

REVIEW

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Targeting mitochondrial biogenesis: a potential approach for preventing and controlling diabetes

Ritika Singh, Lucy Mohapatra* and Alok Shiomurthi Tripathi

Abstract

Background: Diabetes mellitus is a lingering hyperglycemic ailment resulting in several life-threatening difficulties. Enduring hyperglycemia often persuades the buildup of reactive oxygen species that are the significant pathological makers of diabetic complications. The mitochondrial dysfunction, with mitochondrial damage and too much production of reactive oxygen species, have been proposed to be convoluted in the progress of insulin resistance. Numerous studies advocate that agents that enhance the mitochondrial number and/or decrease their dysfunction, could be greatly helpful in management of diabetes and its complications.

Main body: Mitochondrial biogenesis is an extremely delimited procedure arbitrated by numerous transcription influences, in which mitochondrial fusion and fission happen in synchronization in a standard vigorous cell. But this synchronization is greatly disturbed in diabetic condition designated by modification in the working of several important transcription factors regulating the expressions of different genes. Numerous preclinical and clinical investigations have suggested that, the compromised functions of mitochondria play a significant protagonist in development of pancreatic β -cell dysfunction, skeletal muscle insulin resistance and several diabetic complications. However, there are several phytoconstituents performing through numerous alleyways, either unswervingly by motivating biogenesis or indirectly by constraining or averting dysfunction and producing a beneficial effect on overall function of the mitochondria.

Conclusion: This review describes standard mitochondrial physiology and anomalous modifications that transpire in answer to persistent hyperglycemia in diabetes condition. It also discusses about the different phytoconstituents that can affect the biogenesis pathways of mitochondria and thus can be used in the treatment and prevention of diabetes.

Keywords: Diabetic complications, Mitochondrial dysfunction, Mitochondrial biogenesis, Phytoconstituents

Background

Mitochondria are recognized as the powerhouses of the cell. These are the organelles that act identical to a digestive system which processes the nutrients, breakdowns them and ultimately produces energy rich particles for the cell in the form of ATP molecules. These biochemical procedures of the cell are recognized as

cellular respiration. Several of the responses particularized in cellular respiration usually occur in mitochondria. Many cells may have up to thousand mitochondria whereas other cells might not have any of such organelles [1]. For instance, muscle cells need loads of energy, therefore they have masses of mitochondria within them while neurons don't prerequisite much of them. If a cell senses it isn't receiving plentiful of energy to live on, supplementary mitochondria could be generated. From time to time, mitochondria can raise bigger or even get associated with other mitochondria [1]. It all hinge on

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the requirements of the cell. It is normally believed that mitochondria advanced billions of years before from the “symbiotic relationship amid a glycolytic proto-eukaryotic cell and oxidative bacterium” [2]. Figure 1 depicts the structure of a mitochondrion. Modern mitochondria have summoned up firm advents’ characteristic of their bacterial beginning. Undeniably, the structure of a mitochondrion is considered by a double membrane, which is further divided into the mitochondrial matrix arising especially from the cytoplasm of the cell. The external membrane of mitochondrion is comparatively permeable whereas the internal membrane is resilient to maximum ingredients and definite transportation arrangements have recognized to let the drive of convinced particles into and out of the mitochondria. The existence of cristae rises the surface area of the internal mitochondrial membrane and permit for the premeditated locating of interior mitochondrial proteins [2]. Mitochondria have correspondingly reserved from their bacterial starting point; their own DNA known as the mitochondrial DNA (mt-DNA) and bear the competence to reproduce and express mt-DNA genes. Mitochondria play a multifaceted protagonist in the cell. Apart from their chief title role in ATP generation, they seize calcium, and both produce and cleanse reactive oxygen species (ROS). These are closely inter-linked functions taking place in the inner membrane of mitochondria [2]. Insufficiencies in energy use, the bioenergetic let-down distinctive of both mitochondrial and epigenomic ailment circumstances, have been drawn in a diversity of human disease states including type 2 diabetes mellitus, glaucoma, different

forms of neoplasms, neurodegenerative diseases, and tissue inflammations [3, 4]. These connections are partly unstated, and in this review, we explore the possibly combining supposition that the characteristics of type 2 diabetes mellitus are attributed to flaws in mitochondria.

Main text

Diabetes mellitus (DM) is a serious chronic noncommunicable disease that is growing at an enormous rate worldwide. It is accountable for abridged life expectation and augmented indisposition due to propagation of diabetic vascular complications. The major concern associated with DM is the development of chronic complications associated with the disorder, which have been classified into two broad categories, namely macrovascular complications including cerebrovascular diseases, peripheral vascular diseases, and cardiovascular diseases. Secondly, microvascular complications including nephropathy, neuropathy, and retinopathy. There are dual main forms of DM. Type 1 DM, which is instigated by a damage of beta cells of the pancreas known as the insulin-secreting cells and type 2 DM, which is categorized by resistance developed to insulin action by insulin-target tissues, like skeletal muscle and adipose tissues [5]. Individuals presenting type 2 DM comprise approximately 90% of total diabetic cases and this form of diabetes is sturdily allied with lifestyle regime and obesity. Of even more worrying matter is that type 2 DM is hastily flattering a worldwide epidemic and it has been anticipated to distress more than 300 million entities universal by the year 2025, with maximum of the expansion stirring in

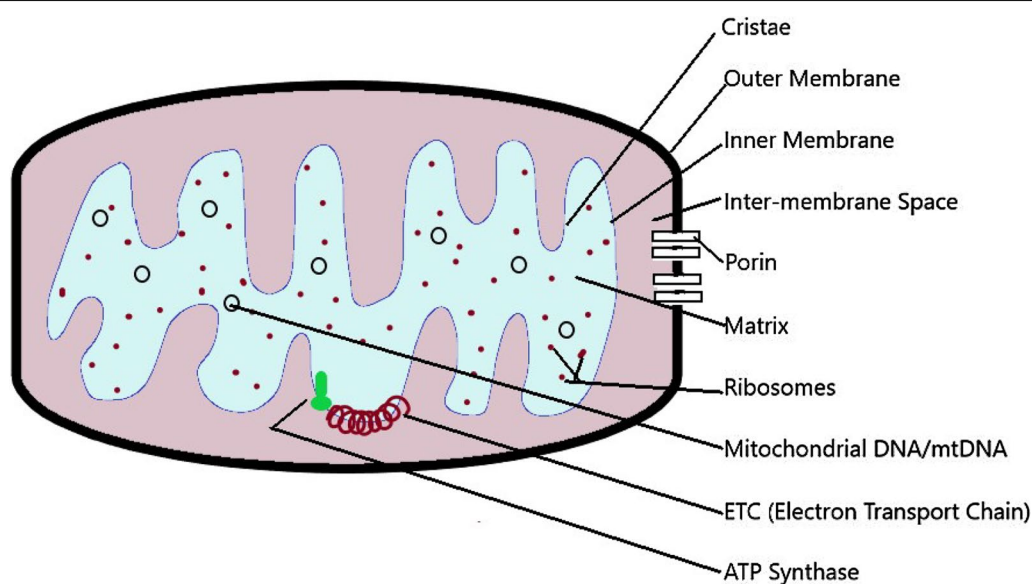


Fig. 1 Structure of a mitochondrion

India and Asia [6]. This astounding upsurge of the patient progress rate has attracted cumulative figure of biomedical investigators and clinicians to slog collectively to recognize the pathogenesis of diabetes.

