Mitochondria perform numerous functions, including synthesis of adenosine triphosphate (ATP) and generation of reactive oxygen species (ROS). Most of the organs depend on ATP to perform. Therefore, in depleted or dysfunctional mitochondrial states, there is less energy production coupled with the accumulation of oxidants. Oxidative stress is involved in the pathophysiology of various disorders especially involving neurons and the cardiovascular system. Mitochondrial diseases are a clinically heterogeneous group of disorders resulting from either inherited or spontaneous mutations in mitochondrial deoxyribonucleic acid (mtDNA) or nuclear DNA. In primary mitochondrial dysfunction disease, the mutation affects the oxidative phosphorylation (OXPHOS) functioning, while secondary mitochondrial dysfunction does not involve OXPHOS genes. Since mutations of genes are involved, therefore, the mitochondrial dysfunctional states are not easy to treat. However, number of strategies that lead to increase ATP production, counter ROS facilitates improvement. The current strategy is to focus on stimulating the biogenesis of mitochondria, antioxidants, and cofactors to enhance ATP synthesis. The role of non-pharmaceuticals cannot be underestimated either. The exercise, diet, and environment influence have well-established beneficial outcome in these disorders. Gene therapy holds promise in the future management of these complex disorders.

Keywords: Mitochondrial disorders, Treatment, Energy metabolism, Coenzyme Q10, Thiamine, Riboflavin, Carnitine, Arginine, Beazafibrate, Resveratrol, Gene therapy.

INTRODUCTION
Mitochondrial diseases are a clinically heterogeneous group of disorders due to mutation affecting either mitochondrial deoxyribonucleic acid (DNA) or nuclear DNA [1]. These disorders are of two types. Primary mitochondrial disease has mitochondrial or nuclear DNA mutation affecting oxidative phosphorylation (OXPHOS) functioning while secondary mitochondrial dysfunction (SMD) does not involve OXPHOS genes [2]. These disorders are not easy to treat [3]. However, diet, exercise, and specific vitamin supplements have a role in their management [4]. It is also of utmost importance to avoid mitochondrial toxic drugs such as valproic acid (VPA) and aminoglycosides.

PHARMACOLOGICAL INTERVENTION
Foremost among therapeutic interventions include CO-FACTORS of OXPHOS for promoting adenosine triphosphate (ATP) production. Coenzyme Q10 (CoQ10 as ubiquinone) is an essential electron carrier in OXPHOS process for ATP production. It is known to diminish with advancing age and result in the production of less ATP. Its deficiency is found to be autosomal recessive in inheritance and associated with five major clinical phenotypes encephalopathy, severe infantile multisystemic disease, cerebellar ataxia, isolated myopathy, and nephrotic syndrome. Primary CoQ10 deficiency occurs when there is a mutation of genes involved in its biosynthesis. Respiratory chain defects, reactive oxygen species (ROS) production, and apoptosis contribute toward primary CoQ10 deficiency. While in secondary deficiency, biosynthesis genes are not affected [5].

CoQ10 is not water-soluble and has low bioavailability and this causes a delay in attaining peak concentrations. It has shown to be beneficial in mitochondrial dysfunctional states. CoQ10 and its analogs restore electron flow and increase mitochondrial antioxidant capacity [6].

Its supplementation increases energy production and reduces fatigue [7]. It also has strong antioxidant properties [8]. Dietary CoQ10 causes improvement in exercise capacity and as such is useful in cardiovascular conditions such as hypertension, heart failure, and improves endothelial functions [9]. It is useful in neurodegenerative conditions such as Alzheimer’s disease (AD), Parkinsonism, and Huntington’s disease [10]. CoQ10 supplementation also benefits muscle pains in patients associated with statins therapy [11].

CoQ10 is one of the most widely used natural supplement. Dose in the pediatric group is 2-4 mg/kg/day while in adults, it ranges between 50 and 600 mg/day. CoQ10 is a safe option in the treatment of mitochondrial states. Meat, poultry, fish, soybeans, canola oils, and nuts are the rich sources of CoQ10. Fruits, vegetables, eggs, and dairy products are moderate sources of CoQ10.

MitoQ or mitoquinone is an orally active, water-soluble antioxidant that helps in mitochondrial dysfunction. It reduces mitochondrial overproduction of ROS and has high bioavailability and attains peak levels quickly in body. It does not need to be taken with food unlike CoQ10 [12].

