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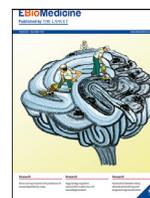
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## Review

## Pharmacological advances in mitochondrial therapy

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## ABSTRACT

Mitochondria play a vital role in cellular metabolism and are central mediator of intracellular signalling, cell differentiation, morphogenesis and demise. An increasingly higher number of pathologies is linked with mitochondrial dysfunction, which can arise from either genetic defects affecting core mitochondrial components or malfunctioning pathways impairing mitochondrial homeostasis. As such, mitochondria are considered an important target in several pathologies spanning from neoplastic to neurodegenerative diseases as well as metabolic syndromes. In this review we provide an overview of the state-of-the-art in mitochondrial pharmacology, focusing on the novel compounds that have been generated in the bid to correct mitochondrial aberrations. Our work aims to serve the scientific community working on translational medical science by highlighting the most promising pharmacological approaches to target mitochondrial dysfunction in disease.

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## 1. Introduction

Mitochondria are core regulators of cellular homeostasis by contributing to a variety of cellular functions including metabolism, apoptosis, intracellular signalling and immunity [1].

Due to the vast number of conditions linked with mitochondrial dysfunction, there is growing interest in the development of pharmacological tools to restore mitochondrial integrity. Here, we will describe the most promising therapeutic strategies, which can be divided into three major classes: (i) targeted and (ii) untargeted mitochondrial drugs, and inhibitors of mitochondrial translation (iii).

Primary mitochondrial diseases (PMD) are a group of rare genetic metabolic disorders characterized by the presence of malfunctioning mitochondria due defects in oxidative phosphorylation (OXPHOS) [2]. Mitochondria contain their own genetic material (mtDNA), which ensures the synthesis of 13 subunits of the respiratory chain. All other mitochondrial components are encoded by the nuclear DNA (nDNA). While mutations in the mtDNA only affect the integrity of the respiratory chain [3], nuclear gene defects disrupt OXPHOS by also impairing pathways involved in mitochondrial protein import, translation and assembly [4]. PMD manifest with diverse clinical symptoms, age of onset and progression [5,6], and the most affected tissues are those that highly depend on oxidative metabolism, such as heart, skeletal muscle, brain and retina [2]. Symptoms often affect multiple organs

and range from muscle weakness to exercise intolerance, cardiomyopathy, cognitive disabilities, metabolic deficiencies, vision and/or hearing loss. Differently from mitochondrial impairments caused by primary OXPHOS impairments, secondary mitochondrial dysfunctions (SMD) arise when other pathological processes negatively impact on mitochondrial homeostasis. SMD is often involved in the development of age-related diseases, such as neurodegeneration, cancer, diabetes and cardiovascular diseases. In these pathologies, SMD can result from defects in (i) mitochondrial dynamics, (ii) biogenesis, (iii) quality control and (iv) metabolism.

The heterogenic aetiology of mitochondrial diseases demands for alternative pharmacological strategies to target mitochondrial defects and many compounds have therefore been devised. Here, we will focus on the ones that are already in clinical development and thereby bear promise as tools to treat mitochondrial diseases and other pathological conditions highly affected by SMD.

## 2. Mitochondria-targeted agents

## 2.1. OXPHOS modulators

One of the widest class of mitochondria-targeted therapeutic agents comprises compounds that exert their function through interaction with respiratory chain components. Among these, some of the most promising ones are the antioxidant molecules idebenone and OP2113, and the insulin sensitizer imeglimin.

Idebenone (also known as Raxone, Catena, Sovrima, Puldysa, CV-2619) is a synthetic short chain analogue of coenzyme Q<sub>10</sub> with

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improved solubility and pharmacokinetics [7,8]. Originally described as a lipophilic electron carrier with antioxidant properties, idebenone is predicted to act as an antioxidant in the transfer of electrons from respiratory complex II to complex III [9]. Due to its antioxidant properties and safety profile, idebenone has been evaluated in several clinical trials for a variety of mitochondria-related disorders (Table 1). The trials generated inconclusive results for many of the tested diseases, including Friederich's ataxia (FRDA) and Alzheimer's disease (AD). In spite of this, the drug retains promising potential for the treatment of Leber's hereditary optic neuropathy (LHON) [10] and Duchenne muscular dystrophy (DMD) [11]. At this regard, idebenone has received fast track and orphan drug designation by the United States Food and Drug Administration (FDA) for the treatment of DMD [12]. Marketed as Raxone, the drug is being reviewed by the European Medicines Agency (EMA) for the treatment of visual impairments in patients with LHON [13]. Under the trade name Puldysa, idebenone has also been granted orphan drug designation by the EMA, which is currently reviewing its marketing authorization application in the treatment of DMD patients who are not using glucocorticoids, with decision likely to be made this year [14]. The successful applications of this small molecule have warranted further studies aimed at improving bioavailability and effectiveness [15].

Another compound targeting mitochondrial ROS production is OP2113 [(5-(4-methoxyphenyl)dithiole-3-thione)], also known as anethole trithione and marketed as Sulfarlem. Two independent studies demonstrated that OP2113 inhibits up to 80% superoxide and hydrogen peroxide production by respiratory complex I ( $I_Q$  site), without disrupting OXPHOS, thereby exerting cardioprotecting function [16,17]. Though there are currently no clinical trials to document the efficacy of OP2113 for targeting mitochondrial dysfunction, the drug is already available for alternative therapies given its safety profile in humans. Hence, any new clinical trials could emerge and proceed quickly.