It has been well established that, chronic hyperglycaemic condition of DM often persuades the creation of ROS that are the crucial pathological generators of diabetic complications and apart from that, insulin resistance is an imperative characteristic feature of type 2 DM. The mitochondrial dysfunction with loss of mitochondria and over production of ROS, has been anticipated to be longwinded in the advance of insulin resistance [7, 8]. Mitochondrial biogenesis is an extremely controlled procedure refereed by numerous transcription factors, in which fusion and fission of mitochondria happen in synchronizing in a normal healthy cell. Numerous phytoconstituents act through these pathways, either straight by exciting biogenesis or ramblingly by hindering or preventing dysfunction and create an advantageous consequence on total mitochondrial function. These phytoconstituents have massive probability in improvement of diabetic complications by reinstating usual mitochondrial physiology. However, these evidence prerequisite exhaustive assessment proof by preclinical and clinical studies. This review designates typical mitochondrial growth, multiplication, functioning and atypical changes that ensue in retort to hyperglycaemia. Further, we have tried to concise current development in pharmaceutical and dietary revisions of drugs and nutrients aiming mitochondria by triggering mitochondrial biogenesis and decreasing this organelle deprivation, to recover usual functioning of the mitochondria and declining oxidative stress for averting insulin resistance. We have also fixated on some natural metabolites exciting the biogenesis of this cell organelle in several in vitro and in vivo studies, that will aid to comprehend the importance of mitochondrial biogenesis in insulin resistance. This in turn will offer anticipation for emerging mitochondria-targeting agents for avoiding and treating type 2 DM.

Conceded mitochondrial functions and type 2 DM

Clinical studies have revealed that there occurs an intensification in the rate of recurrence of 4,977-bp obliteration and several other significant omissions in mt-DNA of the skeletal muscles of diabetic patients as equated to the age matched/sex-matched control subjects [9]. In addition, studies also proved that, peroxisome proliferator-activated receptor gamma, coactivator 1 alpha (PGC-1 α), the main controller of mitochondrial biogenesis and NRF1 (nuclear respiratory factor 1) were reduced in diabetic patients and non-diabetic subjects from families with a family antiquity of type 2 DM [10]. These consequences designate that the proteins of mitochondria

determined by these genes might be underprovided to perform oxidative phosphorylation in diabetic individuals. Additionally, in skeletal muscle tissues of obese individuals it has been found that there is derangement of the ultrastructure of the mitochondria, the cristae are poorly defined, and complex I action of the ETC (electron transport chain) is diminished. Furthermost, improper functioning of mitochondria has been usually detected in the skeletal muscle tissues of type 2 DM [11]. In addition to the clinical explanations, compromised mitochondrial function as one of the important causal factors for precepting type 2 DM, has been well established in a mouse model. The researchers found a diminution in the quantity of mitochondria, contents of mt-DNA and respiratory enzymes in the adipose tissues of the mice with type 2 DM [12]. Hence, the findings of these studies suggest that the reduced mitochondrial function was typically detected in insulin targeted tissues including skeletal muscle tissues and adipose tissues and the mitochondrial flaws are extremely interrelated with insulin insensitivity associated with the pathophysiology of type 2 DM.

Oxidative stress, mitochondrial dysfunction, and type 2 DM

The hypothetical lessening of oxygen to water via the ETC includes a synchronized 4 electron transference. Throughout this procedure, many forms of ROS including hydroxyl radical, hydrogen peroxide, superoxide and nitric oxide are being produced. These ROS might form the basis of oxidative impairment to biomolecules including nucleic acids, lipids, proteins etc. [13]. Type 2 DM is a consequence of imbalance of oxidative stress, immune defense, and metabolic regulators. Furthermore, insulin confrontation is considered as a topmost characteristic of the pathophysiology of type 2 DM. A rising number of studies designate that augmented ROS levels get up due to a significant inequity amid the manufacture of ROS and antioxidant barricades. This plays a main protagonist in major variations in stress signaling ways and possibly end-organ damage [14]. An adjacent connotation amid ROS level and insulin confrontation and improvement in the insulin effects on its target tissue by antioxidant treatment has been confirmed [15–18]. These information advocate that ROS levels are significant causes for insulin resistance.

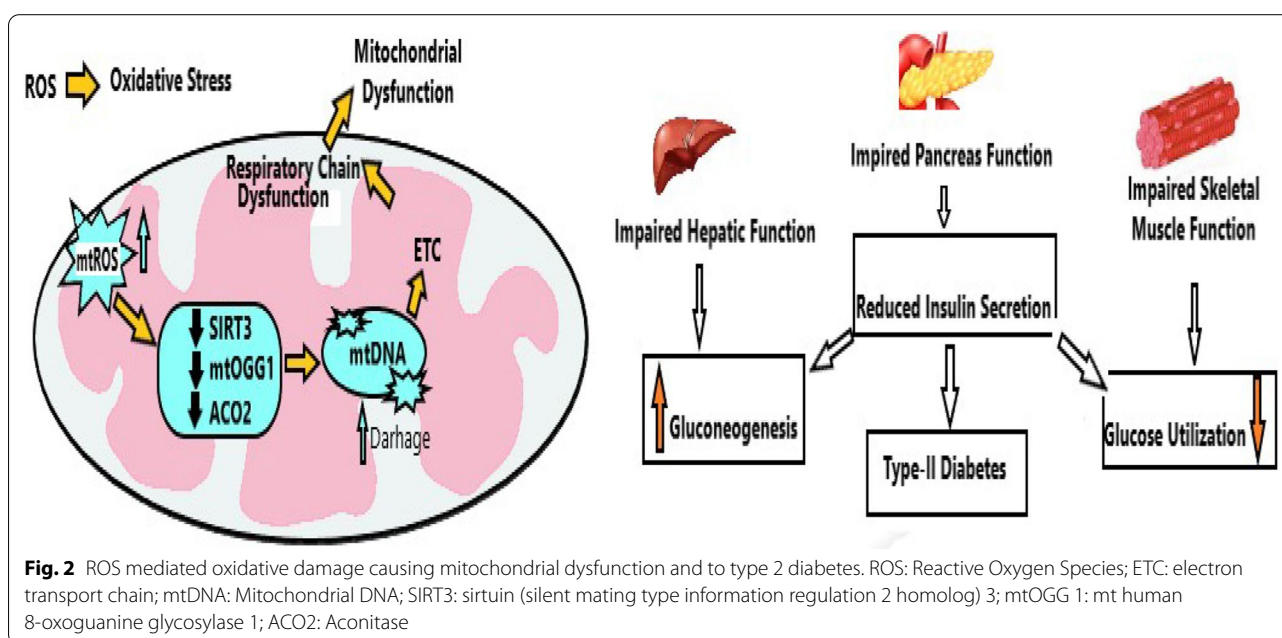
Mitochondria are the foremost locations of ROS production and they are also the major targets of ROS. ROS in the mitochondria is primarily formed as significance of electron seepage from the ETC all through the oxidative phosphorylation. It has been well accepted that complexes I and III of the ETC are the two chief spots of ROS manufacture in the mitochondria. The oxidative denaturation of mt-DNA in DNA induced

