.

A variety of sub-mechanisms including the impairment of mitochondrial respiratory complex (MRC), disruptions in Ca^{2+} homeostasis, abnormality in transcription factor myocyte enhancer factor 2D (MEF2D), dysfunction in mitochondrial biogenesis and mitochondrial DNA (mtDNA) depletion are associated with mitochondrial dysfunction (Mohammadipour et al., 2020; Rani and Mondal 2020; Macdonald et al., 2018; Surmeier et al., 2017; Gao et al., 2014; Golpich et al., 2017; Rani and Yang et al., 2008). Therefore the discovery of molecules to prevent or suppress these mechanisms can be neuroprotective and therapeutic for neurodegeneration and PD. This review discusses, in detail, natural products and therapeutic agents effective on mitochondrial dysfunction to shed light on finding an effective treatment for PD.

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Natural neuroprotectors from MRC impairment in PD

The main function of mitochondria is ATP production through the tricarboxylic acid cycle and the respiratory chain system. The respiratory chain (also known as the electron-transport chain) is located within the inner membrane of the mitochondrion and consists of five multiprotein complexes, including complex I (NADH dehydrogenase), complex II (succinate dehydrogenase), complex III (ubiquinol cytochrome C oxidoreductase), complex IV (cytochrome C oxidase) and complex V (ATP synthase) (Golchin, 2016; Perier and Vila, 2010; Cousse et al., 2011). Damage to any of these complexes causes severe cell dysfunction.

It has been proven that deficiency in these complexes is associated with various neurodegenerative diseases. For instance, deficiency in complex I, Complex II, and Complex IV is associated with PD, Huntington's disease, and Alzheimer's disease (Mohammadipour et al. 2020; Arun et al., 2016). It is important to note that dysfunction of each complex is not exclusively related to a specific disorder and also, deficiency in more than one complex may occur in each of the mentioned disorders. For example, Complex I, II and IV deficiency has been found in the SN neurons of PD patients (Cabral-Costa and Kowaltowski, 2020; Grunewald et al., 2016; Golpich et al., 2017). Grunewald et al. (2016), in a post mortem study, reported a ~60% Complex I and ~65% Complex II deficiency in the SN of PD patients (Grunewald et al., 2016). Overall, defects in MRC lead to decreased energy levels, increased production of free radicals, and incomplete oxygen consumption (Weise et al., 2005). Table 1 shows that natural protectives are able to attenuate MRC deficiency and can be considered as valuable therapeutic agents against MRC-deficiency related diseases including PD.

L-theanine

L-theanine (γ -glutamylethylamide) is a non-protein amino acid and abundantly found in tea (Deb et al., 2019). Many studies have reported that L-theanine possesses neuroprotectivity through various mechanisms (Li et al., 2017; Thangarajan et al., 2014; Nishida et al., 2008). A study on the rat striatum showed that intraperitoneal injection of L-theanine at 100 and 200 mg/kg doses could significantly improve mitochondrial complex II (succinate dehydrogenase) activity (Thangarajan et al., 2014).

The effect of L-theanine on the other complexes (particularly complex I) is unclear (table 1). Since complex I deficiency is a hallmark of PD, discovering a new protective agent for this complex would be valuable. Further studies to investigate the effect of L-theanine on this complex is suggestable.

Urtica dioica

Urtica dioica, known also as common nettle, is traditional medicine widely used for its antioxidant, anti-inflammatory and anti-cancer features (Mavi et al., 2004; Akbay et al., 2003). Its protective effects against 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) was investigated in an animal study and found that Post-treatment of this traditional medicine (40 and 80 mg/kg, 14 days) in combination with minocycline (30mg/kg) significantly attenuates mitochondrial complexes (I, II, III, and IV) dysfunction (Bisht et al., 2017).

Caffeine

Caffeine is the most widely used psychostimulant in the world, especially in western countries (Xu et al., 2015; Ullrich et al., 2015) and found in tea, coffee, cocoa as well as several energetic and soft drinks (Ullrich et al., 2015;

Table 1. Assessment of MRC-protectivity of protective agents. The protective effect of each protective is shown with +.