Mitochondrial dysfunction has recently emerged as a key component of diabetes pathophysiology, promoting both hepatic and skeletal muscle insulin resistance and insulin secretory defects in pancreatic  $\beta$ -cells [18,19]. Despite this, there are no known therapies for type 2 diabetes (T2D) that aim at preserving mitochondrial function. Ibiglimin is a recently developed antidiabetic compound targeting and correcting mitochondrial dysfunction in all affected organs of T2D patients, namely pancreas, liver and skeletal muscle [20]. However, the precise mitochondrial mechanism of action of the compound remains unknown. Studies conducted on rat hepatocytes and isolated liver mitochondria found that imeglimin is a competitive inhibitor of respiratory complex I and restores the hyperglycemia-induced reduction in complex III content and activity, lowering reverse electron flow-associated ROS production and improving mitochondrial respiration [21]. Amelioration of mitochondrial function by imeglimin was also confirmed by following studies demonstrating prevention of mitochondrial permeability transition-induced cell death in endothelial and islet cells [22,23]. The compound has so far successfully passed several multi-country phase 1 and 2 clinical trials assessing the efficacy, safety and tolerability profiles in patients with T2D, both as monotherapy and add-on therapy in patients inadequately controlled with the glucose-lowering medications metformin or sitagliptin (Table 1). Recently concluded phase 3 clinical trials showed significant improvement in patients with T2D without causing severe hypoglycemia events [24]. The compound is being prepared for regulatory submission and prospective 2021 approval, which would result in the release of this innovative first oral antidiabetic agent in the upcoming year.

## 2.2. Compounds controlling the transport of metabolites

Another potential mitochondrial target to treat metabolic disorders is the mitochondrial pyruvate carrier (MPC), that mediates

the import of pyruvate into the mitochondrial matrix across the mitochondrial inner membrane thereby linking glycolysis to OXPHOS [25]. Aberrant mitochondrial pyruvate uptake, which is linked to mitochondrial dysfunction and metabolic rewiring, plays an important role in the pathogenesis of metabolic diseases [26,27], including non-alcoholic fatty liver disease (NAFLD). Hepatic mitochondrial dysfunction, characterized by excessive oxidative metabolism and predisposing cells to oxidative damage, plays a key role in the pathophysiology of NAFLD [28]. Therefore, pharmacological inhibition of MPC is being explored as potential strategy to correct mitochondrial dysfunction in NAFLD, especially in patients suffering from its most severe form, called non-alcoholic steatohepatitis (NASH), for which there are no approved pharmacological therapies.

Thiazolidinediones (TZDs), also called glitazones, are a class of peroxisomal proliferator-activated receptor (PPAR)- $\gamma$  agonists with insulin-sensitizing activity that also exert an inhibitory effect on MPC [29]. Pilot studies provided evidence for mild beneficial effects of glitazone compounds in the treatment of NAFLD-NASH (Table 1). Therefore, PPAR- $\gamma$ -sparing glitazone derivatives have been developed to improve the therapeutic effect of glitazones in NASH patients specifically through inhibition of MPC. Among these are MSDC-0602K and PXL065, both of which are now being tested at phase 2 clinical trials (Table 1).

The promising therapeutic potential of the next-generation glitazone MSDC-0602K in NASH treatment was suggested in a pre-clinical study conducted in a murine model of the disease [30]. However, subsequent clinical trials indicate that the compound has little effect on reversing either liver steatosis or fibrosis in patients with NASH [31]. The compound might therefore be better suited as a therapeutic agent for T2D associated with NASH, with a phase 3 clinical trial currently ongoing (Table 1).

PXL065 (deuterium-stabilized R-pioglitazone, formerly known as DRX065) is another valuable promising molecule for the treatment of NASH. Encouraging results showing symptom reduction come from pre-clinical studies in a mouse model of NASH [32], while safety and tolerability in NASH patients were assessed in a phase 1 clinical study [33]. PXL065 is advancing into a phase 2 clinical trial assessing dose-efficacy in subjects with NASH (Table 1).

Pharmacological inhibition of MCP is also explored for treating neurodegenerative diseases [26,27]. The MSDC-0602K analogue MSDC-0160 is being investigated in AD and Parkinson's disease (PD) therapies. A phase 2 clinical trial showed improved cerebral glucose metabolism and reduced brain damage in AD patients (Table 1), while a pre-clinical study in experimental models of PD confirmed the neuroprotective and anti-inflammatory properties of the compound [34].

## 2.3. Other strategies

Considering the large number of trials with positive outcomes and the clinical success of idebenone, direct modulation of the mitochondrial respiratory chain components represents one of the most promising approaches to tackle mitochondrial dysfunction in human disease.

Along with OXPHOS modulators and MPC blockers, other mitochondria-targeted compounds are currently being tested. Two pharmacological strategies that will not be discussed in this review due to inconsistent results comprise inhibitors of the mitochondrial permeability transition pore (mPTP), such as (i) cyclosporine A (CsA), and (ii) lipid-binding molecules that regulate mitochondrial function and structure through modulation of mitochondrial membrane properties, including the cardiolipin (CL)-binding peptide elamipretide (formerly known as Bendavia, MTP-131 and SS-31).