by ROS includes the common deletion of base pair as discussed previously in this article. This further deletes several other gene involved in oxidative phosphorylation. It was found by Fukagawa et al., that miscellaneous mutations among base pair 8468 and 13,446 in mt-DNA happens in the skeletal muscle tissues of aged human subjects with impaired glucose tolerance. They furtherer established that, animals especially rats having insulin resistance have amplified vulnerability to mt-DNA deletions in vivo and the correlation of hyperglycemia with ROS induced mt-DNA mutations in vitro. Their findings altogether suggest that hyperglycemia induced oxidative stress contribute to changes in mitochondrial gene veracity [19]. Apart from that, a transcriptomic slant confirmed that a foremost alteration amid prediabetic and diabetic patients to healthy entities is that genes tangled in oxidative phosphorylation are usually downregulated [20]. Consequently, we suggest that ROS mediated oxidative damage underwrites to the improper functioning of mitochondria and this further leads to type 2 DM [21]. Figure 2 depicts a projected model of mt-DNA impairment in facilitating numerous organ dysfunction including liver, pancreas, skeletal muscle leading to type 2 DM. Oxidative stress persuaded mitochondrial ROS encourages mt-DNA impairment by declining SIRT3, ACo-2 and mt-OGG1 in these organs [9, 10]. Further, mt-DNA injury sources a faulty ETC that could endorse mitochondrial dysfunction, cell apoptosis, in these organs and lead to loss of functions of these organs.

Skeletal muscle resistance, mtochondrial dysfunction and type 2 DM

The diminution in insulin discharge of β -cells or insulin inattentiveness of myocytes and adipocytes can cause type 2 DM. Numerous investigators have described about this. It has been well recognized that the ATP insufficiency caused due to mitochondrial dysfunction may damage the regulation of K^+ and Ca^{+} channels and in that way inhibits the exocytosis of insulin vesicles in the β -cells of the pancreas [12]. In this review, we emphasis on the imperative mitochondrial role in insulin sensitivity of the muscle and adipose tissues and on the significances of mitochondrial dysfunction provoked insulin insensitivity in the human being.

Skeletal muscles require the prime part of glucose in the whole body, since they need the principal quantity of energy for their high bioenergetic purpose which is completely directed by insulin. This is the reason why; scientists prefer skeletal muscle tissue to examine the protagonist of muscle mitochondria in understanding their rejoinder to insulin. It was found in a study, that mt-DNA were depleted by the enduring treatment with ethidium bromide (EtBr) resulting in a damage of rejoinder to insulin in muscle tissue, but the repletion of mt-DNA re-established insulin sensitivity [22]. In another study, Pravenec et al. established that the dissimilarity of mitochondrial genome straight directed to metabolic dysregulation, including glucose intolerance, which is an important forecast of type 2 DM, in these copasetic strains [23]. In addition to these in vivo studies, mitochondrial flaws in murine C2C12 myotube cells produced



by action of respirational inhibitors exposed a failure of insulin inspired glucose uptake. In the same study it was also found that there was tremendous decline of Protein kinase-B and Insulin receptor substrate-1 in the insulin signaling pathway [24]. Further studies have also suggested that mitochondrial dysfunction provokes excess creation of ROS and these tremendously effect insulin signaling pathways. ROS/oxidative stress possibly persuade initiation of multiple serine/threonine kinase motioning cascades, including p38 mitogen activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK). This in turn can act on several possible targets of insulin signaling pathway. It was revealed that inactivation of class I phosphoinositide 3-kinase (PI3K) reduced the translocation of glucose transporter 4 (GLUT4) to the plasma membrane, which further directed to a reduction in glucose uptake by skeletal muscle cells upon insulin inspiration [25]. These studies recommend that the mitochondrial dysfunction provoked ROS might be tangled in the dysregulation of insulin signaling pathway leading to the development of insulin resistance in skeletal muscle tissue.