Protectives	Complex I protectivity	Complex II protectivity	Complex III protectivity	Complex IV protectivity	Complex V protectivity
<i>Urtica dioica</i>	+	+	+	+	
Caffeine	+	+	+		
Silibinine		+		+	+
Quercetin	+				
Baicalein	+				
Embelin	+				
Ginseng	+				
Rosmarinic acid	+				
L-theanine		+			
Curcumin		+			

Pong et al., 2015). Caffeine has been shown to have many neuroprotective effects and its protective effects against PD have been reported in previous studies (Kolahdouzan and Hamadeh, 2017). Caffeine can be considered a therapeutic agent for PD through various mechanisms, including mitochondrial protection, oxidative stress and inflammation reduction, and apoptosis inhibition. It can also reduce the activation of protein kinase A (PKA) by inhibiting the binding of adenosine to its receptor that inhibits the increase in the amount of intracellular Ca^{2+} . The results of another study released by Mishra and Kumar (2014) show that caffeine administration at the dose of 40 mg/kg for 21 days can restore mitochondrial complexes I, II, and III activity (Mishra and Kumar, 2014). The large-scale multi-central clinical trial can be helpful to define the clinical effects on the progression of PD.

Quercetin

Quercetin is one of the major flavonoids in plants and is abundantly found in fruits and vegetables. So far, many protective effects have been reported for this natural polyphenol. Due to its anti-inflammatory and antioxidant effects and its ability to cross the blood-brain barrier, quercetin has shown a therapeutic potential for preventing and treating neurodegenerative diseases (Haleagrahara et al. 2011; Ishisaka et al. 2011; Ansari et al. 2009).

Karuppagounder and et al. in 2013 evaluated the mitochondrial protective effect of quercetin. Their results revealed that post-treatment of quercetin (25–75 mg/kg) for four days could attenuate rotenone-induced complex I disability in a dose-dependent manner (Ay et al., 2017).

Silibinin

Silibinin is the major active ingredient of silymarin and is well known as hepatoprotective and neuroprotective (Regodi et al., 2015). The effect of this polyphenolic flavonoid against MPTP was investigated in a previous study and the results showed that post-treatment of silibinin at the dose of 100 and 200 mg/kg has a mitochondrial protective effect by increasing the activity of mitochondrial complexes II, IV and V (Geed et al., 2014).

Rosmarinic acid

Rosmarinic acid is a polyphenolic compound present in many medicinal plants, and lots of studies have reported its protective effects. For instance, antiviral, antibacterial, anti-inflammatory and antioxidant activities have been reported (Petersen and Simmonds, 2003).

Previously, the mitochondrial protective effect of rosmarinic acid was evaluated in an *in vitro* study and

pretreatment with this polyphenol was able to completely block the MPP⁺-induced inhibition of mitochondrial complex I activity (Du et al., 2010).

We did not find any *in vivo* designed research about the protective effects of rosmarinic acid on the MRC. Thus, we suggest investigating the mitochondrial protective effects of this polyphenolic compound in *in vivo* model of PD.

Curcumin

Curcumin (chemically known as 1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3, 5-dione) is a natural polyphenolic compound and is the main active ingredient of rhizomes of *Curcuma longa* (turmeric) (Bagheri et al., 2020; Priyadarsini, 2014). Protective effect of this valuable compound on the mitochondrial respiratory complexes was investigated by Khatri and Juvekar (2016). They treated mice with rotenone (a dopaminergic toxin) and curcumin at the dose of 50, 100 and 200 mg/kg for 21 days and assessed the mitochondrial protective effect of curcumin against rotenone. Their results demonstrated that rotenone decreases the complex II activity. However, curcumin in all 3 different doses was able to alleviate the mitochondrial toxicity effect of rotenone and could increase the activity of this important complex (Khatri and Juvekar, 2016).