**Table 1**  
Mitochondria-targeted agents

Drug	Disease	Clinical trial	Participants	Doses	Outcome
Idebenone	FRDA	NCT00229632	51	5, 15 or 45 mg/kg	Treatment with idebenone in higher dosages was well tolerated and correlated with a dose-dependent improvement in neurological function and scoring of activities of daily living (ADL) [35].
		NCT00537680	70	450 or 900 mg/day, 1350 or 2250 mg/day depending on weight	Though statistically significant data was not quantified, overall an improvement in the International Cooperative Ataxia Rating Scale (ICARS) scoring was noted in treatment groups. FRDA Rating Scale (FARS) score improved by 1.6 in the treated group whereas for placebo group a decline was observed by 0.6 points [36].
		NCT00697073	68	1350 or 2250 mg/day depending on weight	12-month extension study of NCT00537680. FRDA patients receiving idebenone over an 18-month period (combination of the two studies) showed a significant improvement in neurological function (as assessed by ICARS score) [37].
		NCT00905268	232	180 or 360 mg/day, 450 or 900 mg/day, 1350 or 2250 mg/day depending on weight	No clinical benefit suggested.
		NCT00993967	200	1350 or 2250 mg/day depending on weight abd 450 or 900 mg/day if poor tolerability	Extension study of NCT00905268. Less fatigue and improved speech and general function were reported.
		NCT01303406	29	450 mg/day	Patients that had previously participated in a 12-month randomised clinical trial were asked to assess their treatment assignment. The study concluded that none of the patients were accurately able to ascertain their treatment assignment, though a significant difference in ICARS score was measured when ambulatory patients alone were considered [38].
		DMD	NCT00654784	21	150 mg tid
	NCT00758225		21	150 or 300 mg tid depending on weight	Completed, no results reported.
	NCT01027884		65	300 mg tid	In patients with DMD, treatment with idebenone yielded a significant reduction in the percentage predicated peak expiratory flow (PEF% <sub>p</sub> ). Similarly, other parameters of respiratory function including PEF, Forced Vital Capacity (FVC) and forced expiratory volume in 1 s (FEV <sup>1</sup> ) were also demonstrated to be significantly improved [40].
	MELAS	NCT02814019	255	300 mg tid	Active, not recruiting.
		NCT03603288	266	300 mg tid	Recruiting.
		NCT00887562	27	900 or 2250 mg	Completed, no results reported.
	LHON	NCT00747487	85	900 mg/day	Treatment with idebenone in patients with LHON was well-tolerated. Though best recovery in visual acuity post-treatment was not observed, treatment with idebenone appeared to be beneficial in patients with discordant visual acuities [41].
			39		Treatment with idebenone improved tritan and protan color vision, most prominently in patients with discordant visual acuity [42].
		NCT01421381	85	900 mg/day	Visual acuity was preserved only in patients treated with idebenone. This effect was maintained at least 2.5 years post-treatment, supporting the therapeutic potential of idebenone in recovery of vision and attenuating vision loss [43].
		NCT01495715	N/A	N/A	Withdrawn (no reason given).
		NCT02771379	250	900 mg/day	Active, not recruiting.
		NCT02774005	250	N/A	Active, not recruiting.
		NCT04381091	N/A	900 mg/day	Extension study of NCT02774005.
Multiple sclerosis	NCT01854359	61	2250 mg/day	Active, not recruiting.	
	PD	NCT03727295	180 (estimated)	180 or 360 mg/day	Not yet recruiting.
		NCT04152655	180	30 mg tid	Recruiting.
HD	N/A	91	90 mg tid	No significant differences between treatment and placebo groups were scored, as assessed by cognitive and functional tests such as measurements of ADL or Quantitative Neurologic Examination (QNE) [44].	
AD	Private trial	102	45 mg bid	Treatment was well-tolerated. Significant improvements in patients treated with idebenone were measured using the Randt memory test of global mesic capability. Similar improvements with treatment were observed in scoring of "intellectual impairment" and "emotional impairment", as well as measurements of reaction time. The placebo group deteriorated progressively [45].	

(continued)

Table 1 (Continued)

Drug	Disease	Clinical trial	Participants	Doses	Outcome
Imeglimin	T2DM	Private trial	536	120, 240 or 360 mg tid	Patients treated with idebenone showed significant dose-dependent improvement in Alzheimer's Disease Assessment Scale (ADAS-total), ADAS-Cognitive Subscale (ADA-Cog) and ADAS-Non-Cognitive Subscale (ADAS-NonCog) scores [46].
		Private trial	450	90 or 120 mg	Patients treated with idebenone showed significant dose-dependent improvement in ADAS-total, ADAS-Cog and ADAS-NonCog scores [47].
		EudraCT N. 2006-000909-29	N/A	2000 mg/day, 500 or 1500 mg bid	Imeglimin treatment was well-tolerated. Treatment reduced glucose plasma level during a prolonged meal. Fasting plasma glucose and glycated haemoglobin (HbA1c) were also shown to be reduced at similar levels to that achieved by metformin [48]. Completed, no results reported.
		EudraCT N. 2011-004086-32	N/A	N/A	
		EudraCT N. 2010-018580-42	156	1500 mg bid	Patients that were being treated with metformin for T2DM were given imeglimin as an add-on medication. Metformin-imeglimin treatment resulted in a 0.44% decrease in HbA1c compared to placebo ( $p < 0.001$ ), while metformin treatment also reduced fasting glucose levels [49].
MSDC-0160	T2DM	EudraCT N. 2010-023915-33	170	1500 mg bid	Patients that were being treated with sitagliptin for T2DM were given imeglimin as an add-on medication. Add-on treatment with imeglimin reduced levels of HbA1C, which increased in the placebo group ( $p < 0.001$ ). Similarly, fasting plasma glucose (FPG) levels were lower with treatment ( $p < 0.014$ ) [50].
		NCT00760578	86	90 or 220 mg	Completed, no results reported.
		NCT01103414	356	50, 100 or 150 mg	Completed, no results reported.
MSDC-0160	AD	NCT01374438	29	150 mg/day	Patients with AD treated with MSDC-0160 demonstrated that while no significant alterations in cerebral metabolic glucose rate when regions of interest associated with AD were referenced to either pons or whole brain. Upon using the cerebellum as reference then the baseline levels in cerebral metabolic rate of glucose for treatment patients group while a significant decline was observed for placebo for the lateral temporal cortex, medial temporal cortex and anterior cingulate-medial frontal cortex [51].
		NCT02784444	392	62.5, 125 or 250 mg	Patients diagnosed with NASH and fibrosis received one of three doses of MSDC-0602K. The patients receiving the highest dosages showed significant reductions in insulin, glucose, HbA1c and sodium serum levels compared to placebo, while statistically significant hepatic histological improvements were not observed. Nonetheless, the application of the drug was deemed safe with potential efficacy for patients with T2DM and liver injury [31].
MSDC-0602K	T2DM	NCT01280695	129	100 or 250 mg	Treatment promotes glucose metabolism [52].
		NCT03970031	1800 (estimated)	N/A	Not yet recruiting.
PXL065	NASH	NCT04321343	120 (estimated)	N/A	Not yet recruiting.
SBT-272	ALS	N/A	N/A	N/A	Recruiting (announced by Stealth BioTherapeutics).

