Targeting mitochondria: a great boon to fight type 2 diabetes

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Abstract
Type 2 diabetes is a chronic metabolic disease characterized by the development of low-grade systemic inflammation, hyperglycaemia, and hyperlipidaemia. These pathogenic traits have a profound impact on mitochondrial function as mitochondria serve as intermediary organelles between nutrients and energy production. Moreover, the mitochondrial quality control system is also altered and rendered defective by type 2 diabetes. These alterations entail the accumulation of defective mitochondria, which causes the diabetic background to deteriorate further. In this context, it is of paramount importance to improve mitochondrial function and ameliorate the consequences of mitochondrial dysfunction. This review assesses different treatments that target mitochondrial dysfunction as a way of treating type 2 diabetes. Lifestyle interventions and pharmacological treatments such as biguanides, thiazolidinediones, α-glucosidase inhibitors, glucagon-like peptide 1 receptor agonists, or sodium-glucose co-transporter-2 inhibitors protect mitochondrial function, while novel mitochondria-targeted molecules including natural compounds, mitochondria-targeted antioxidants, inhibitors of mitochondria pore transition pore opening, NO and H2S donors, and inhibitors of mitochondrial fission positively impact on mitochondrial function and its quality control mechanisms. Most of these therapeutic tools require more research, but they already show promising therapeutic mechanisms that improve type 2 diabetes and its cellular consequences.

Key Words
- mitochondria
- diabetes
- treatments
- natural compounds

Introduction
Type 2 diabetes (T2D) is a chronic metabolic disease triggered by sustained high levels of circulating glucose and lipids and insulin signalling impairment. These alterations induce a generalized proinflammatory state and an impairment in the redox balance of the organism. While reactive oxygen species (ROS) act as signalling molecules and are necessary for correct cellular function, their accumulation can alter the function and the structure of important regulatory proteins, causing oxidative stress. There are several pathways of ROS overproduction in T2D, which can be divided into cytoplasmic pathways and mitochondrial pathways. The first group includes the activation of NAPDH oxidases, the polyl pathway, and the enzyme protein kinase C. In the case of the mitochondrial pathway, the main source of the production of ROS is the electron transport chain (ETC). When this mechanism is overactivated, free electrons can escape and react with undesired targets, thus creating ROS. This usually happens in complex I and III, in the Q cycle and during the reverse electron transport. ROS production by all these mechanisms causes cellular and systemic
alterations such as the formation of advanced glycation end-products, oxidized LDL (oxLDL), or activation of signalling pathways including JNK, nuclear factor kB (NFkB), or apoptosis. These pathways contribute to the generation of proinflammatory cytokines that, in turn, lead to the pathogenesis of T2D. Experimental evidence shows that ROS and the proper function of mitochondria are central to the pathogenesis of T2D. Those cellular alterations, if not properly controlled, can affect the normal function of the organs. Precisely, poorly controlled T2D patients can develop vascular complications, which can be divided into two groups: macrovascular complications and microvascular complications (Fig. 1). The first type is related to the formation of atherosclerotic plaque and the malfunction of vessels and cardiac tissue (coronary heart disease, myocardial ischaemia, stroke, peripheral arterial disease...); the former is originated in insulin-independent tissues with small vessels that experiment a steep and chronic increase in the glucose concentrations (including retinopathy, neuropathy, and nephropathy) (Zheng et al. 2018). Those complications can reduce the quality of life and the life expectancy of T2D patients and therefore need to be addressed and prevented with the existing therapies or new ones.

Role of mitochondria in type 2 diabetes

Mitochondria are vital organelles in T2D, as they couple glucose and lipid metabolism with energy production through oxidative phosphorylation. Thus, proper mitochondrial function is vital in T2D. There are several mitochondrial alterations in T2D, such as reduced respiratory rate and metabolic inflexibility (Bajpeyi et al. 2017, Haythorne et al. 2019) or defects in mitochondrial dynamics and biogenesis (Rovira-Llopis et al. 2017). The cell has various pathways by which it maintains a functioning pool of mitochondria, named mitochondrial quality control pathways. These pathways include mitochondrial biogenesis, mitochondrial dynamics, and mitophagy (Liang & Kobayashi 2016). However, it is usual to find defects in these mechanisms in different tissues affected by T2D and which explain most of the pathophysiological traits of this disease (Rovira-Llopis et al. 2017, Wang et al. 2018). In this sense, therapeutic approaches that tackle mitochondrial dysfunction are of interest as a potential way of ameliorating or treating T2D (Fig. 2). Different approaches could range from preventing dysfunction by reducing ROS production to modifying mitochondrial quality control mechanisms. In this review, we will explain some of these different approaches in new and already existing treatments.