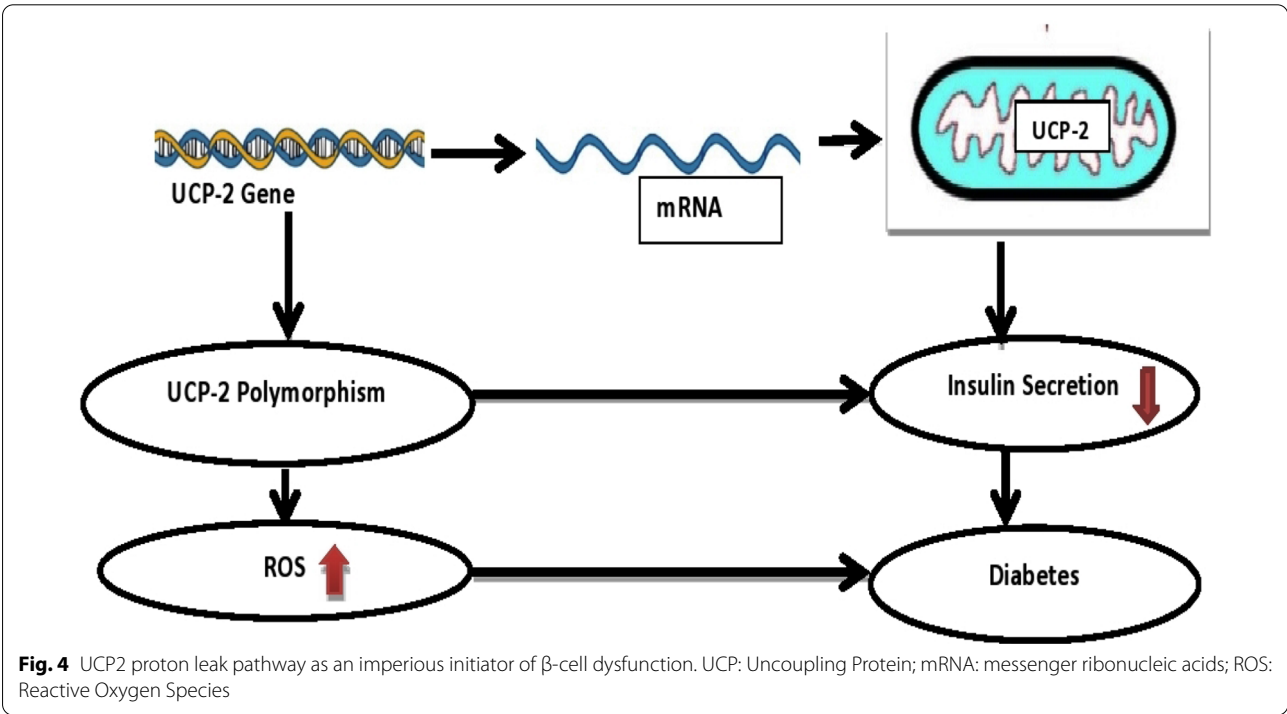
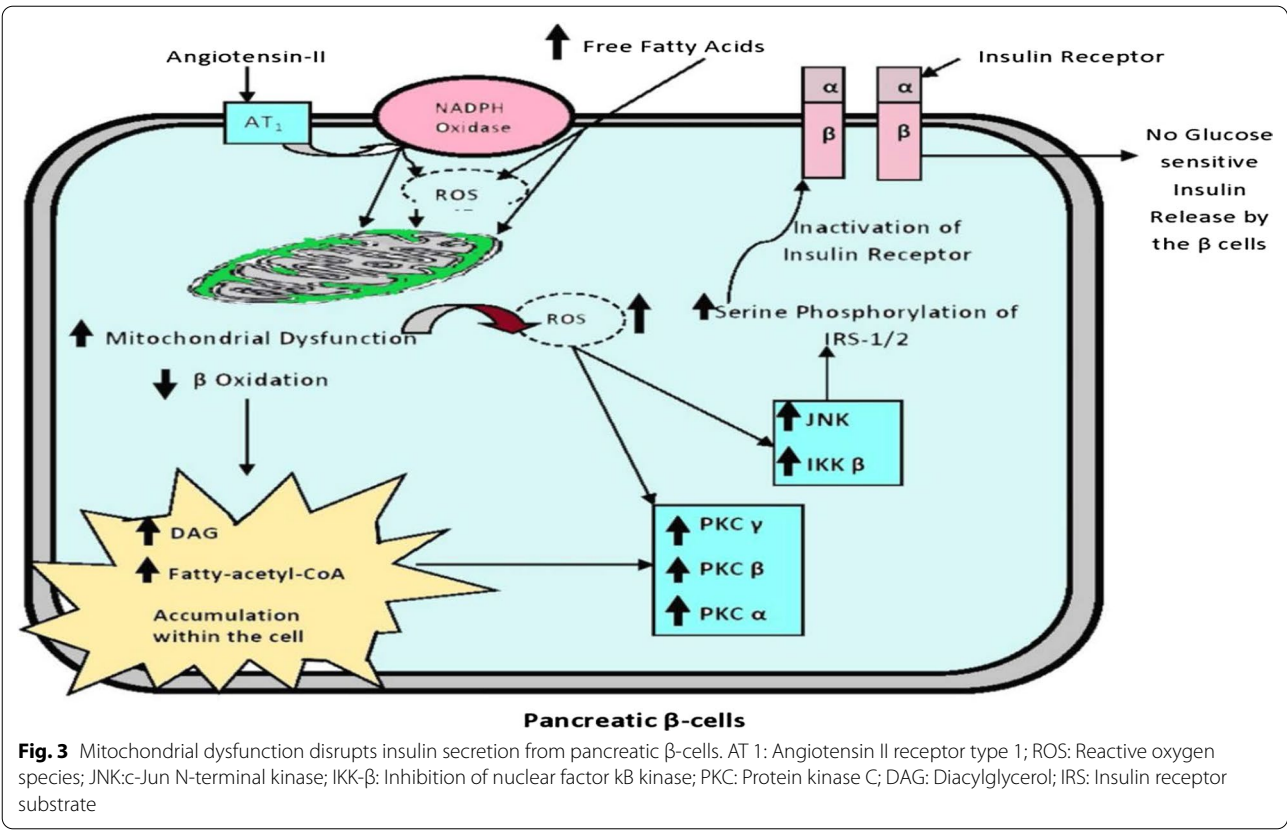
Pancreatic β -cells, mitochondrial dysfunction, and type 2 DM

Entities with noticeable insulin resistance do not grow diabetes suddenly. In these individuals, the pancreatic β -cells acclimatize to encounter the body's obviously augmented mandate for insulin. This version includes extension of β -cells mass along with the conservation of usual sensitivity to glucose. Whereas, individuals meant to advance type 2 DM, these β -cells do not secrete enough insulin to recompense for the augmented demand for insulin. This β -cell dysfunction, further lead to the development of the β -cells mass and/or let down of the prevailing β -cell mass to respond to glucose [26]. β -cell mass is ruled by numerous factors. The important features include the β -cell size, their replication rate, their rate of differentiation and their apoptotic cell death. Studies have revealed that, β -cell mass seems to be lessened in type 2 diabetic individuals comparative to corresponding entities with comparable grades of insulin resistance [27, 28]. The possible reason of this may be an increased rate of apoptosis [27]. Many scientific investigations have recognized that, even β -cells in type 2 diabetic individuals are insensitive to glucose and due to this they could not secrete suitable quantities of insulin [29].

Insulin resistance in human beings greatly rises from flaws in mitochondrial fatty acid oxidation that disturb the insulin signaling functions as shown in Fig. 3. Glucose sensitivity of β -cells necessitates oxidative mitochondrial metabolism that is responsible to produce ATP molecules and which in turn is required increase

the ratio of ATP to adenosine diphosphate (ADP) in the cell. This then induces a succession of measures including depletion of the ATP/ADP-regulated potassium channel (KATP), plasma membrane depolarization, opening of voltage-gated calcium channel, calcium influx and finally secretion of insulin. Whereas a reduction in mitochondrial fatty acid oxidation, because of either due to mitochondrial dysfunction or compact mitochondrial content, produces augmented amount fatty acyl CoA and diacylglycerol accumulation within the β -cell. These further activate the protein kinase C, which in turn triggers a serine kinase cataract leading to augmented serine phosphorylation of IRS-1. This could be possibly due to the reserve of nuclear factor κ B kinase (IKK) and JNK. Besides, increased serine phosphorylation of IRS-1 further inhibits the IRS-1 tyrosine phosphorylation by the insulin receptor. This action in turn constrains the action of phosphatidyl inositol 3-kinase (PI 3-kinase). This hang-up finally causes the clampdown of insulin mediated glucose transport due to prohibition of translocation of GLUT4 transporters to the membrane surfaces as discussed above in muscle cells, the prime process by virtue of which glucose is removed from the blood [30].