### 3. Untargeted mitochondrial agents

#### 3.1. Mitochondrial biogenesis

An encouraging therapeutic approach to treat mitochondrial diseases is represented by the pharmacological induction of mitochondrial biogenesis to overcome inherent OXPHOS deficiency. Mitochondrial biogenesis refers to the processes that increment mitochondrial mass through import and membrane integration of newly synthesized proteins and division of pre-existing mitochondria [53]. In the past years, considerable research focused on the development of molecules able to potentiate the transcription of nuclear and mitochondrial genes encoding respiratory chain subunits to improve OXPHOS activity. A promising strategy consists of targeting peroxisomal proliferator-activated receptors (PPARs), a group of transcription factors governing a multitude of cellular functions, including mitochondrial metabolism and energy homeostasis. Among the downstream targets of PPARs is PPAR- $\gamma$  coactivator-1 $\alpha$  (PGC-1 $\alpha$ ) that, once activated, binds to and stimulates transcription factors involved in mitochondrial biogenesis [54]. To date, several agonists of PPARs are being tested as potential treatments for mitochondrial disorders and neurodegenerative syndromes.

Among them, TZDs have shown the highest clinical significance. TZDs are PPAR- $\gamma$  activators with insulin-sensitizing and

hypolipidemic effects currently used for management of T2D in lieu of or in combination with metformin. One of the most promising TZDs for the treatment of mitochondrial dysfunction is the FDA-approved drug pioglitazone, which has been shown to promote mitochondrial biogenesis and function in diabetic patients [55,56]. Pre-clinical studies provided auspicious results suggesting its applicability to the treatment of mitochondria-related neurological disorders [57–59]. A phase 2 clinical trial is ongoing to assess the effectiveness of pioglitazone in ameliorating neurological symptoms in patients suffering from X-linked adrenoleukodystrophy (X-ALD), a severe chronic neurodegenerative disorder characterized by peroxisomal and mitochondrial dysfunction. Moreover, a recently developed pioglitazone metabolite with optimal brain penetration, MIN-102 (leriglitazone), has entered phase 2/3 clinical trials to test its efficacy and safety on X-ALD and FRDA (Table 2).

Other PPAR agonists that entered clinical trials for mitochondria-related diseases are bezafibrate and RENO01. Bezafibrate is a pan-PPAR activator [60] currently used as antilipemic agent (not FDA-approved). The repurposing of bezafibrate to correct metabolic defects in mitochondrial myopathies through induction of mitochondrial biogenesis has been the subject of a recently completed phase 2 clinical trial (Table 2). Although the beneficial effects of bezafibrate on patients suffering from mitochondrial disorders were confirmed