Interventions targeting mitochondria

Exercise and lifestyle interventions

Among the easiest ways to target mitochondrial function in T2D are exercise and other lifestyle interventions, such
as nutritional intervention. Regarding exercise, Sparks et al. report that 9 months of aerobic and resistance training increased mitochondrial content and function in muscle tissue (Sparks et al. 2013). In agreement with these results, 12 weeks of aerobic training increase mitochondrial function and peroxisome proliferator-activated receptor-gamma coactivator 1 alpha (PGC1α) expression and lead to a pro-fission phenotype in muscle samples of T2D patients (Axelrod et al. 2019).

Regarding nutritional intervention, there are different strategies that can alter mitochondrial function, including diets or nutrient supplementation. Some dietary patterns are associated with worse mitochondrial function, for example, a diet high in lipids. In this sense, lipid infusions in T2D patients increase fission and mitophagy proteins and induce the disorganization of mitochondrial cristae (Axelrod et al. 2021). Similarly, high-fat diet (HFD)-induced insulin intolerance reduces respiration and ATP synthesis (Miotto et al. 2018). Some dietary patterns are related to an improvement in mitochondrial function. As an example, db/db mice on a ketogenic diet (KD) display improved mitochondrial function and reduced oxidative stress in cardiac muscle (Guo et al. 2020). Likewise, a 3-week very low-calorie diet improves mitochondrial function and mitochondrial biogenesis in peripheral blood monocytes but has little effect on adipose tissue in T2D patients (Urbanová et al. 2017).

**Pharmacological approaches**

Several already developed T2D treatments improve mitochondrial function, which might be key to its beneficial effect. Biguanides, which include metformin, the most prescribed antidiabetic drug, have a positive effect on mitochondrial function and performance. Pharmacological concentrations of metformin improve diverse parameters of mitochondrial function through AMP-activated protein kinase (AMPK) action in a cell model of T2D hepatocytes and in liver tissue from HFD-T2D mice (Wang et al. 2019). In addition, in peripheral blood from T2D diabetic patients, metformin reduces mitochondrial ROS (mtROS) production, boosts the antioxidant response, prevents pro-fission mitochondrial morphology, and induces an increase in mitophagy, possibly through AMPK action (de Marañón et al. 2021, 2022). Similarly, in adipose tissue, metformin reduces the pro-fission phenotype in an AMPK-dependent manner (Li et al. 2016).

Thiazolidinediones are another therapeutic group in which we can find drugs such as rosiglitazone and pioglitazone. This pharmacological group acts by enhancing insulin sensitivity in muscle, liver, and adipose tissue by stimulating the action of peroxisome proliferator-activated receptor (PPAR) nuclear receptors. PPARs increase mitochondrial function and mass, and this might explain, in part, the beneficial effect of these drugs (Lee et al. 2017). According to the data, pioglitazone...
activates PGC1A through PPARg signalling in rabbit cardiac tissue, ameliorating mitochondrial dynamics and biogenesis and mitochondrial structure and function compared to those from non-treated diabetic rabbits (Zhang et al. 2021b). Another study involving healthy and human T2D subjects illustrated the effect of pioglitazone treatment on mitochondrial function in skeletal muscle samples. They conclude that pioglitazone treatment increases the protein expression of ETC complexes and fatty acid oxidation enzymes (Fiorentino et al. 2021). Similar results were obtained in muscle biopsies from T2D patients compared to those not receiving treatment. In the same study, the researchers analyse the effect of rosiglitazone, obtaining the opposite effects: the treatment decreases mitochondrial respiration and has no effect on ETC complex expression compared to untreated T2D subjects (Rabøl et al. 2010).