Ginseng

Ginseng, as one of the most well-known Chinese herbal medicine has gained popularity throughout the recent decades. The results of previous researches indicate the protective effects of this herbal against neurotoxicity within SN. Ginseng can increase dopamine contents and decrease locomotor dysfunction in PD (Gonzalez-Burgos et al., 2015). It has also been proven that administration of the ginseng protein to PINK1 mutant *Drosophila*, can restore mitochondrial respiratory complex I and is also able to enhance mitochondrial respiration. The results also indicate that administration of ginseng protein increases mtDNA content and ATP production in the PINK1 mutant *Drosophila* (Liu et al., 2020).

Thus, ginseng illustrated mitochondrial protective effects by protecting MRC complex and increasing mtDNA content (Tables 1 and 2). Other possible mechanisms remain elusive and further studies are recommended to find out more about other protective effects of ginseng.

Baicalein

Baicalein is a traditional Chinese herbal medicine, which extracted from the roots of *Scutellaria baicalensis* Georgi and is widely being used for treatment of inflammation (Zhang et al., 2017). A previous study investigated the effects of baicalein against rotenone-induced complex I

Table 2. This table shows the protective (prt.) effects of agents on mechanisms associated with PD. The effect of each agent is shown with +.

Protectives	MRC protectivity	ca ²⁺ homeostasis protectivity	mtDNA protectivity	MEF2D protectivity	Biogenesis protectivity
Quercetin	+		+		+
Baicalein	+		+		+
Embelin	+		+		
Ginseng	+		+		
Allicin			+		+
Resveratrol			+		+
L-theanine	+	+			
Urtica dioica	+				
Caffeine	+				
Silibinine	+				
Rosmarinic acid	+				
Curcumin	+				
Chrysin				+	
Ferulic acid					+

impairment. In this study, the rats were treated by intraperitoneal injection of rotenone at a dose of 2.5 mg/kg for 42 consecutive days in order to induce PD. In the rotenone + baicalein groups, animals were administered 100, 200 and 400 mg/kg baicalein by gavage from day 15 to day 42. The results indicated that treatment with 200 mg/kg baicalein is able to restore the complex I activity (Zhang et al., 2017).

Embelin

Embelin chemically is known as 2,5-dihydroxy-3-undecyl-1,4-benzoquinone and is the major active ingredient of fruits from *Embelia ribes* Burm. Since, embelin has a structure similar to ubiquinone, a recent study investigated its effect against MPP⁺-induced PD. A significant decrease in the ratio of NAD/NADH was observed following MPP⁺ treatment, which indicated the complex I impairment. However, this effect was mitigated when cells were pretreated with embelin at the doses of 2.5 and 5 μ M for 2h before the exposure to MPP⁺ (0.5 mM for 8h) (Rao et al., 2020).

In our searches, we found that no study has been performed about the mitochondrial protective effects of embelin in *in vivo*. Since, *in vitro* conditions are different from those in *in vivo*, to further substantiate the protective effects of this flavonoid, it is necessary to try it in animals. Thus, *in vivo* designed studies are suggested to evaluate embelin effects against PD.

Natural products effective on Ca²⁺ homeostasis in PD

Ca²⁺ is one of the most important ions in cells because it modulates various cellular functions, including excitability,

neurotransmitter release, ATP-production, apoptosis, general regulation of enzymes, and gene expression (Duda et al., 2016; Brini et al. 2014; Burgoyne and Haynes 2014). In addition, Intracellular Ca²⁺ is essential for signal transduction and in neurons, this ion acts as the main second messenger (Gleichmann and Mattson, 2011). Mitochondria are responsible for accumulation, maintenance and releasing of Ca²⁺. Under normal circumstances, an increase in intracellular Ca²⁺ level occurs only transiently and have no damaging effects on neurons. Whereas in PD due to Ca²⁺ homeostasis impairment, permanent increase in intracellular Ca²⁺ concentration is occurred and leads to neuronal damage in SN. The results of the previous studies have shown a significant relationship between mitochondrial Ca²⁺ homeostasis and PD. It has been proven that PD decreases mitochondrial Ca²⁺ uptake and increases cytosolic free Ca²⁺ (Gleichmann and Mattson, 2011), which this event is able to increase ATP synthesis and open the mitochondrial permeability transition pore (mPTP). Opening of the mPTP leads to increased ROS production, cytochrome c releasing and activation of apoptosis (Ludtmann and Abramov, 2018; Liu et al., 2014).