**Table 2**  
Untargeted mitochondrial agents

Drug	Disease	Clinical trial	Participants	Doses	Outcome
Acipimox	T2DM/ cardiomyopathy	NCT00943059	9	250 mg tid	Administration of acipimox to patients already diagnosed with diabetes increased insulin sensitivity by approx 27% and reduced hydrogen peroxide production by approx 45%. However, no improvements in mitochondrial oxidative capacity were measured [99].
			21		Acipimox treatment increased plasma non-esterified fatty acids (NEFA) levels ( $p < 0.01$ ) and skeletal muscle lipid content, while decreasing insulin sensitivity. Despite the elevation in plasma NEFA levels, mitochondrial respiration in skeletal muscle was found increased [100].
	T2DM/obesity	N/A	22	250 mg every 6 h	Patients with T2DM and normal glucose tolerant (NGT) individuals were given acipimox, which significantly reduced fasting plasma free fatty acid (FFA) concentration. This decrease correlated with an increase in insulin sensitivity in both control and T2DM patients [101].
Bezafibrate	Obesity	NCT01488409	39	250 mg tid	The study tested the effect of acipimox on reducing FFA and increase insulin sensitivity in NGT obese patients. While effects were not seen on insulin-stimulated glucose uptake, the levels of fasting glucose decreased significantly with treatment.
		T1D Mitochondrial Myopathy	NCT01816165 ISRCTN12895613	40 (estimated) N/A	250 mg qid N/A
	Mitochondrial Myopathy	NCT02398201	6	200–400 mg	Bezafibrate was given to patients with mitochondrial myopathy in varying doses for 12 weeks. No major adverse effects were observed. The results showed a modest improvement in cardiac function and a reduction in the number of immunodeficient muscle fibres [102].
MIN-102	FRDA X-ALD	NCT03917225 NCT03231878	36 105 (estimated)	15 mg/ml N/A	Active, not recruiting. Active, not recruiting.
Pioglitazone	NASH	NCT00063622	247	30 mg	Patients that were diagnosed with NASH without diabetes were treated with pioglitazone. Treatment did not yield significant rates of improvement in NASH but reduced serum alanine aminotransferase (ALT) levels, lobular inflammation and hepatic steatosis [103].
		ISRCTN10319160	74	30 mg/day	Patients that were diagnosed with NASH without diabetes were treated with pioglitazone. The patients in the treatment group showed reduction in glucose and insulin C-peptide levels (not statistically significant). Hepatocellular injury and fibrosis were significantly reduced with pioglitazone treatment. Significant reductions in metabolic parameters including ALT aminotransferase, gamma-glutamyltransferase and ferritin were also observed [104].
	NCT00994682	101	30 mg initially, then titrated to 45 mg	Patients with either pre-diabetes or T2DM and NASH were treated with pioglitazone. 58% of patients showed at least a 2 point reduction in NAFLD score when compared to placebo (statistically significant). Histologic scores also showed improvements in fibrosis and adipose tissue, hepatic and muscle insulin sensitivity. Resolution of NASH was demonstrated in 44% of patients with T2DM compared to 26% in patients without diabetes. Significant reduction in fibrosis and insulin sensitivity in adipose tissue was observed in patients with diabetes when compared to those without diabetes [105] [106].	
	N/A	18	30 mg/day	Patients with NASH without diabetes were treated with pioglitazone. Treatment was well tolerated and sufficient to rescue serum ALT levels to normal in 72% of the patients. Improvement in glucose and FFA sensitivity to insulin was also measured. Steatosis, cellular injury and fibrosis were significantly reduced compared to baseline values [107].	
	T2DM	N/A	60	45 mg/day	Patients with T2DM received pioglitazone. The treatment significantly increased mitochondrial copy number, and mitochondrial biogenesis factors, such as mitochondrial transcription factor A (MtfA). FAO pathway gene expression was also stimulated [55].
		NCT00816218	26	45 mg/day	T2DM patients received either treatment with pioglitazone or nutritional therapy. Treatment yielded statistically significant 35% reduction in fasting plasma non-esterified fatty acids (NEFA) and 79% increase in plasma adiponectin concentration. Treatment also increased

(continued)

Table 2 (Continued)

Drug	Disease	Clinical trial	Participants	Doses	Outcome
	FRDA	NCT00811681	40	15 mg/day, up to 45 mg/day	acetyl CoA carboxylase (ACC) phosphorylation and insulin-stimulated glucose disposal [56]. Completed, no results reported.
	PD	NCT01280123	210	15 or 45 mg/day	Patients diagnosed with PD received one of two doses of pioglitazone in a bid to assess whether treatment with the drug was sufficient to change the total Unified Parkinson's Disease Rating Scale (UPDRS) score before and after treatment. The study found that no significant changes in scoring could be observed in either dosage groups compared to placebo, though there was a small decrease in scores with treatment [108].
		N/A	8396	Variable	Patients that were identified to be on the anti-diabetic glitazone were studied to evaluate the incidence rates of PD. Usage of glitazone demonstrated a statistically significant decrease risk of incident PD when compared to use of metformin only to treat diabetes ( $p < 0.01$ ) [109].
PXL770	T2DM	NCT03886103	8	N/A	Completed, no results reported.
		NCT03395470	60	N/A	Completed, no results reported.
	NASH	NCT03763877	120 (estimated)	N/A	Recruiting.
		NCT03950882	32 (estimated)	N/A	Not yet recruiting.
REN001	Mitochondrial myopathy	NCT03862846	23	N/A	Terminated (COVID-19 Pandemic sufficient data gathered to achieve the study objective).
	FAOD	NCT03833128	12 (estimated)	N/A	Recruiting.
Resveratrol	AD	NCT00678431	39	5 mg	Patients with AD were treated with a preparation of 5 g dextrose, 5 g malate and 5 mg resveratrol. Though no statistically significant changes were observed between treatment and control groups, there was less deterioration in the former according to ADAS-Cog, Alzheimer's Disease Cooperative Study-Activities of Daily Living Scale (ADCS-ADL) and Neuropsychiatric Inventory scores [110].
		NCT01504854	119	500 mg/day, followed by 1 g bid at week 13	In a retrospective study, AD patients that were treated with 1 g of resveratrol were compared to placebo-treated patients. Treatment reduced levels of metalloproteinases with increased interleukin-4 and fibroblast growth factor (FGF) in CSF. Further the decline in Mini-Mental Status Examination (MMSE) and ADCS-ADL scores was attenuated with treatment [111].
	FRDA	NCT01339884	24	1 or 5 g/day	FRDA patients were treated with varying doses of resveratrol. While the drug was found to be safe and well-tolerated, no alteration in peripheral blood mononuclear cell frataxin levels were observed between the dosage groups. An improvement in Friedreich Ataxia Rating Scale and audiologists and speech measurements were observed in the high dose group only [112].
		NCT03933163	40 (estimated)	1 g tid	Recruiting.
	Mitochondrial myopathy/FAOD	NCT03728777	20	1000 mg/day	Completed, no results reported.
Sonlicromanol	Mitochondrial diseases	NCT02544217	30	400 to 2000 mg	Sonlicromanol treatment was safe and well tolerated, with effect on cardiac function at high doses (800 mg/day) [113].
		NCT02909400	18	100 mg	Though no significant improvement in outcome measures was obtained in m.3243A > G MELAS patients without cardiovascular involvement, the treatment was well-tolerated and safe [114].
		NCT04165239	27 (estimated)	50 or 100 mg tid	Recruiting.

for short term usage, the results of the trial argued against the safety of long-term use due to the development of mitochondrial toxicity.