In Mito Q, the lipophilic triphenylphosphonium cation is bound to ubiquinone moiety of co-enzyme Q10 [13,14]. Once targeted to the matrix, ubiquinone is reduced to ubiquinol that facilitates electron transfer between complexes I/II to complex III and acts as an antioxidant by decreasing lipid peroxidation. MitoQ10 has been found to improve endothelial nitric acid (NO) bioavailability and blood pressure [9]. Addition of MitoQ10 to treatment with Angiotensin receptor blocker (Losartan) is beneficial against target organ damage development in hypertension [15].

It improves electron transport chain (ETC) function and protects cardioplip which is a mitochondrial phospholipid found exclusively at the inner mitochondrial membrane. It has therapeutic potential for AP- and oxidative stress-associated neurodegenerative disorders, particularly Alzheimer’s disease (AD) [16].

MitoTEMPOL is a combination of the antioxidant piperidine nitrooxide. TEMPOL with the lipophilic cation triphenyl phosphonium gives...
MitoTEMPOL the ability to pass through lipid bilayers with ease and accumulate several hundred-fold in mitochondria. Its antioxidant action detoxifies superoxide by cycling between its nitroso and oxoanion forms, as well as oxidizing ferrous iron to limit hydroxyl radical formation [17].

MitoTEMPOL effectively reduces ROS production in both mitochondrial and cytosolic compartments in failing myocytes in animal studies [18]. Interestingly, this compound has been shown to be protective against oxidative injury in various pathologies, such as endotoxin-induced liver injury, sepsis-induced acute kidney injury, hypertension, or colitis [19-22].

**NUTRACEUTICALS**

Nutraceuticals are derived from food products. They are not traditionally recognized nutrients but have positive physiological effects on the body and have potential in the management of dyslipidemic states [23]. These are either vitamins or metabolic supplements. Nutraceuticals commonly used are thiamine (Vitamin B1), riboflavin (Vitamin B2), nicotinamide (Vitamin B3), dihydroacetate, creatine monohydrate, carnitine, L-arginine, or vitamin combinations.

All nutraceuticals increase the biological activity of complexes in the ETC. Enhancement of nitric oxide (NO) production is useful in mitochondrial ecephalomyopathies, lactic acidosis, and stroke-like episodes (MELAS), cystamine (in Huntington’s disease).

**Riboflavin**

It is a water-soluble B Vitamin (B2) and is a precursor of flavoprotein. Riboflavin plays an important part in the number of metabolic pathways. Its active derivatives, the flavin mononucleotide and flavin adenine dinucleotide, ensure the functions of numerous flavoprotein, including dehydrogenases, oxidases, monoxygenases, and reductases. They play a pivotal role in mitochondrial ETC, β-oxidation of fatty acids, redox homeostasis, citric acid cycle, branched-chain amino acid catabolism, chromatin remodeling, DNA repair, protein folding, and apoptosis.

Number of inborn errors of flavin metabolism and flavoenzyme functions such as multiple acyl-CoA dehydrogenation deficiency (MADD) and riboflavin transporter deficiencies respond to riboflavin supplementation [24,25].

Alteration in riboflavin levels will result in mitochondrial dysfunction and reduced energy levels will cause disorders such as neurodegenerative, cataract, and cardiovascular diseases. Mutations of mitochondrial DNA or nuclear DNA encoding for flavin transporters and flavo-enzyme in mitochondrial dysfunction are associated with neurological disorders [26]. Riboflavin treatment has been also tested in children with complex II (or succinate dehydrogenase) deficiency [27].

**Arginine**

(L-α-methyl-Dopa) (L-arginine) is an amino acid used in the biosynthesis of proteins. It is an immediate precursor of nitric oxide (NO) and is also necessary for the synthesis of important biological molecules such as creatine, ornithine, polyamines, agmatine, proline, glutamate, dimethyl-arginine, and urea. NO is an important neurotransmitter and possesses vasodilator properties.

Mitochondria in their dysfunctional states are unable to generate sufficient ATP for body needs. In MELAS syndrome, which is a primary mitochondrial disorder, there is ample evidence of deficiency of NO, L-arginine, and cyclic guanosine monophosphate due to endothelial dysfunction resulting from impaired blood perfusion. It contributes to stroke-like episodes, myopathy, and lactic acidosis in MELAS. Since arginine and citrulline both are NO precursors; they increase NO production and therefore, their administration alleviates endothelial dysfunction and helps in managing mitochondrial disorders [28].

Administration of L-arginine (500 mg/kg/dose) decreases the severity of stroke-like symptoms, enhances the dynamics of microcirculation, and reduces tissue injury from ischemia in patients with MELAS [29].