Another important group of drugs developed in recent years are glucagon-like peptide 1 receptor agonists (GLP1-RAs), such as exenatide, dulaglutide, semaglutide, liiraglutide, and lixisenatide. To date, liiraglutide has been shown to exert a strong effect on mitochondrial function, improving mitochondrial content and function in the muscle of spontaneous diabetic Torii (SDT) rats (Yamada et al. 2022). These mechanisms imply the blocking of mitochondrial dysfunction and triggering of apoptosis, as seen in a study on human renal mesangial cells subjected to hyperglycaemia. Treatment with liiraglutide upregulates sirtuin 3 (SIRT3), preventing the activation of apoptosis in a SIRT3-dependent manner (Li et al. 2019a). It has also been shown to protect against hyperglycaemia and hyperlipidaemia in RIN-m5F beta cells by upregulating the antioxidant response and restoring mitophagy (Kornelius et al. 2019). Liiraglutide was found to increase mitochondria number and area in cardiac muscle from KKAY mice compared with non-treated counterparts, possibly through protein tyrosine phosphatase 1B and activation of phosphoinositol-3 kinase (Ji et al. 2014). Most studies have demonstrated the benefits of liiraglutide with respect to mitochondrial function, and exenatide has also been shown to exert a protective effect on mitochondrial function in cardiac muscle from two T2D models (genetic KK or spontaneous DIO), increasing mitochondrial size and improving mitochondrial structure. Surprisingly, exenatide not only undermined mitophagy and mitochondrial dynamics but also corrected the oxidative stress caused by diabetes (Monji et al. 2013) in mice models of genetic and acquired (HFD-induced) T2D. Lixisenatide was also shown to improve mitochondrial function through the activation of PGC1A and c-AMP responsive element-binding protein in human umbilical cord endothelial cells, but the study in question did not assess T2D conditions (Zhao & Pu 2019).

Lastly, SGLT2 inhibitors are a pharmacologic group that block the reabsorption of glucose in the kidney. The SGLT2 isofrom is expressed mainly by proximal tubule cells in the kidney, but other isoforms can be expressed in other tissues, including muscle, intestine, and the endothelium. This pharmacologic group is known to protect against cardiac damage; in this sense, the protection of the heart’s mitochondrial function after a myocardial infarction has been confirmed by a study in Otsuka Long-Evans Tokushima Fatty (OLETF) diabetic rats. The group receiving empagliflozin shows larger mitochondria, increased Bcl2-interacting protein 3 expression, and reduced fission protein 1 expression compared to non-treated counterparts. This indicates that empagliflozin can normalize mitochondrial alterations in cardiac muscle caused by diabetes and protects from further alterations caused by the infarction (Mizuno et al. 2018). Interestingly, empagliflozin also reduces the production of mtROS and proinflammatory cytokines in leukocytes of T2D patients (Canet et al. 2021). Regarding dapagliflozin, it has beneficial effects on the mitochondrial ultrastructure and function in the liver of HFD-STZ mice. In the study in question, the treatment improves respiratory function and mitochondrial dynamics and biogenesis and normalizes their size and number (Belosludtsev et al. 2021).

The other pharmacological groups of antidiabetics, such as alpha-glucosidase inhibitors, meglitinides (nateglinide and repaglinide), and sulfonylureas (glibenclamide, glipizide and glimepiride), have not been studied in depth regarding mitochondrial function. Possibly, their glucose-lowering effect benefits mitochondrial function indirectly, but this is an area that needs more research.

Novel therapeutic approaches targeting mitochondria

In recent years, several molecules have been described to ameliorate mitochondrial function and benefit T2D patients (Table 1). These therapeutic molecules can be divided into those groups:

Natural compounds

Natural compounds are usually obtained from fruits or vegetables, and most of them are members of the polyphenol or terpenoid families.
Molecules that upregulate PGC1A: Quercetin abrogates oxidative stress and improves mitochondrial morphology and ATP synthesis through the upregulation of the AMPK-PGC1A pathway in RSC96 dorsal ganglion neurons (Zhang et al. 2021a). This molecule also upregulates PGC1A in skeletal muscle from HFD-insulin-resistant mice (Henagan et al. 2014, Houghton et al. 2018). Another compound capable of upregulating PGC1A is a-lipoic acid. This molecule impedes the degeneration of mitochondria in retinal endothelial cells under 20 mM glucose through the activation of PGC1A and its targets nuclear respiratory factor 1 (NRF1) and mitochondrial transcription factor A (TFAM) (Santos & Kowluru 2011). PGC1A is also upregulated by catalpol, which is able to revert the drop in the mitochondrial membrane potential, ATP production, and mitochondrial DNA copy number observed in HFD-STZ-induced T2D mice (Li et al. 2014). Resveratrol is among the best characterized and studied molecules with pharmacological activity. Despite this molecule’s many mechanisms of action, the improvement it produces in mitochondrial function is mainly triggered through PGC1A activation. In particular, deacetylation of PGC1A by SIRT1 reduces mitochondrial oxidative stress in hyperglycaemic podocytes (Zhang et al. 2019).