Several premises have been projected to elucidate how glucolipotoxicity induce significant β -cell dysfunction. One of these important hypotheses is the variations in the expression and function of one of the most prominent mitochondrial inner membrane proteins named uncoupling protein-2 (UCP2) [31, 32] as shown in Fig. 4. However, to recognize the protagonist of UCP2 in β -cell dysfunction and precipitation of type 2 DM, it is very much essential to analyze the pertinent features of "mitochondrial oxidative metabolism". Oxidative metabolism of glucose molecule includes the allocation of energy kept within the carbon bonds of glucose to the third phosphate bond of ATP. This whole complex process initiates with the transfer of electrons within the carbon bonds to the dinucleotide electron carriers including NADH and flavin adenine dinucleotide (FADH₂). Then electrons are donated to the mitochondrial ETC in the mitochondrial inner membrane. Eventually, the electrons are directed to their concluding terminus wherein reduction of oxygen to water takes place. Complexes I, III and IV of the ETC are reduction and oxidation driven proton pumps. These complexes use energy carried by the electrons to pump protons out of the mitochondrial matrix, generating a proton based electrochemical potential gradient across the mitochondrial inner membrane. These protons then turn back into the mitochondrial matrix via ATP synthase utilizing the energy kept within the electrochemical gradient to initiate the synthesis of ATP from ADP. However, activation of UCP2 leads to the leakage of protons across the inner membrane of the mitochondrion and in



turn separates glucose oxidative metabolism from ATP production. Hence, UCP2 negatively controls glucose-stimulated insulin secretion. Investigational evidence in some cell cultures has also shown that, enforced over stimulation and expression of UCP2 in β -cell declines glucose stimulated insulin secretion [33]. Whereas inactivation of the UCP2 gene in mice model has revealed the reverse outcome [32]. Findings of enhanced UCP2 expression in vitro and in vivo, by hyperglycemia (glucotoxicity) and hyperlipidemia (lipotoxicity) in animal models with type 2 DM, provides enough evidence of the causal role of UCP2 in β -cell dysfunction in type 2 DM [34, 35]. An analogous role appears likely in human type 2 diabetic subjects, where enhanced UCP2 expression in human β -cell were extensively increased by hyperglycemia [36]. Moreover, a polymorphism pattern, that seems to upsurge UCP2 expression in the promoter of the human UCP2 gene has been connected to decreased insulin secretion and earlier onset of type 2 DM [37]. Hence, UCP2 proton leak pathway is an imperative founder to β -cell dysfunction and play avital role in the pathogenesis of type 2 DM.

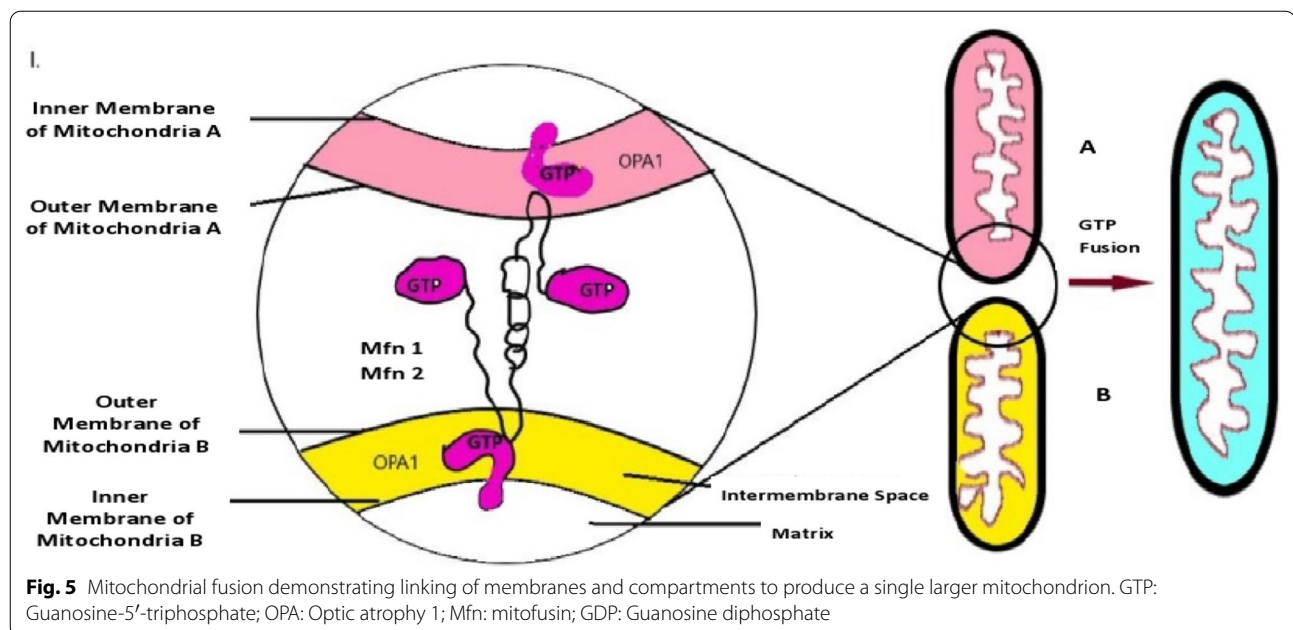
Adipocytes, mitochondrial dysfunction, and type 2 DM

Adipocytes are also important target tissue of insulin alike skeletal muscle cells. It has been depicted that, they are less insulin sensitive tissues as compared to muscle cells, because of their less glucose disposal (about 15%). However, findings of some recent studies depicting glucose intolerance and insulin insensitivity in adipocyte specific GLUT4 knockout mice model [38] proves the importance of adipose tissues in the pathophysiology of insulin resistance and type 2 DM. Recently, the role of mitochondria in insulin sensitivity of adipocytes has been confirmed in many studies. It has been observed that the insulin stirred glucose utilization was significantly diminished in adipocytes by treatment of respiratory inhibitors like carbonyl cyanide-p-trifluoro methoxy phenyl hydrazone (FCCP). Moreover, recently it has been found that, when mitochondrial transcription factor A (mt-TFA) was knockdown using RNA interference technique, the insulin stirred glucose uptake was diminished [38]. Apart from that, adipose tissues secrete many cytokines called adipokines (leptin, tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), resistin). Through these so called adipokines, adipocytes can control glucose metabolism even in other tissues such as the liver and muscle to maintain glucose homeostasis [39]. Besides, it has been reported that the plasma level of adiponectin is decreased in obese subjects or type 2 diabetes patients, and adiponectin deficiency could lead to insulin resistance in mice [40]. Importantly, this study also showed that improvement of mitochondrial biogenesis by over

expression of nuclear respiratory factor 1 (NRF1), augmented the countenance of adiponectin in adipocytes. Hence, these observations designate that mitochondrial dysfunction not only leads to loss of insulin sensitivity of adipocytes but also spoils their adipokines secretion, which in turn also leads to the conciliation of glucose utilization by other specified tissue leading to type 2 DM.