The key question is why dopaminergic neurons in SN are more vulnerable to Ca²⁺ than other neurons? While most other neurons depend on monovalent cation channels for pace making, dopaminergic neurons of the substantia nigra pars compacta (SNpc) are autonomously active and generate action potentials in the absence of synaptic input by using L-type Cav 1.3 Ca²⁺ channels (Chen et al., 2019). On the other hand, a large number of Cav 1.3 channels are within dopaminergic neurons of the SNpc (Liu et al., 2014; Chan et al. 2007), which results in an increase in intracellular Ca²⁺ level. High level of intracellular Ca²⁺ plays a crucial role in neuronal death through various ways including: induction

of mitochondrial dysfunctions, ROS production, and protein folding (Bagatini et al., 2011; Chan et al. 2009).

Moreover, it is reported that Ca^{2+} entry through L-type Ca^{2+} channels (LTCC) increases dopamine metabolism in these neurons to a toxic range (Mosharov et al., 2009). In PD, these channels produce an extra mitochondrial oxidative stress and leads to cell death (Surmeier et al., 2011). Altogether, $\text{CaV}1.3$ channels cause excessive oxidative stress on mitochondria, which contribute to the selectively vulnerability of SN neurons (Chen et al., 2019) and the results of researches show that inhibiting of these channels can protect SN dopaminergic neurons against PD (Ilijic et al., 2011; Surmeier et al., 2017).

L-theanine

L-theanine is a non-protein amino acid and chemically known as γ -glutamylethylamide. It is abundantly present in tea and 200 ml of black tea has been reported to contain about 25 mg of this amino acid (Keenan et al., 2011). L-theanine selectively inhibits the binding of glutamate to ionotropic receptors such as KA, AMPA and NMDA as well as metabotropic receptor type I that results in reduction of the influx of Ca^{2+} (Deb et al., 2019). L-theanine has been found to prevent an increase in the Ca^{2+} influx through glutamate binding inhibition, but its effect on the LTCC remain elusive and further studies are needed to illustrate the probable effects of L-theanine on LTCC.

Piperine and paeonol

It has been demonstrated that piperine and paeonol are inhibitor for both MAO-A and MAO-B in *in vitro* (Kong et al., 2004). On the other hand, it has been proven that MAO inhibitors suppress the Ca^{2+} efflux from mitochondria and have anti-apoptotic effects (Wu et al., 2015). Therefore, MAO-inhibitors such as selegiline and rasagiline can be protective against PD. However, so far no animal-based studies have been performed on the effects of these agents on PD. We suggest that the effects of these herbal medicines could be investigated in future studies.

Neuroprotection targeting mtDNA impairment

Within cells, in addition to nucleus, mitochondria also contain DNA. In other words, mitochondrion has its own DNA (each mitochondrion contains 4–10 DNA molecules), which is known as mitochondrial DNA (mtDNA). The human mtDNA contains genetic coding information of 13 proteins that are subunits of mitochondrial respiratory chain (Subramaniam and Chesselet, 2013) and this shows importance of mtDNA. mtDNA is very sensitive and vulnerable to oxidative stress agents because of two main reasons: 1) mtDNA

is located in the vicinity of inner mitochondrial membrane, where oxidative agents are formed. 2) mtDNA either lack of protective histones or has small amounts of them (Yang et al., 2008). On the other hand, oxidative stress is one of the main events in PD that could cause a severe damage in neurons.

Recent molecular studies have shown that some changes occur in mtDNA during PD including low mtDNA replication, high Heavy strand transcription, and 7sDNA accumulation (Podlesniy et al. 2019). The increase of mtDNA deletions leads to the development of respiratory chain complex deficiency and causes impaired mitochondrial membrane potential, reduced synthesis of ATP, and an increase in ROS release that eventuate to oxidative stress production (Chen et al., 2019). Grunewald et al. showed that mtDNA deletion is associated with mitochondrial transcription factor A (TFAM) and lack of TFAM, causes destabilization of D-loop as well as suppression of mtDNA transcription and replication (Grunewald et al., 2016).