**Folinic acid**

Folinic acid a reduced form of folic acid is a water-soluble B Vitamin (B9). It is a cofactor in multiple metabolic reactions. ATP-driven folate transporter causes folate to enter brain through choroid plexus cells. Kearns-Sayre syndrome (KSS) which is a mitochondrial DNA syndrome, there is a reduce folate transport into brain due depletion of ATP, resulting in low spinal fluid (CSF) 5-methyltetrahydrofolate (5MTHF) levels. Early treatment with high-dose folic acid is effective in the treatment of KSS [30].

Patients with mitochondrial complex I encephalomyopathies also present with low 5MTHF level and respond to treatment with folic acid in addition to supplementation with radical scavengers and cofactors of deficient respiratory enzymes [31]. Folic acid supplementation is of use in some patients of mitochondrial disease [32].

**Nicotinamide adenine dinucleotide (NAD)**

NADH is a substrate for enzymes and cofactor in more than 200 cellular redox reactions. NADH has a vital role in ETC as it delivers electron from metabolite hydrolysis to transport chain in mitochondria. NADH possesses antioxidant properties and is such is used to neurodegenerative disorders such as Parkinson’s disease (PD) and Alzheimer’s disease (AD), where basic pathology is oxidative damage [33,34]. In chronic fatigue, NADH is also reported to reduce symptoms [35]. The most preferred supplementation of NADH is orally in its precursor forms such as nicotinamide and nicotinamide. Conventionally, prime indication of NADH remains pellagra, where it is deficient and is a disease of four D’s (dermatitis, diarrhea, dementia, and ultimately death).

Another therapeutic target is the stimulation of NAD biosynthetic pathway which increases protein deacetylation through SIRT and improves mitochondrial biogenesis [36]. Similarly, in animal trials, it delayed the progression to diabetic cardiomyopathy [37]. Nicotinamide riboside has been reported to effectively delay early and late-stage myopathy progression by robustly inducing mitochondrial biogenesis in skeletal muscle and brown adipose tissue, preventing mitochondrial abnormalities and mtDNA deletion formation [38].

**Membrane phospholipids**

– dietary phospholipids (PL) can be employed to replace the damaged oxidized membrane mitochondrial lipids to enhance its function [39]. Phospholipids and antioxidants combination has been found useful in chronic fatigue, aging, and fibromyalgia syndrome [40].

**Carnitine**

transports fatty acids into mitochondria for beta-oxidation and increases ATP production. It is, therefore, very useful in reducing exercise-induced fatigue as fat is utilized during extreme physical effort. Carnitine also modulates coenzyme A and removes excessive acyl groups from body [41]. Carnitine deficiency or impaired fatty acid oxidation is associated with reduced mitochondrial function, insulin resistance, and coronary heart disease, sepsis, and renal disease [41]. In aging, where there is a reduced mitochondrial OXPHOS leading to increased oxidants and reduced energy production, supplementation of carnitine corrects these adverse events. L-carnitine is found to have cardiac beneficial potential in patients of heart failure [42,43] through decreased ROS production. Dose in the pediatric group is orally 0.1 g/kg/d, while in adults, it is 5 g/d orally.

**Polyphenols**

(flavolons, theafolin, and epicatechin) have antioxidant actions and found to be useful in long-standing disorders, including cardiovascular diseases [44]. Polyphenols are naturally occurring compounds rich in red wine, green tea, olive oil, and dark chocolate. Mitochondrial pathways are involved in cardioprotective action of some flavonoids [45].

**Quercetin**

is a plant pigment (flavonoid) found in green tea, apples, berries, Ginkgo biloba, St. John’s Wort, American elder; and buckwheat tea has a large amount of quercetin. It increases endothelial NO synthase activity and hemeoxygenase-1 [46]. Quercetin also has significant antioxidant properties [47].
Polyphenols of olive oil and red wine reduce intracellular ROS levels [48], while epicatechin in green tea lowers the expression of pro-inflammatory molecules [49].

**DRUGS WITH ANTIOXIDANT ACTIVITY**

Vitamins C and E are the most popular antioxidant therapy in chronic diseases. However, their role in mitochondrial dysfunction in not clearly substantiated as mitochondria absorb only a small amount of these vitamins or they may interact with other therapeutic agents [50]. ROS scavengers and Vitamin K3, lipoic acid, tricarboxylidine, melatonin, N-acetylcysteine are effective antioxidants and are quite effective in mitochondrial disorders, carvedilol though a beta-blocker has been found useful in heart failure because of its antioxidant properties [51].