PPARg: a-lipoic acid and acetyl-l-carnitine increase mitochondrial respiration, fatty acid oxidation, and mitochondrial biogenesis through PPARg in the cell culture of 3T3-L1 adipocytes (Shen et al. 2008). Carnitine is also associated with PPARg-dependent improvement of mitochondrial ultrastructure in skeletal muscle of insulin-resistant mice (Choi et al. 2018).

SIRT1 activators: SIRT are a family of histone deacetylases that are involved in the antioxidant response, and resveratrol is among the best-characterized activators. In H9c2 mouse cardiac

### Table 1

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cells under high glucose and/or Sirt1 knockdown, resveratrol was capable of inducing the expression of PGC1α, NRF1, NRF2, oestrogen-related receptor alpha, and TFAM through SIRT1 signalling (Ma et al. 2017). It also maintains a correct mitochondrial function and reduces oxidative stress through SIRT1 signalling in rat mesangial cells subjected to hyperglycaemia (Xia et al. 2012). In INS1E cells, resveratrol stimulates glucose-induced insulin release through SIRT1 and the induction of its targets glucose transporter 2, pancreatic and duodenal homeobox-1, glucokinase (GK), and TFAM (Vetterli et al. 2011). Fisetin is a bioactive flavanol that potently induces SIRT activity. To be specific, in peripheral blood mononuclear cells (PBMC) under hyperglycaemic conditions, fisetin inhibits p47phox expression and induces SIRT1, SIRT3, SIRT6, and forkhead box 3a protein expression, which are abrogated in hyperglycaemia (Kim et al. 2017). Lastly, curcumin also boosts SIRT1 activity and expression in a diabetic background and prevents oxidative stress. In HF/HG-STZ type 2 diabetic rats and H9c2 cardiomyocytes, curcumin downregulates the expression of superoxide dismutase (SOD), malonyldialdehyde (MDA), cytosolic CytC and downregulates the expression of superoxide dismutase 2 (SOD2) and blocks the transforming growth factor b (TGFb)/SMAD family member 3 (Smad3) profibrotic effect in HF/HG-STZ mice models and in HG-treated H9c2 cells (Li et al. 2019).

• AMPK activators: Salicylates or its bioactive compound, salsalate, induces the activity of AMPK, which activates several downstream pathways (PPARg, PGC1α, or SIRT1). In fact, treatment with salicylates induces the activation and phosphorylation of AMPK and the subsequent activation of PGC1α, NRF2, and TFAM, leading to an increase in mitochondrial biogenesis in murine 3T3-L1 adipocytes. Additionally, salicylates improve citrate synthase activity and the expression of the ETC (Yan et al. 2017). Salsalate and salicylate induce FOXO phosphorylation by AMPK in palmitate-treated Hep3b cells, HFD male Sprague–Dawley rats, and represses the palmitate-induced increase on selenoprotein P (a marker of aggravated insulin resistance (IR)) in male db/db mice (Jung et al. 2013). Berberine has been employed for diverse therapeutic problems; in T2D, it reduces the cellular alterations of diabetes via AMPK. The activation could occur through many mechanisms, such as liver kinase B1 (LKB) upregulation, which phosphorylates AMPK and downregulates the expression of glycogenic enzymes, as seen in the liver of HFD-STZ rats (Jiang et al. 2015). Berberine also inhibits mitochondrial complex I, as described in a study which analysed the effect of berberine in LKB−/− myotubes or HFD-diabetic mice (Turner et al. 2008).