TFAM is an essential mtDNA nucleoid protein and this important protein has been shown to have low levels of expression in PD. As mentioned above, the inner mitochondrial membrane is where that oxidative agents are formed during phosphorylation. One of these agents is superoxide anion radical (O^{2-}), which is present in high amounts in mitochondria. This agent can damage mtDNA, but is normally detoxified by conversion to hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD). The important point is that, interaction of H_2O_2 with ferrous and copper ions generates the hydroxyl radical (OH.), which is highly detrimental to mtDNA (Mattson 2004). In addition, OH. is a potent inducer of membrane lipid peroxidation that results in the production of the 4-hydroxynonenal. 4-hydroxynonenal is a toxic aldehyde implicated in brain aging and neurodegenerative disorders (Yang et al., 2008; Keller and Mattson, 1998), which has been shown to cause DNA damage by binding with DNA bases (Luczaj and Skrzydlewska 2003).

MtDNA damage results in the formation of pores in the mitochondrial membrane and it leads to the release of cytochrome c from intermembrane matrix into the cytosol. Cytochrome c forms a complex with Apaf-1 and caspase 9, which leads to activation of caspase 3 and eventuate to the cell death (Antonsson 2004; Polster and Fiskum, 2004).

Quercetin

Quercetin is one of the major flavonoids found in many plants including fruits and vegetables. The protective effects of this flavonoid against PD was investigated previously in an *in vitro* study and the results indicated that quercetin (10 and 30 μM) treatment for 24 h can increase the mtDNA content (Ay et al., 2017).

Allicin

Allicin (diallyl thiosulfinate) is a major component of garlic (Bigham et al., 2021) and its mtDNA-protectivity was assessed by treating the PC12 cells with 50 μ M of allicin, 30 min before exposure to 100 μ M of 6-OHDA. After 24 h, measurement of the mtDNA content revealed that allicin can protect mitochondria against 6-OHDA toxicity and is able to increase the mtDNA content in *in vitro* (Liu et al., 2015).

Baicalein

Zhang et al., 2017 investigated the mitochondrial protective effect of baicalein against rotenone in an *in vitro* study. They induced toxicity in cells by treatment with 1 μ M rotenone for 24 h and evaluated the protective effect of baicalein. They reported that rotenone reduced the mtDNA copy number, but this reduction was inhibited by baicalein at the dose of 10 μ M (Zhang et al. 2017).

Ginseng

The protective effects of ginseng protein on PD were investigated in a recent study using PINK1 mutant *Drosophila* and the results indicated that ginseng protein can increase mtDNA content and ATP levels in the PINK1 mutant *Drosophila* (Liu et al., 2020).

Embelin

Embelin can be found abundantly in fruits as one of the major active ingredients. Since, its structure is similar to ubiquinone, researchers tend to study its mitochondrial protective effects. A recent study shows that pretreatment with embelin (2.5 and 5 μ M) increases mtDNA content (Rao et al., 2020).

Resveratrol

Resveratrol chemically is known as trans-3,4,5-trihydroxystilbene and is a nature derived compound found in peanuts, red grapes and red wine (Blanchet et al., 2008). Peng et al. (2016) investigated the mitochondrial protective effect of Resveratrol and found that pretreatment of cells with Resveratrol for 24 h is able to increase the mtDNA copy number (Peng et al., 2016).

Neuroprotection aiming at MEF2D impairment

Myocyte enhancer factor 2D (MEF2D) is a transcription factor that has a critical role in the survival of dopaminergic neurons (Gao et al., 2014). This factor is present in mitochondria and regulates mitochondrial complex I

activity (Gao et al., 2014; She et al. 2011). Several studies have reported that MEF2D function is impaired in PD and increases MEF2D activity in dopaminergic neurons of SNpc, protecting them from oxidative stress toxicity (Gao et al., 2014; She et al. 2011; Smith et al. 2006).