Mitochondrial biogenesis imperious in improving insulin resistance

To completely recognize the beneficial involvement of mitochondrial biogenesis in diabetes, it is significant to first comprehend the physiology of mitochondrial biogenesis. Mitochondrial biogenesis is defined as rebirth of mitochondria, a method crucial in preserving its integrity. New mitochondria are produced from prevailing mitochondria by two highly controlled procedures, namely, fusion and fission. Mitochondrial fusion encompasses linking of membranes and compartments to yield a single larger mitochondrion (Fig. 5). Whereas, mitochondrial fission is a procedure matching to cell division, in which a mitochondrion stretches and rises in volume beforehand parting, giving rise to two physically distinct mitochondria (Fig. 6). Under normal physiological situations, there is a dynamic steadiness between fission and fusion in mammalian cells. Disturbance of this fission–fusion equilibrium changes mitochondrial morphology. Unnecessary fission produces fragmented mitochondria, whereas extreme fusion consequences in lengthened mitochondrial tubules. The mammalian mitochondrial fusion apparatus includes mitofusin 1 (Mfn1) and mitofusin 2 (Mfn 2), a type of nuclear-encoded dynamin-related guanosine triphosphate (GTPase). Mitofusins are proteins accountable for roping and fusion of outer mitochondrial membrane. On the other hand, fusion of inner mitochondrial membrane (IMM) is controlled by alternative dynamic family GTPase, namely, optic atrophy 1 (OPA1). Mitochondrial fission is measured by mitochondrial fission machinery comprising dynamin-related protein 1 (Drp1), a type of dynamin-related GTPase, and fission protein 1 (Fis1). Fis1 employees Drp1, a cytosolic protein, to scission positions on outer mitochondrial membrane to encourage mitochondrial fission. Mitochondrial dysfunction increases from an inadequate number of mitochondria, an inability to offer vital substrates to mitochondria, or a dysfunction in their electron transportation and ATP-synthesis functions. The quantity and purposeful situation of mitochondria in a cell can be changed by fusion of temperately dysfunctional mitochondria and combination of their unspoiled elements to recover overall function. The generation of utterly new mitochondria (fission), and the removal and whole deprivation of dysfunctional mitochondria (mitophagy) can



also be achieved. These proceedings are controlled by multifaceted cellular events that sense the deterioration of mitochondria, such as the depolarization of mitochondrial membranes or the commencement of certain transcription pathways [41, 42].

Genetic endorsing factors in mitochondrial biogenesis

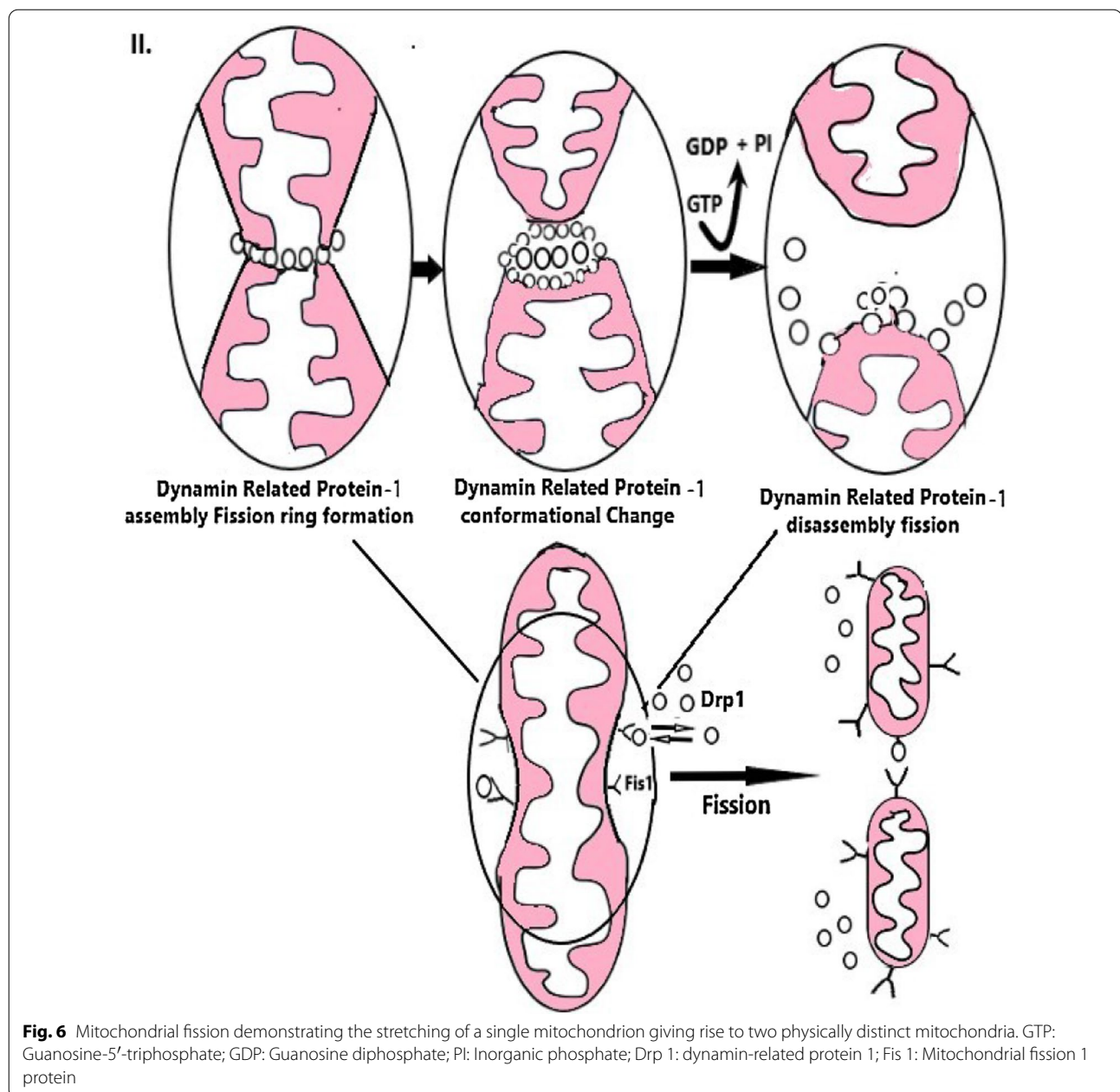
The events of mitochondrial biogenesis in mammalian tissues are modified through control of the prime factor including peroxisome proliferator activated receptor- γ coactivator-1 α (PGC-1 α) countenance. It has been suggested by many genetical studies that the perilous features tangled in mitochondrial biogenesis include, firstly those that arouse PGC-1 α genera transcription (calcium/calmodulin-dependent protein kinase IV (CaMKIV), AMP-activated protein kinase (AMPK), and nitric oxide) and secondly those biological markers that are stirred by PGC-1 α in turn, including nuclear respiratory factors (NRFs) and PPARs. In addition to that, enhanced mitochondrial transcription factor A (Tfam) expression and commencement of mitochondrial DNA replication also play a major role in the whole process of mitochondrial biogenesis [43, 44]. The signal transduction pathways that control mitochondrial biogenesis are represented in Fig. 7.