ACE inhibitors and angiotensin receptor-II blockers improve mitochondrial dysfunction. Captopril in animal studies is found to increase mitochondrial biogenesis, while losartan restored mitochondrial dysfunction and kidney damage through preservation of glutathione and SOD activity [52]. Statins (atorvastatin and simvastatin) have antioxidant stress potential and reduced the activity of mitochondrial NO synthase, cytochrome c release, and lipid peroxidation [53]. Oral antidiabetic thiazolidinediones (rosiglitazone) reduce lipid oxidation and hinders the development of atherosclerosis through up-regulation of peroxisome proliferator–activated receptor (PPARγ) [54]. Even the mainstay drug of diabetes the metformin, is found to reduce mitochondrial ROS production, enhances the activity of antioxidant enzymes and decreases inflammation attributed to I/R injury beneficial in diabetic cardiomyopathy.

Inhibition of the mitochondrial permeability and transition pore (mtPTP) and apoptosis. Cyclosporin, nortriptyline, and dimebon are the inhibitors of mtPTP and apoptosis. These are beneficial in mitochondrial dysfunctional conditions such as AD, PD, acute kidney injury, and myocardial infarction [55,56].

**ENHANCEMENT OF MITOCHONDRIAL BIOGENESIS**

Sirtuin analogs

Sirtuin analogs are a family of NAD-dependent deacetylases comprised of SIRT 1 to 7. Sirtuins affect the activity of multiple metabolic enzymes through stimulation of the PPAR family, PPAR signaling regulates gene expression of multiple metabolic pathways. These lead to beneficial effects of exercise, lean diets and found to even delay aging. In advancing age, obesity, sedentary habits, the NAD, and sirtuin level declines while, exercise has beneficial effects. SIRT1, SIRT4, and SIRT5 localize to mitochondria and regulate targets involved in biochemical pathways. Mitochondrial sirtuin has an important role in aging and age-related diseases [57,58].

Enkayrotes, mitochondria carry out numerous functions central to cellular and organismal health. How mitochondrial activities are regulated in response to different environmental conditions, such as variations in diet, remains an important unsolved question in biology. Here we review emerging evidence suggesting that reversible acetylation of mitochondrial proteins on lysine residues represents a key mechanism by which mitochondrial functions are adjusted to meet environmental demands. In mammals, three members of the sirtuin class of NAD-dependent deacetylases – SIRT3, SIRT4, and SIRT5 – localize to mitochondria and regulate targets involved in a diverse array of biochemical pathways. The importance of this activity is highlighted by recent studies of SIRT3, indicating that this protein suppresses the emergence of diverse age-related pathologies: hearing loss, cardiac fibrosis, and malignancy. Together, these findings argue that mitochondrial protein acetylation represents a central means by which mammals regulate mitochondrial functions to maintain cellular and organismal homeostasis.

Resveratrol is found in grapes and red wine, is an antioxidant, an apoptosis inhibitor, and an SIRT-1 agonist. Resveratrol has a potential role in the treatment of diabetes, cardiovascular disease, neurodegenerative disease, cancer, obesity, and aging. Its effects as antioxidant are associated with an induction of genes for OXPHOS and mitochondrial biogenesis and decrease in PGC-1α acetylation and an increase in PGC-1α activity.

Cardiomyocyte protective action of resveratrol is because it inhibits ROS generation in cardiomyocytes. Resveratrol also increases mitochondrial contents in endothelial cells [29-63]. Resveratrol restores mitochondrial functions and decreases insulin resistance. Hypoglycemia observed with resveratrol is because of a decrease in ROS and an increase in glucagon-like peptide [64].

Resveratrol also exhibits glioprotective action in azide-produced oxidative damage [65].

Bezafibrate is a hypolipidemic drug and a PPAR agonist increase mitochondrial transcription, mtRNA synthesis, and biogenesis [66]. Its short-term use has been shown to reduce number of complex IV-immunodeficient muscle fibers by inducing mitochondrial biogenesis and improved cardiac function. However, there are concerns about its long-term complications [67].

Taurine is a non-essential amino acid and is important for protein translation in mitochondria and has a therapeutic role in mitochondrial disorders [68,69]. Its therapy provides a substrate for the taurine conjugation reaction and restores mitochondrial protein biosynthesis, thereby improving mitochondrial function and reducing ROS generation [70].