• Upregulating the antioxidant response via kelch-like Ech associated protein 1 (KEAP1)/NRF pathway: Bardoxolone reverts the impact of hyperglycaemia on mitochondrial membrane potential, ROS reduction, and mitochondrial oxygen consumption rate in PC12 cells (Kalvala et al. 2020). Sulforaphane is also an effective NRF2 activator, as shown by diverse studies. The treatment induces NRF2, which reverts the increase in ROS production and mitochondrial dysfunction, as well as the accumulation of methylglyoxal in human microvascular endothelial cells cultured in hyperglycaemic conditions (Xue et al. 2008). Lastly, curcumin is another effective inducer of NRF2 translocation. Treatment of HFD-insulin-resistant mice with curcumin induces NRF2 and its target HO-1 and reduces the increment in MDA and ROS in mitochondria isolated from skeletal muscle (He et al. (2012)). A13, an analogue of curcumin, has been synthesized and tested in HFD-STZ type 2 diabetes rats. Both compounds reduce MDA concentrations and rise the antioxidant SOD, NQO1, catalase, and NRF2 in myocardial tissue, thus resolving the oxidative stress caused by T2D (Xiang et al. 2020).

Mitochondria-targeted antioxidants

In recent years, there has been intense research in the field of mitochondrial-targeted antioxidants. The result has been a wide group of molecules specially designed for entering and accumulating within the mitochondrial matrix. There are two main groups: quinone conjugates and synthetic peptides. Quinone conjugates include mitoquinone (MitoQ), MitoE, MitoTempo, and SkQ1. In the case of the peptides, the main molecules are Serto-Schiller peptides and mitochondrial penetrating peptides (MPPs).

For example, our group has described how MitoQ can correct the T2D-driven alterations in the mononuclear cells of T2D patients. The treatment reduces the production of mtROS and increases glutathione peroxidase 1 protein levels. It also reduces inflammation, as reflected by a reduction in the expression of TNF alpha (TNFα) and...
NFκB, and decreases the interactions of these cells with the endothelium (Escribano-Lopez et al. 2016). In a similar study, we analysed the effect of MitoQ in INS-1E cells subjected to hyperglycaemia and palmitate treatments. The results are comparable to those of the previous study, but MitoQ also increases oxygen consumption and reduces the ER stress markers, glucose-regulated protein 78 and phospho-eukaryotic initiation factor 2 alpha (Escritá-Hlavatá et al. 2019). The treatment also prevents the development of T2D-associated complications such as diabetic nephropathy. In this sense, in a study employing tubular cells of db/db mice and hyperglycaemia-treated HK-2 cells, mitoQ reduces ROS and balances mitochondrial fragmentation — altered in the T2D models — and activates the mitophagy driven by PINK/PARKIN proteins. Moreover, the treatment restores the expression of NRF2 and KEAP1 and their interaction (Xiao et al. 2017).

In the case of mitoTEMPO, few reviews have assessed its beneficial effect on different complications of T2D. This molecule reduces mtROS production and the activation of the NLR-family pyrin domain containing 3 inflammasome, and the subsequent production of cytokine secretion in LPS-stimulated PBMCs and monocyte-derived macrophages (Lee et al. 2013). MitoTEMPO also reduces cardiomyopathy changes in T2D by reducing mtROS production and downregulating extracellular signal-regulated kinase 1/2 (ERK1/2) signalling and apoptosis in adult cardiomyocytes subjected to hyperglycaemia, or hearts from db/db mice (Ni et al. 2016).

SKQ1 has been less studied than the previously mentioned antioxidants. However, promising results have been reported in diverse articles. For example, the treatment of db/db mice with SkQ1 accelerates wound closure by promoting epithelization and vascularization. It also reduces lipid oxidation and increments myofibroblasts and macrophage recruitment. However, there is not a decrease in proinflammatory cytokines (Demyanenko et al. 2017, p. 1). The antioxidant effect was further confirmed by reductions in mtROS and prevention of mitochondrial fragmentation in INS-1E cells and in isolated mouse pancreatic islets under high glucose (Plecitá-Hlavatá et al. 2019).

Mitochondria-targeted antioxidant peptides such as SS-31 also have beneficial effects in diverse T2D-related alterations. To be precise, our group previously described how the treatment of PBMCs cells from T2D patients with SS31 reduces ROS production and increases glutathione content and mitochondrial membrane potential compared to healthy subjects, possibly by the reported upregulation of SIRT1 expression. Additionally, it prevents the expression of TNFα and NFκB and the increase in interactions with the endothelium. We hypothesize that the mechanism at work was the improvement of mitochondrial function, which reduces endoplasmic reticulum stress and autophagy markers (Escribano-Lopez et al. 2018, Escribano-López et al. 2019). The antioxidant effect is corroborated in a study which analyses the improvement in mitochondrial function exerted by SS31 in Tallyho/JngJ mice. In the study in question, Bhatti et al. describe that SS31 reduced oxidative stress markers and the production of H2O2 and upregulated mitochondrial biogenesis and mitochondrial fusion genes and proteins (Bhatti et al. 2021).