Neurotoxins including 6-OHDA as well as aging induce MEF2D oxidation. In addition, oxidized MEF2D level in the brains of postmortem PD is much higher than healthy brains. Oxidation of MEF2D disrupts the function of this important factor because oxidized MEF2D loses its DNA binding ability and gene transcription control (Gao et al., 2014). MEF2D is regulated by chaperone-mediated autophagy (CMA) and oxidized MEF2D is removed by that. Any disruption in the deletion of damaged MEF2D by CMA is associated with an increase in sensitivity to oxidative stress-induced toxicity (Gao et al., 2014). Some studies implicate that disruption in damaged MEF2D removing, causes α -synuclein-induced toxicity (Yang et al., 2009). In addition, decreases in nigral MEF2D have been observed in α -synuclein aggregation conditions (Chu et al., 2011).

Another important factor related to MEF2D is cyclin dependent kinase 5 (Cdk5). Under stress conditions, MEF2D is phosphorylated by Cdk5 (Gong et al., 2003), which leads to an impairment of MEF2D transcriptional function and ultimately causes a reduction in MEF2D level and neuronal death (Tang et al., 2005). Since high MEF2D activity protects the dopaminergic neurons of the SNpc from oxidative stress in PD animal models, it can be considered an effective therapeutic strategy for PD.

Chrysin

Chrysin (5,7-dihydroxyflavone) is a phytochemical and found in various fruits and Vegetables especially in blue passion flowers such as *Oroxylum indicum*, *Passiflora incarnata* and *Passiflora caerulea*. It is also found in *Scutellaria baicalensis* and mushrooms (Mani and Natesan, 2018; Zhao et al., 2016). Many neuroprotective effects have been reported for chrysin (Angelopoulou et al., 2020; Naz et al., 2019). The results of Gao et al. (2014) showed that chrysin administration in animals is able to protect dopaminergic neurons against MPTP by activating MEF2D (Gao et al., 2014). This activation was occurred by regulating the Protein kinase B/Glycogen synthase kinase 3 beta (Akt/GSK3 β) pathway.

Neuroprotection targeting mitochondrial biogenesis impairment

Mitochondrial biogenesis is a regulated process that is crucial for the main functions of mitochondria and plays a key role in maintaining the mitochondrial homeostasis. In simpler terms, mitochondrial biogenesis is a process that new

mitochondria are formed from the existing mitochondria. Thus, Mitochondria are dynamic organelles and continuously are involved in fission/fusion process (Mohammadipour et al., 2020; Friedman and Nunnari, 2004). Impairment of mitochondrial fission/fusion and biogenesis is another important cause for the reduction of number of mitochondria in PD (Mohammadipour et al., 2020; Li et al., 2017; Chan 2006; Cui et al., 2006). In other words, impairment of mitochondrial fission/fusion and biogenesis is strongly associated with neurodegenerative disorders.

This important process is regulated by peroxisome regulated-activated receptor gamma coactivator-1 alpha (PGC-1 α), which is master promoter of oxidative metabolism and mitochondrial biogenesis (Peng et al., 2017). It activates nuclear respiratory factor 1 and 2 (NRF-1,2) and subsequently these factors activate the mitochondrial transcription factor A (TFAM). Thus, synthesis of mitochondrial DNA and proteins for generation of new mitochondria is depended on the activation of PGC-1 α -NRF-TFAM pathway (Li et al., 2017). This important pathway has been reported to be impaired in PD. The study of Grunewald et al. revealed that TFAM expression is low in dopaminergic neurons of the PD patients (Grunewald et al., 2016).

Besides TFAM, the expression of PGC-1 α and NRF is also reduced in PD (Li et al., 2017). Low expression of PGC-1 α results in mitochondrial dysfunction and leads to an excessive ROS formation and decrease in ATP production (Mohammadipour et al., 2020; Li et al., 2017). Fu et al. (2018) showed that a part of this decrease in PGC-1 α -NRF-TFAM expression is due to α -synuclein accumulation (Fig. 1). They found that overexpression of α -synuclein can decrease the PGC-1 α , NRF and TFAM amounts in mitochondria (Fu et al., 2018).