REN001 is a recently developed PPAR  $\beta/\delta$  agonist that, like bezafibrate, is under investigation as potential treatment for severe mitochondrial diseases including primary mitochondrial myopathies and fatty acid oxidation disorders (FAOD). Phase 1 clinical trials are ongoing to test its safety and tolerability (Table 2).

Other potential targets to modulate PGC-1 $\alpha$  activity and restore mitochondrial function are sirtuin 1 (Sirt1) and AMP-protein activated kinase (AMPK). Several activating compounds have been identified for both proteins, with some already in clinical trials for mitochondria-related diseases.

Sirt1 is a nicotinamide adenine dinucleotide (NAD<sup>+</sup>)-dependent histone deacetylase that plays a prominent role in metabolic tissues,

promoting mitochondrial biogenesis and turnover [61]. Sirt1 activity can be pharmacologically regulated by means of allosteric modulators, often referred to as Sirt1-activating compounds (STACs). Alternatively, Sirt1 activation can be promoted by using NAD<sup>+</sup> precursors, also called NAD<sup>+</sup> boosting molecules (NBMs), which target enzymes promoting the synthesis of NAD<sup>+</sup> or inhibiting its degradation. Studies conducted on murine models suggest the applicability of STACs and NBMs as potential therapeutic agents for mitochondrial diseases and neurodegenerative disorders linked with mitochondrial dysfunction [62,63].

One of the most studied STAC is resveratrol, a naturally occurring antioxidant compound, the use of which as a dietary supplement has been linked to prevention of various aging-associated diseases [64]. Resveratrol is currently undergoing clinical trials to evaluate its

beneficial effects on diseases associated with mitochondrial dysfunction. However, based on the available results, no definitive conclusions can be drawn on its efficacy. Two independent phase 2 clinical trials conducted on patients with AD had opposite outcomes, with one reporting no differences between control and treatment groups, and the other proposing reduced neuro-inflammation and cognitive decline associated with the use of resveratrol (Table 2). Similarly, a study conducted on subjects suffering from FRDA revealed that high-dose resveratrol ameliorates symptoms, despite having no effects on mitochondrial function and causing development of gastrointestinal adverse reactions (Table 2). Regarding primary mitochondrial syndromes, a trial to study the therapeutic effects of resveratrol on subjects suffering from mitochondrial myopathy or fatty acid oxidation defects has recently been completed, but the results have not yet been disclosed (Table 2).

An example of NBMs is instead the niacin derivative acipimox (also known as Olbetam), a NAD<sup>+</sup> precursor that is not yet approved by FDA and currently used only as additional or alternative treatment for hyperlipidaemia and insulin resistance. The use of acipimox to improve mitochondrial function has been studied in several clinical trials, evaluating efficacy of treatment in obesity, diabetes and mitochondrial myopathy (Table 2). The results of these studies are contradictory. While some studies confirmed the positive effect of acipimox on skeletal muscle mitochondrial function in diabetic and obese patients, including increased respiration and ATP synthesis, others reported that the insulin-sensitizing and lipid-lowering effects of the drug were not matched by alterations in mitochondrial function between treated and control groups (Table 2). To explore whether acipimox is an alternative to treat mitochondrial disease, a clinical trial is currently underway testing the ability of the compound to reduce symptoms in patients with mitochondrial myopathy (Table 2).

Together with modulation of PPARs and Sirt1 activities, activation of AMPK is recognized as another therapeutic strategy to restore mitochondrial function [65]. Several direct and indirect AMPK activators have been identified so far, the majority of which were mainly developed to treat metabolic diseases such as diabetes and non-alcoholic liver conditions, independently of their effect on mitochondrial function. Among these, the direct AMPK activator PXL770 is instead under investigation as potential treatment for mitochondria-related diseases [66]. After successful completion of phase 1 clinical trials to assess safety and tolerability on diabetic subjects [67], PXL770 demonstrated promising therapeutic potential in a preclinical study involving a murine model of NASH [68]. PXL770 is currently in phase 2 trials to evaluate its effectiveness in NASH patients and already demonstrated good efficacy, safety and tolerability profiles [69].

### 3.2. Mitochondrial redox state

Oxidative stress is unanimously acknowledged as a main driving factor for the onset and progression of many age-related, chronic human diseases [70]. Mitochondria are a major intracellular source of reactive oxygen species (ROS) [71], the toxic potential of which affects many cellular and mitochondrial components. Among the diseases whose pathogenesis depends on ROS-induced cellular damage are mitochondrial disorders and neurodegenerative diseases [72, 73]. Mitochondrial redox balance is therefore a target to treat diseases dominated by mitochondrial dysfunction. Among the antioxidant agents with highest therapeutic potential are those targeting the glutathione (GSH) and thioredoxin (Trx) redox systems.