MELAS has a defective taurine modification of the mutant mt RNAs, which result in a deficiency in protein synthesis. Taurine orally reduces the recurrence of stroke-like episodes and increases taurine modification in mitochondrial RNA in MELAS [71]. It also possesses neuroprotective in nickel toxicity by reducing oxidative stress and restores mitochondrial function [72].

**REDUCING MITOCHONDRIAL FISSION AND ENHANCING MITOCHONDRIAL FUSION**

Normally mitochondria constantly undergo fission and fusion and there is a balance between two. In neurodegenerative diseases such as AD, PD, and Huntington’s disease, the fragmentation takes the upper hand due to increased oxidation and generation of ROS, resulting in mitochondrial structural changes and dysfunction and cell damage. Hence, there is always an effort to develop inhibitors of mitochondrial fission.

Normal mitochondrial fission is regulated and maintained by two GTPase genes: Fis1 and Dynamin-related protein 1 (Drp1), effectively influences cell survival and apoptosis by mediating the mitochondrial fission process, which is an intricate process regulating both cellular and organ dynamics, including development, apoptosis, acute organ injury, and various diseases. It is suggested that Drp1 can reduce mitochondrial fission and elevate mitochondrial fusion [73].

Mammalian target of rapamycin complex 1 controls protein synthesis. It is a cytosolic Ser/Thr kinase belonging to the phosphatidylinositol kinase-related protein kinases family is a regulator of many cellular processes, including mRNA translation, and is a vital regulator in mitochondrial functions and increase ATP production capacity [74,75]. In cancer cells, the inhibitors of mTORC1 are of interest as inhibitors of cellular metabolism (femrrolimus and everolimus) [76].

**GENE THERAPY**

Current treatment strategies in mitochondrial disorders are largely supportive rather than curative. Gene therapy in the future may prove to be a deciding factor and completely change the approach to treat
mitochondrial dysfunctional disorders. Such techniques may target the mitochondrial genome in oocyte [77-80].

The most prominent gene therapy is mitochondrial replacement therapy (MRT), aims to prevent the transmission of heritable disorders caused by mutations in the mitochondrial genome. MRT is a pre-conception intervention that involves replacing the pathogenic mitochondrial DNA of an embryo with healthy mitochondrial DNA from a donor.

Targeting the mitochondria in mitochondrial diseases with the restriction endonuclease Smal enzyme has shown elimination of the mutant mtDNA followed with an increase in wild-type mtDNA and restoration of normal ATP levels [81].

NON-PHARMACOLOGICAL MANAGEMENT

Physical exercise

Mitochondria provide energy as ATP for muscle function. In mitochondrial dysfunctional states, there is less energy production coupled with increased excessive ROS, and this can trigger muscle atrophy, weakness, and loss of endurance. Exercise is known to increase mitochondria ETC activity in older human skeletal muscle, especially in sub sarcolemma (SS) mitochondria [82]. Exercise counters mitochondrial dysfunction. The compensatory nature of exercise is through pathways involving molecular signaling to transcription, as well as to post-transcriptional events within the mitochondrial synthesis and degradation [83].

Healthy nutrition

Malnutrition states such as anorexia, starvation, and cachexia result in SMD. Malnutrition leads to OXPHOS abnormalities. Improvement in intake of calories improves mitochondrial health in these patients [84,85].

Natural antioxidants can prevent and treat the disorders related to defective mitochondria as age progresses. Ginkgo biloba, a herbal drug used for the improvement of cognitive dysfunction. Curcumin a yellow pigment derived from the rhizome part of the turmeric plant; omega-3 polyunsaturated fatty acids (ω-3 PUFAs), a group of essential fatty acids and triterpenoids, the derivatives of oleanolic acid are all known to inhibit oxidative stress [86].

AVOIDING MITOCHONDRIAL TOXIC DRUGS

There is number of drugs those have proven mitochondrial toxic effects and such drugs should be avoided in mitochondrial dysfunctional disorders. These mitochondrial toxic drugs cause inhibition of ETC in OXPHOS, inducing oxidative stress, or inhibiting DNA replication, transcription, or translation [87].

Valproic acid (VPA) is a commonly used antiepileptic drug that has well-established hepatotoxicity and steatosis due to mitochondrial dysfunction. It selectively affects α-Lipoamide dehydrogenase in liver. Amide analogs of VPA show inhibitory effects on mitochondrial OXPHOS [88-90]. VPA produces inhibition of fatty acid oxidation, the citric acid cycle, OXPHOS, complex IV, and results in carnitine depletion [91].