**Inhibitors of mPTP opening**

Mitochondria contain channels in the inner membrane that allow the passage of molecules below a certain size. The opening of these channels is usually associated with mitochondrial dysfunction or apoptosis. One of the most described mitochondria pore transition pore (mPTP) inhibitors is cyclosporin A, which is reported to block the calcium and glucose/fructose-induced mPTP opening, thereby reducing cell death in INS1 cells (Lablanche et al. 2011). The proposed mechanism of action of cyclosporine A is a direct interaction with the mPTP that is independent of other signalling cascades, as observed in a study in the odontoblast cell line mDPC6T under glucose oxidase-induced oxidative stress. Cyclosporin A reduces the production of mtROS, corrects the mitochondrial membrane potential, and increases ATP levels but does not affect AKT or glucose synthase kinase 3B (Wu et al. 2022, p. 3). Another molecule involved in the inhibition of mPTP opening is alisporivir, a cyclosporin derivative. When tested in HFD-STZ T2D mice, alisporivir improves mitochondrial swelling and structural alterations in cardiomyocytes from diabetic mice. The treatment also reduces the accumulation of peroxidized lipids and increases the gene expression of Pink and Parkin, suggesting an increase in mitophagy (Belosludtseva et al. 2021).

**Donors of nitric oxide and hydrogen sulfide**

Nitric oxide is an important chemical mediator with diverse functions, including maintaining vascular tone, regulating platelet aggregation, and protecting vessels from external aggressions. It is normally synthesized by the cytosolic enzyme endothelial nitric oxide synthase (eNOS), but in T2D, its function is usually impaired (Ren et al. 2017). Additionally, NO participates in the maintenance of mitochondrial respiration and its
biogenesis. NO can control complexes IV and V, regulating oxygen consumption and ATP production (Tengan & Moraes 2017). The most studied process regarding NO and mitochondria is the induction of mitochondrial biogenesis through a PGC1A/AMPK-dependent process. This has been characterized in different animal and cellular models treated with NONOate or DETA-NONOate, such as muscle cell fibres from patients with mitochondrial diseases, mice lacking eNOS, and different cell lines (Rodrigues et al. 2016, Tengan & Moraes 2017). More precisely, it has been observed that NONOate increases mitochondrial mass and respiration and improves its architecture in insulin-resistant Huh-7 cells and primary rat hepatocytes. NONOate enhances mitochondrial fusion by the coordinated induction of soluble guanylyl cyclase and protein kinase G (Bassot et al. 2019).

Hydrogen sulfide is a molecule naturally produced during the metabolism of L-cysteine and has diverse cellular activities. Its benefits in T2D are due to the direct scavenging of ROS and the upregulation of the antioxidant defence system. A recent report shows that treatment with exogenous H\textsubscript{2}S (NaHS) of db/db mice or a hyperglycaemic cardiomyocyte cell model increases the activity of SIRT3 (a mitochondrial isoform), leading to the deacetylation of ETC complexes and subsequent activation of ETC activity and ATP production (Sun et al. 2019). Another antioxidant pathway activated by H\textsubscript{2}S through direct sulfhydrlation is the KEAP1/NRF2 pathway. H\textsubscript{2}S reduces diabetes-accelerated atherosclerosis through a reduction in O\textsubscript{2} production and generation of adhesion molecules in the endothelium of STZ-induced LDL-/– mice but not when NRF2 is knocked out. In an in vitro system with oxLDL/high glucose-treated macrophages, H\textsubscript{2}S reduces foam cell formation and superoxide formation and increases the expression of NRF2. The direct sulfhydrlation of KEAP1 leads to the dissociation of KEAP1/NRF2 complexes and activates this antioxidant pathway (Xie et al. 2016). A direct effect on mitochondrial function is observed in bEnd3 endothelial cells under hyperglycaemic conditions, which produces more ROS and exhausts the cell storage of H\textsubscript{2}S. Treatment with H\textsubscript{2}S or induction of the precursor enzyme reduces ROS formation and increases cell viability and oxidative phosphorylation (Suzuki et al. 2011).