Two compounds known to increase GSH levels and optimizing GSH detoxification pathways and the effectiveness of which in the treatment of mitochondrial conditions is currently being tested are the vitamin E analogue EPI-743 [74] (also called vincerinone, vatiquinone or  $\alpha$ -tocotrienol quinone) and RP103 [75] (cysteamine bitartrate delayed-release). Since the applicability of both compounds to treat mitochondrial dysfunction has been extensively covered in

recent publications [76–77], we will focus on Sonlicromanol (KH176), a novel antioxidant agent targeting the Trx system [78]. The drug interacts with peroxiredoxins (Prxs), increasing their peroxidase activity and reducing ROS-induced cell death [78]. The safety, efficacy and tolerability of Sonlicromanol in patients with mitochondrial diseases including MELAS, LHON and Leigh syndrome, were tested in phase 1 and 2 clinical trials, confirming mild positive effects in m.3243A>G patients (Table 2). Sonlicromanol was recently granted orphan drug designation from the European Commission for maternally inherited diabetes and deafness (MIDD) and larger trials are being implemented to establish the clinical relevance of the compound [79].

### 3.3. Mitochondrial dynamics

Mitochondria are highly dynamic organelles that constantly change their shape and organizational complexity, ranging from isolated, discrete entities to connected, highly branched networks that allow spatial and temporal synchronization. Mitochondrial dynamics is an essential physiological process that, through coordinated fusion and fission events, orchestrates proper intracellular positioning of mitochondria at areas of high-energy requirements [80]. Alterations in mitochondrial dynamics are associated with cancer development and progression of cardiovascular and neurodegenerative conditions [81,82], besides representing a causative event in some mitochondria-related neuropathies, such as Charcot-Marie-Tooth type 2 subtype A (CMT2A) and autosomal dominant optic atrophy (ADOA) [83,84]. There is therefore a growing interest in the development of compounds to restore mitochondrial dynamics. Recent studies focused on targeting the pro-fission protein dynamin related protein 1 (Drp1) and the pro-fusion protein mitofusin 2 (Mfn2) as potential strategies to treat neurodegenerative conditions.

The quinazolinone derivative mdivi-1 (mitochondrial division inhibitor) was the first inhibitor of mitochondrial fission discovered [85]; it attenuates mitochondrial fission by interfering with the Drp1 filament assembly at mitochondrial constriction sites protecting from apoptosis via inhibition of their mitochondrial outer membrane permeabilization (MOMP) [85]. More recent studies have suggested that mdivi-1-mediated repression of mitochondrial fragmentation and improvement in mitochondrial function might be independent of Drp1 and might be linked to inhibition of complex I-mediated ROS production [86] or regulation of mitochondrial Ca<sup>2+</sup> uptake [87]. The clinical potential of mdivi-1 in the treatment of neurodegenerative diseases has been evaluated in a few pre-clinical studies. A study in an AD mouse model found that the compound reduces mitochondrial fragmentation and energy imbalance thereby improving learning and memory deficits as well as preventing deposition of amyloid- $\beta$  (A $\beta$ ) plaques in the brain [88]. Mdivi-1 has also shown protective effects against the development of MS. In EAE mice, mdivi-1 reduced infiltration of inflammatory cells in the spinal cords and inflammation-mediated demyelination [89]. Additionally, studies conducted on murine models of heart diseases, including myocardial infarction, ischaemia/reperfusion injury and diabetic cardiomyopathy revealed that the Drp1 inhibitor preserved cardiac function and reduced severity of symptoms [90–93]. Mdivi-1 represents therefore a valuable candidate compound for the development of cardioprotective drugs.

In the search for molecules reverting pathological mitochondrial fragmentation, a novel Drp1-derived peptide, P110, has been designed [94]. Differently from mdivi-1, P110 is selective for Drp1 and inhibits both Drp1 enzymatic activity and interaction with the mitochondrial adaptor protein mitochondrial fission 1 (Fis1). Subsequently, P110 administration in animal models of neurodegeneration and myocardial infarction results in improved mitochondrial function and decreased cell damage [94]. Administration of P110 has also been shown to exert a neuroprotective effect in murine models of PD [95],

**Table 3**  
Inhibitors of mitochondrial translation

Drug	Disease	Clinical trial	Participants	Doses	Outcome
COL-3	Advanced solid tumors Brain tumors	NCT00003721	33	N/A	Completed, no results reported. The study was designed to evaluate the maximum tolerate dose of COL-3 in patients with recurrent high-grade glioma in combination with enzyme-inducing anti-seizure drugs. It showed that administration of COL-3 alone only had a partial response and didn't warrant further studies as a standalone therapy [127].
		NCT00004147	33	25 mg/m <sup>2</sup> /day	
	Kaposi's sarcoma	N/A	18	25, 50 or 70 mg/m <sup>2</sup> /day	Patients with AIDS-related Kaposi's sarcoma were assessed for changes in blood levels of metalloproteinases (MMP)-2, -9 and vascular endothelial growth factor (VEGF). The treatment was well tolerated and induced both a decline in MMP-2 serum levels and tumour regression [128]. Patients with AIDS-related Kaposi's sarcoma were given one of two doses of COL-3. The lower daily dosage of COL-3 was shown to have a greater response rate compared to the higher dose group. In both dose groups a significant decrease in MMP-2 and MMP-9 serum levels was observed, along with antitumour activity [129].
		NCT00020683	75	50 or 100 mg	
Soft tissue sarcomas	N/A	15	50 mg/m <sup>2</sup> /day	Patients with soft tissue sarcomas were treated with COL-3 to assess the effects of the drug on disease progression and survival. Treatment did not yield an attenuation of disease progression [130].	
Tigecycline	AML	NCT01332786	27	50 to 350 mg/day	Completed, no results reported.
	CML	NCT02883036	100 (estimated)	N/A	Not yet recruiting.

AD [96] and ALS [97], preventing locomotor deficits, cognitive decline and muscle atrophy, respectively.