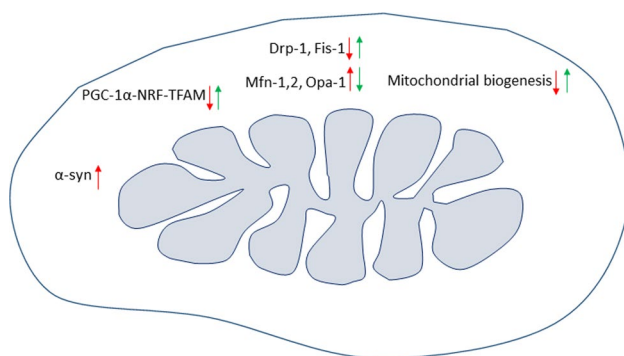


Fig. 1. In PD, alpha-synuclein is increased, which in turn reduces the function of the PGC-1 α -NRF-TFAM pathway (red arrow). Following this decrease, DRP-1 and Fis-1 are decreased whereas Mfn-1 and 2 are increased along with Opa-1 (red arrow), which results in a decrease in mitochondrial biogenesis (red arrow). Natural Products act against these processes (green arrows) and increase mitochondrial biogenesis.

In addition to mentioned factors, there are some other factors related to mitochondrial fission/fusion. Dynamin-1-like protein (Drp-1) and mitochondrial fission 1 (Fis-1) are known as key factors for mitochondrial fission, and mitofusin 1,2 (Mfn-1,2) with optic atrophy-1 (Opa-1) are key factors for mitochondrial fusion (Fig. 1). Any disorder in normal amount of these factors will result in mitochondrial dysfunction (Mohammadipour et al., 2020). It is important to note that these fission/fusion factors are regulated by PGC-1 α . Therefore, any impairment in this factor will lead to decrease in mitochondrial dynamic and biogenesis (Mohammadipour et al., 2020; Peng et al. 2017).

Quercetin

Protective effect of quercetin on the mitochondrial biogenesis was investigated by treating dopaminergic cells at the dose of 10 and 30 μ M (Ay et al., 2017). Cells were treated with quercetin for 24h and measurement of the PGC1- α expression showed a significant increase in PGC1- α expression in the quercetin treated group. Thus, quercetin can be considered as a therapeutic ingredient due to its potential to regulate mitochondrial biogenesis against mitochondrial toxins by increasing the PGC-1. Since mitochondrial biogenesis impairment is one of the most important mechanisms in PD, investigation of quercetin therapeutic effects in *in vivo* studies would be helpful to reveal its protective effects against this disease.

Allicin

To study the effect of allicin against 6-OHDA (100 μ M), PC12 cells were treated with this ingredient at the dose of 50 μ M and the expressions of PGC-1, NRF-1 and TFAM were measured. Pretreatment with allicin 30 min before 6-OHDA, could preserve the mitochondrial biogenesis and the results showed that allicin is able to increase the expression level of PGC-1, NRF-1 and TFAM. In addition, allicin prevented 6-OHDA-induced elevation of the Drp-1 and Fis-1 (key factors for mitochondrial fission) and reduction of the Mfn-1 and Opa-1 (key factors for mitochondrial fusion) (Liu et al., 2015).

In general, by evaluating the previous studies, we can conclude that allicin has great protective effects on mitochondria through preserving the mitochondrial biogenesis and ATP synthesis. Thus, allicin is strongly suggested to be considered as a potent therapeutic agent.

Baicalein

Zhang et al. investigated the therapeutic effects of this flavonoid in both *in vitro* and *in vivo*. For *in vitro* study, they treated SH-SY5Y cells with baicalein (0.1, 1, 10 μ M),

incubated with 1 μM rotenone for 24 h and evaluated the mitochondrial protective effect of baicalein by measuring the mtDNA content and mitochondrial biogenesis (Zhang et al., 2017). The results indicated a mitochondrial protective effect of baicalein against rotenone.

For *in vivo* study, the rats were treated by intraperitoneal injection of rotenone with the dosage of 2.5 mg/kg for 42 consecutive days in order to induce PD. In the rotenone + baicalein groups, animals were administered 100, 200 and 400 mg/kg baicalein by gavage from day 15 to day 42. The results showed that administration of baicalein (200 or 400 mg/kg) for 28 days can increase the mitochondrial number in the SN. In addition, reducing effect of rotenone on the expression of mitochondrial biogenesis key regulators (PGC-1 α , NRF-1 and TFAM) was prevented by baicalein 200 and 400 mg/kg (Zhang et al., 2017).