PGC-1 α activates NRFs 1, 2 and mitochondrial transcription factor A and PPAR- γ and PPAR- α . These factors in turn regulate the expression of genes intricate in mitochondrial replication and oxidative phosphorylation. PGC-1 α also helps to coactivate transcription aspects for numerous other genes involved in energy homeostasis.

Given its standing in bioenergetics, PGC-1 α transcription or commotion or both are heightened by two significant enzymes regarded as metabolic sensors: AMP- activated protein kinase (AMPK) and the mammalian complement of silent information regulator 2 (SIRT1). These factors mainly alter PGC-1 α through phosphorylation or deacetylation processes. Conditions of energy diminution concentrated caloric intake and exercise result in an upsurge in the proportion of AMP to ATP, in that way triggering AMPK. In turn, this upsurges PGC-1 α transcription and unswervingly triggers PGC-1 α through phosphorylation. In addition to that, caloric restriction or exercise also upsurges tissue nicotinamide adenine dinucleotide (NAD⁺) amount to NADH and further activates the NAD⁺ p-dependent histone deacetylase, SIRT1. SIRT1 enhances PGC-1 α by deacetylation at specific lysine residues [43–46].

Altered mitochondrial dynamics and type 2 DM

Growing evidence display the fact of decreased mitochondrial number and function in various aged and diseased mammalian tissues including diabetes and obesity. The important roles of adipose tissue with respect to energy metabolism and pathogenesis of insulin resistant has been already discussed in this review article. Some studies have come with the findings that, reduced amounts of adiponectin are release by the adipocytes of visceral adipose tissue of obese subjects leading to reduced activation of the AMPK/ PGC-1 α pathway in muscle tissue [47, 48]. Since, PGC-1 α is an important controller of mitochondrial biogenesis, its down

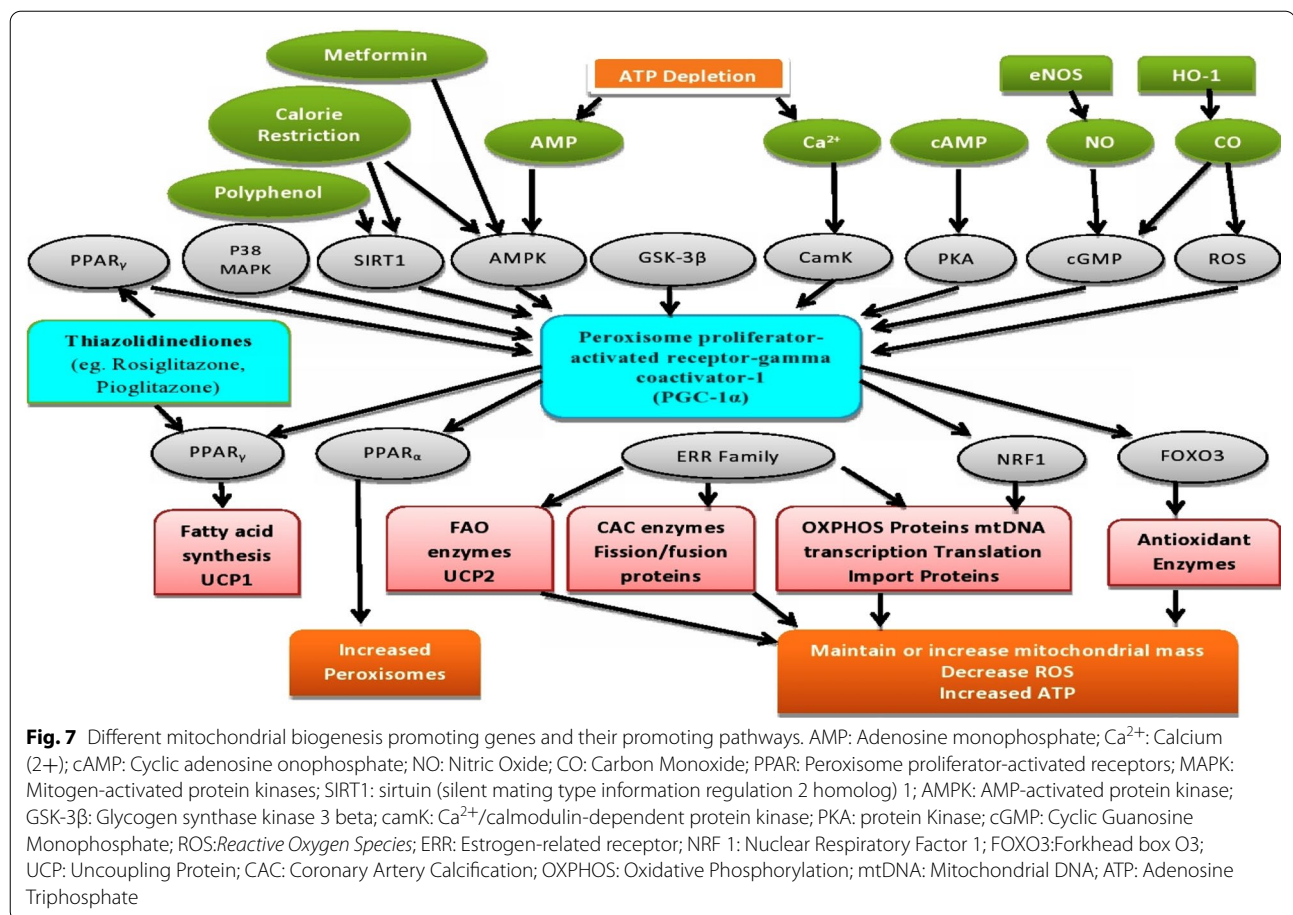


regulation by abridged adiponectin levels might be vital for the abridged dimensions for oxidative phosphorylation. Therefore, it can be concluded that, abridged PGC-1 α countenance appears to be intricate in obesity and the prediabetic state in skeletal muscle [49–51]. Adipocytes and skeletal muscle mitochondria in patients with type 2 DM and obesity exhibit impaired bioenergetic capacity and impaired mitochondrial activity [52]. The abridged mitochondrial function designated above substantially donate to the jeopardy for developing insulin resistance and diabetes in obese subjects as

intramuscular lipid accumulation is related to insulin resistance.