Another promising approach to correct defective mitochondrial dynamics consists in promoting mitochondrial fusion through stimulation of MFNs fusogenic activity. A recent study showed that treatment of neuronal cells expressing CMT2A Mfn2 mutant clones with a chimeric MFN2 agonist (B/A-1) restores mitochondrial fusion along with improved mitochondrial function and motility [98]. More importantly, the use of the Mfn2 agonist in the Mfn2 T105M murine model of CMT2A reverted axonal mitochondrial dysmotility [98], thus suggesting its potential application to treat neurodegenerative conditions caused by defective axonal mitochondrial transport.

Even though the safety and efficacy of P110 in humans is to be yet tested, all of the above supports the viability of Drp1 and Mfn2 modulators as therapeutic agents in mitochondria-related diseases.

#### 4. Inhibitors of mitochondrial translation

In addition to strategies aimed at restoring mitochondrial function in diseased tissues, other compounds are currently being tested to target mitochondrial protein synthesis in rapidly proliferating cancerous cells. This approach seems to be particularly promising to selectively kill cancer cells under chemotherapy, irradiation and during metastasis, when they are highly reliant on mitochondrial metabolism [115].

Like their bacterial progenitors, not only do mitochondria contain their own genome, but also possess a dedicated machinery for protein synthesis. This comprises 22 transfer ribonucleic acids (tRNAs) and two ribosomes that allow the synthesis of all the mitochondrially encoded protein subunits of the OXPHOS system [116]. Pharmacological interference with the mitochondrial translation apparatus would lead to mitochondrial dysfunction without impairing cytosolic protein synthesis, thereby ensuring selectivity of targeting. This assumption has made the repurposing of antimicrobial drugs an elected strategy to target cancer cells.

Currently, only the FDA-approved antibiotic tigecycline has entered clinical trials for cancer treatment. Tigecycline belongs to the glycylcycline class of antibiotics and was developed to treat tetracycline-resistant bacterial infections. Like tetracyclines, tigecycline binds the 30S subunit of elongating ribosomes and halt bacterial protein synthesis through inhibition of tRNA entry [117]. To date, tigecycline is being tested for both acute and chronic myeloid leukaemia (Table 3), but several studies also suggest its applicability to other hematologic and solid tumours, including lymphomas [118], ovarian

cancer [119] and nonsmall lung cancer [120]. Other FDA-approved tetracycline derivatives, such as doxycycline and tetracycline-3 (COL-3), have also been enrolled in trials to treat solid and hematologic tumours as well as metastatic cancers (Table 3). Although their repurposing was initially based on their inhibitory activity on metalloproteases [121], the direct link with suppression of mitochondrial translation was proposed at the basis of their anticancer activity [122].

Another molecule whose anticancer effect has been linked to repression of mitochondrial translation is RK-33 (diimidazo[4,5-*d*:4',5'-*f*-1,3]diazepine), an inhibitor of the DEAD-Box RNA Helicase DDX3 [123]. RK-33 showed promising results in preclinical studies as radiosensitizing agent for the treatment of DDX3-overexpressing tumours [124,125]. Differently from tigecycline, RK-33-mediated inhibition of mitochondrial translation causes cancer cell death through OXPHOS impairment and ROS burst [124] and the compound is due to enter clinical trials for treatment of Ewing sarcoma and breast cancer [126].

#### 5. Conclusions

Mitochondria represent a critical therapeutic target for a variety of common debilitating pathologies and significant progresses have recently been made in the development of therapeutic strategies to restore mitochondrial homeostasis in affected tissues. Nevertheless, drug development for mitochondrial medicine still faces many challenges. Despite the large number of mitochondria-specific agents that have been tested in clinical studies, only a few compounds have been approved so far for the treatment of rare mitochondrial diseases. This review detailed the recent achievements in mitochondrial pharmacology, which derived from multi-disciplinary advances in the fields of mitochondrial biology and molecular targeting. Attention should now be focused on mitochondria-controlled processes and mitochondrial interactions with the surrounding organelles.

#### 6. Outstanding questions

Recent advancements have unveiled that a critical aspect in the biology of mitochondria is represented by their interaction through membrane contact sites with the endoplasmic reticulum (ER), lysosomes and the nucleus. As such, can interorganellar contacts represent a novel target to amend mitochondrial defects? And is the signalling between mitochondria and their interacting organelles involved in PMD or SMD?

Impaired mitochondrial quality control has been demonstrated to promote age-related pathologies. Nevertheless, drugs that effectively modulate the process *in vitro* have shown little effect *in vivo*. Does the pharmacological induction of mitochondrial clearance still represent a viable strategy to treat mitochondria-related pathologies or is it accompanied by further cell damage?

## 7. Search strategies and selection criteria

To gather data for this review, references were identified using the MEDLINE/PubMed and Google Scholar databases from relevant articles preferentially published in the last ten years applying the search terms “mitochondrial diseases” or “mitochondrial myopathy” or “Barth syndrome” or “Leigh syndrome” or “LHON” or “MELAS” or “Pearson syndrome” or “neurodegenerative diseases” or “AD” or “AMD” or “DMD” or “FRDA” or “HD” or “multiple sclerosis” “PD” or “diabetes” or “NASH” or “cardiovascular diseases” or “obesity” or “cancer” AND “targeting mitochondria” or “mitochondrial therapies” or “mitochondrial dysfunction”. Clinical trials were searched using ClinicalTrials.gov and ClinicalTrialsRegister.eu databases. All studies were considered regardless of date published with preference for the most recently published articles relevant to compounds included in clinical trials.

## Declaration of Competing Interests

All authors declare that they have no competing interests.

## Contributors

AS, DF and MC conceived the original draft. AS and DF wrote the original manuscript. AS, DF and MC edited the final manuscript.

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