Ferulic acid

Recently, this polyphenol was administered to rats and its protective effect was evaluated. Oral administration of ferulic acid alleviated 6-OHDA-induced mitochondrial impairment and it was shown that ferulic acid is able to decrease mitochondrial Drp-1 expression and increase gene and protein expression of PGC-1 α in animals (Anis et al., 2020).

Resveratrol

In a previous study, mitochondrial protective effects of Resveratrol were investigated by evaluating the mitochondrial fission and fusion factors (Peng et al., 2016). Rotenone exposure to PC12 cells, increased mitochondrial fission and decreased mitochondrial fusion factors. But this damaging effect of rotenone was prevented by pretreatment of cells for 24 h with Resveratrol.

Overview on the mitochondrial protective effects of agents

Here we want to assess all protective and therapeutic agents mentioned in this review to find the best pathway to reach effective cure for PD. Table 2 compares the mitochondrial protectivity of agents with each other. The main purpose of this table is to show which protective role each agent plays. As this table shows, mitochondrial protectivity mechanisms are not completely discovered for presented agents and there are many information gaps. We need to find more relationships between agents and mechanisms. For instance, we have no information about the protective effects of caffeine-related to the Ca^{+2} homeostasis, mtDNA, MEF2D and mitochondrial biogenesis.

We suggest that future studies investigate all the mechanisms presented in this review for all agents to fill the gaps.

We cannot find an effective treatment for PD with the presence of these gaps and we strongly need more information about the relationship between agents and mechanisms. So, researchers can use table 2 to design their future studies to fill the current gaps.

Here we suggest some research ideas for future studies to help to fill the existing information gaps:

- Study of the effects of allicin, resveratrol and ferulic acid on the MRC (especially complex I), MEF2D, Ca^{2+} homeostasis.
- Study of the effects of ginseng on the MEF2D, Ca^{2+} homeostasis, mitochondrial biogenesis.
- Study of the effects of L-thianine, Urtica dioica, caffeine, Silibinin, rosmarinic acid and curcumin on the MEF2D, Ca^{2+} homeostasis, mtDNA, mitochondrial biogenesis.
- Study of the effects of chrysin and TFB5 on the MRC (especially complex I), Ca^{2+} homeostasis and mtDNA.

Our review shows that quercetin and baicalein have mitochondrial protectivity through 3 paths: MRC, mtDNA, and mitochondrial biogenesis protection. We suggest that the effects of these agents be investigated on animal model of PD in combination with isradipine, nimodipine, L-theanine (as Ca^{+2} homeostasis protectives), and chrysin (as MEF2D protectives). Since we know mitochondrial dysfunction in PD is a multiplex disorder and is associated with various pathological mechanisms, it is time for studying the effects of protective agents in combination with each other to get maximum therapeutic results.

Another important point is that mitochondrial dysfunction is not unique to PD and is involved in many other diseases. Therefore, the protectives introduced in this article can be useful in the treatment of other diseases related to mitochondrial dysfunctions.

Conclusion and future perspectives

So far, many protective agents have been proposed against PD, however, as we all know, none of them alone can cure the disease completely. This indicates that these studies are not sufficient and there is a problem with the current research line. It seems that we will not achieve the desired results by introducing more new protectives. Today, it is time to change our research path to get a more effective treatment for PD.

First, we need to assess protective and therapeutic agents related to each mechanism to find the best and the most effective amongst them. In the second step, we must study the effects of these selected agents in combination with each other. Since, PD has multiple mechanisms to progress, so we need to act through multi pathways to suppress all mechanisms. In the current review, we assessed the protective and

therapeutic agents related to mitochondrial dysfunction, which is only one of the several mechanisms associated with the onset of PD. Future studies and reviews should be focused on the other mechanisms to investigate and find the best protective agents for all mechanisms.

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Data Availability All data are included in this published article.

Declarations

Conflicts of interest The authors declare no conflict of interest to publish this review.

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