Enhancing mitochondrial biogenesis and managing type 2 DM

Mitochondrial damage and reduced content, both plays an imperative role in the overproduction of ROS and fatty acids-induced type 2 DM. Hence, it is anticipated that, measures that can intensify the mitochondrial functions and their content in preferred mammalian tissues or remove ROS could be effective cures for



type 2 DM. The foremost intentions of mitochondrial medicine are to develop drugs that mark mitochondria to shield its function, inhibit their damage and cell death connected with various diseases. The main approaches to transport drugs to target the mitochondria comprise of creating lipophilic cations, by means of the mitochondrial protein importation technology and mitochondrial gene therapy [53, 54]. Numerous drugs and a few of natural and nutritious complexes have been found to directly or indirectly target mitochondria to recover their function by exciting the mitochondrial biogenesis pathway (Fig. 7). Therefore, these examples provide a hopeful possibility for prevention and treatment of insulin resistance in type 2 DM and obese patients. However, some existing oral hypoglycemic drugs commonly used in the treatment and management of type 2 DM have been proven to stimulate mitochondrial biogenesis and modifying their impaired functions. The thiazolidinediones (TZDs), frequently used in the treatment of type 2 DM by increasing insulin sensitivity of muscle and adipose tissues, are the drugs belonging to the group of PPAR agonists

and have been found to upregulate number of genes including PGC-1 α , the prime regulator of mitochondrial biogenesis [55]. In addition to that, Metformin and 5-amino-imidazole-4-carboxamide ribonucleoside (AICAR) have been found to inhibit hyperglycemia persuaded intracellular and mitochondrial oxidant creation, stirred AMPK action, augmented them RNA expression of NRF1 and Tfam, stirred mitochondrial production and increased expression of PGC-1 α in human umbilical vein endothelial cells [56]. Hence, this novel intuition in improving mitochondrial function and their numbers by these pre-existing and widely used antidiabetic drugs further reinforced that targeting mitochondria may be a practicable remedy of type 2 diabetes. In addition, it has been described in many studies that the elderly diabetic individuals or animals could expand their insulin secretion and action due to planned regular exercise, and the important reason is because endurance exercises upsurge mitochondrial biogenesis and OXPHOS levels [53, 57]. Thus, a rising sum of studies has dedicated to hunt for the drugs, chemicals and natural products that can intensify

Table 1 Natural components that improve mitochondrial dysfunction and/or their biogenesis

Sl. No.	Name of the agent	Animal models/Human trials	Net effect on mitochondria	References
1	Lipoic acid (LA)	Rat skeletal muscle	Decreased ROS production, Stimulation of mitochondrial biogenesis, Increased Fatty acid oxidation	[58]
2	Acetyl-L-carnitine (ALCAR)	Rat, mice, dogs	Elevates mitochondrial enzyme activity, Improves mitochondrial function	[59]
3	B vitamins (Biotin)	Rat hepatocytes	Promote cGMP, Stimulate PGC-1 α to enhance mitochondrial biogenesis just as nitric oxide does	[60]
4	A combination of LA, ALCAR and B vitamins	Goto–Kakizaki (GK) rats	Enhanced mitochondrial biogenesis, Improved mitochondrial function	[61]
5	Berberine	3T3-L1 adipocytes and L6 myotubes	Increases AMPK activity	[62]
6	Hydroxytyrosol (HT)	3T3-L1 adipocytes	Enhancement of mitochondrial function: it produced, Increases in the activity and protein expression of mitochondrial complexes I, II, III, IV and V	[63]
7	Epigallocatechin gallate (EGCG)	3T3-L1 adipocytes	Increased mitochondrial biogenesis, Increased mitochondrial mass, Increased oxygen consumption and expression of complex I, II, V, mt-DNA, and PGC-1 α	[64]
8	Resveratrol (RSV)	Mice skeletal muscles	Increased mitochondrial biogenesis, Increased PGC-1 α , Increased oxidation	[65]

mitochondrial biogenesis which in turn end or increase insulin sensitivity (Table 1).

Conclusions

Abundant preclinical and clinical experimentations support the suggestion that mitochondrial flaws play a vital protagonist in both insulin resistance and pancreatic β -cell dysfunctions, that further lead to type 2 DM. Stopping mitochondrial dysfunction by increasing biogenesis appears a credible approach for averting or treating type 2 DM. In this review article, many natural composite and nutrients have been identified and their important role in promoting mitochondrial biogenesis and function has been elaborated. We conjectured that, these mitochondrial nutrients and or their blends may be active in modifying PGC-1 α activity. This in turn, will enhance the biogenesis of this important organelle in the targeted insulin resistant tissues including skeletal muscles, adipocytes etc. Such regulations may lead to the inhibition and upgrading of insulin resistance in diabetic individuals. Consequently, aiming mitochondria, such as by enhancing mitochondrial biogenesis, could be an operative policy for developing potent therapeutic agents for prohibiting and treating diabetes. Besides, enhancing mitochondrial biogenesis is also the underlying mechanism of some antidiabetic drugs, endurance exercises, calorie restrictions and a variety of antioxidants and nutrients. But numerous significant queries continue to be replied, such as

whether the lessening in mitochondrial function in vivo is extensively due to mitochondrial loss or other physiological pathways including the involvement of specific biomarkers? Is the downregulation of PGC-1 α /PGC-1 β responding genes play a principal or minor role in the pathogenesis of type 2 DM? If it is a primary event, then what are the major genes accountable for their transformed countenance? Apart from that, the major role of UCP-2 in β -cell dysfunction in type 2 DM need to elaborate. The hopeful possessions of natural products and nutrients afford boundless anticipation for averting and treating diabetes with corresponding benefit for mitochondria. Therefore, the forth coming commands comprise of identifying more strong mitochondrial targeting nutrients from food/herbs. Further with the application of up-to-date expertise of nutrigenomics, proteomics, metabolomics the mixtures of various mitochondrial aiming nutrients must be identified for optimum effects in turn of avoiding and treating diabetes.

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Authors' contributions

LM, significantly contributed to the outset and design of the article, interpreting the relevant literature and drafted the article. RS collected the initial material and evidences to be included in the article and AST revised it judgmentally for significant rational content. All authors read and approved the final manuscript.

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Declarations**Ethics approval and consent to participate**

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Consent for publication

Not applicable as this present review manuscript does not contain any individual person's data in any form.

Competing interests

The authors declare that they have no competing interests.

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