**Inhibitors of mitochondrial fission**

It is widely reported that mitochondrial dysfunction and diseases that cause this alteration increment mitochondrial fission. Hence, preventing this cellular process could revert the cellular consequences of mitochondrial dysfunction.

The molecules that form part of this group are Mdivi, Dynasore, and P110 (Reddy et al. 2014). Mdivi-1 inhibits mitochondrial fragmentation (driven by dynamin-related protein 1 (DRP1)), mitochondrial ROS generation, and mitochondrial depolarization caused by palmitate in C2C12 cells. In the same research article, it was reported that treatment with mdivi-1 reduces plasma insulin levels during oral glucose tolerance test in obese and insulin-resistant mice (Jheng et al. 2012). Mdivi-1 is also capable of reducing ischaemia-reperfusion damage in HFD-STZ mice by reducing mitochondrial fission, improving ETC function, reducing mtROS production, and normalizing ATP synthesis. In addition, it suppresses apoptosis in myocardial tissue, improving the overall cardiac function (Ding et al. 2017). The mechanism of action of mdivi-1 might go beyond its anti-fission effect; in this context, one group proposes that the generation of ROS induces an imbalance in mitochondrial dynamics simulated by a cell hybrid that included the diabetes-susceptible mitochondrial haplogroup B4. This triggers a decrease in IR through AKT and insulin receptor substrate 1 inhibition. When treated with mdivi-1, the increase in fusion reduces the production of mtROS, which stimulates AKT and IRS signalling and normalizes insulin signalling (Lin et al. 2018). Although mdivi-1 is thought to act through the inhibition of DRP1, one research article outlined that it can also inhibit complex I-dependent O\textsubscript{2} consumption and reverts the reverse electron transfer production of ROS in rat primary cortical neurons, mouse embryonic fibroblasts, and COS-7 cells (Bordt et al. 2017).

Dynasore is a competitive inhibitor of GTPase activity of the dynamin and inhibits DRP1, as it is a dynamin-like protein. Thus, it can prevent or alter the endocytic activity of the cell and alter mitochondrial dynamics. Regarding its direct effect on mitochondria, researchers have observed that treatment of an ischaemia/reperfusion mice model reduces the infarct area and prevents the drop in cardiac function. In cultured muscle cells treated with H\textsubscript{2}O\textsubscript{2}, dynasore improves cell survival and viability and increases ATP content due to a rise in mitochondrial fusion (Gao et al. 2013).

The last DRP1 inhibitor, P110, is a direct blocker of DRP1 binding to FIS-1 in cultured neurons, thereby reducing mitochondrial fission and ROS production. Mitochondrial integrity and membrane potential also improve when the 1-methyl-4-phenylpyridinium or carbonyl cyanide m-chlorophenyl hydrazone-treated neurons or isolated mitochondria from mice livers are treated with P110, reducing the induction of apoptosis (Qi et al. 2013). However, limited data explain its effect on T2D, and therefore, this molecule needs further research.
Conclusion
Given the importance of mitochondria in the physiopathology of T2D, it is important to discover and develop new mitochondria-targeted therapies. This review summarizes some of the treatments that improve mitochondrial function and new compounds that specifically target mitochondria. The review makes it clear that mitochondrial targeting is a feasible and effective way of correcting T2D-related alterations. It also illustrates the wide variety of approaches to treat mitochondrial dysfunction, depending on the clinical background. Despite the vast number of treatments currently available, more research is needed to characterize and improve their efficacy in different clinical settings of T2D. Specifically, well-designed studies with controls and experimental groups would help to clarify the effects of the different treatments. Indeed, there is a lack of clinical studies that clarify the precise benefit of some of the existing treatments and how they prevent T2D. Overall, we can confirm that mitochondria targeting is a reliable approach that opens exciting new avenues for the treatment of T2D.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement
Conceptualization, A M d M, S R-L, M R, and V M V; methodology, A M d M, S R-L; data curation, A M d M, S R-L, M R, and V M V; writing – original draft preparation, A M d M, S R-L; writing – review and editing, M R and V M V; visualization, A M d M, S R-L; supervision, M R and V M V; project administration, M R and V M V; funding acquisition, M R and V M V. All authors have read and agreed to the published version of the manuscript.

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