Antitremoridal drugs cause impairment of mtDNA replication resulting in mtDNA depletion; carnitine deficiency, nucleoside reverse transcriptase inhibitors block both HIV reverse transcriptase and mitochondrial DNA polymerase gamma, the latter cause of the adverse effects due to these drugs. Mitochondrial toxicity includes defects in mitochondria DNA replication [92-96].

Statins are known for their efficacy in dyslipidemias but impair mitochondria. Statins cause abnormal mitochondrial morphology, decreased OXPHOS and activate apoptotic pathway, and deficiency of coenzyme Q10 [97]. Statin-induced mitochondrial dysfunction is the most likely cause of statin-associated muscle disease [98,99].

Aminoglycosides antimicrobials are known for hearing loss, renal and cardiac toxicity. They are mitochondrial toxic and impair mtDNA translation [100,101].

Aspirin Reye’s syndrome associated with aspirin is well-established. Aspirin leads to inhibition and uncoupling of OXPHOS. Aspirin causes an increase in ROS production, loss of mitochondrial membrane potential, and inhibition of mitochondrial respiratory functions [102]. Aspirin increases mitochondrial long-chain fatty acid oxidation and mitochondrial protein acetylation [103].

Acetaminophen is widely prescribed as an analgesic and antipyretic. However, its overdose can cause hepatotoxicity. Excess formation of the reactive metabolite N-acetyl-p-benzoquinone imine leads to hepatic glutathione depletion. Oxidative stress and cessation of ATP synthesis occur. It causes nuclear DNA fragmentation and extensive mitochondrial dysfunction result in necrotic cell death [104,105]. Mitochondrial respiratory complex I is affected by a hepatotoxix effect of a high dose of acetaminophen [106]. High dose hepatotoxicity causes an increase in ROS levels and loss of glutathione. Increased oxidative stress impairs mitochondrial function involving permeability transition, resulting in loss of mitochondrial membrane potential and ability to synthesize ATP [107].

Metformin is an anti-diabetic drug used in non-insulin-dependent diabetes mellitus. It inhibits mitophagy and increases the load of mutant mitochondrial DNA and also reduces oxidative stress [108].

CONCLUSIONS

Mitochondria are well known for their ability to synthesize ATP besides, the generation of ROS. In dysfunction of mitochondria, the energy depletion and accumulation of oxidants are likely outcome. The vital organs that exclusively depend on ATP for their function suffer most. Oxidative stress is involved in the pathophysiology of various disorders especially involving neurons and cardiovascular system. Mitochondrial-targeted pharmaceuticals and lifestyle modifications (healthy diet and regular exercise) are useful in these disorders.

AUTHORS’ CONTRIBUTIONS

All authors contributed equally.

CONFLICTS OF INTEREST

The authors declared no conflicts of interest related to the study.

AUTHORS’ FUNDING

The authors did not receive any funding for the research work.

REFERENCES

1. Chinnery PF. Mitochondrial disorders overview. In: Adam MP, Ardinger HH, Pagon RA, editors. GeneReviews®. Seattle, WA: University of Washington, Seattle 1993-2021.

2. Niyazov DM, Kabler SG, Frye RE. Primary mitochondrial disease and secondary mitochondrial dysfunction: Importance of distinction for diagnosis and treatment. Mol Syndromol 2016;7:122-37.

3. Khan NA, Govindaraj P, Meena AK, Thangaraj K. Mitochondrial disorders: Challenges in diagnosis treatment. Indian J Med Res 2015;141:13-26.

4. Avula S, Parikh S, Demarest S, Kurz J, Gropman A. Treatment of mitochondrial disorders. Curr Treat Options Neurol 2014;16:292.

5. Quinzi CM, Hirano M, Coenzyme Q and mitochondrial disease. Dev Disabil Res Rev 2010;16:183-8.

6. Hargreaves IP. Coenzyme Q10 as a therapy for mitochondrial disease. Int J Biochem Cell Biol 2014;49:105-11.

7. Orsucci D, Mancuso M, Ienco EC, LoGerfo A, Siciliano G. Targeting mitochondrial dysfunction and neurodegeneration by means of coenzyme Q10 and its analogues. Curr Med Chem 2011;18:4053-64.

8. Littarru GP, Tiano L. Clinical aspects of coenzyme Q10: An update. Nutrition 2010;26:250-4.
mitochondria-targeted antioxidant MitoQ10 improves endothelial function and attenuates cardiac hypertrophy. J Hypertens 2010;28:1352-9.

10. Isoe C, Abe T, Terayama Y. Levels of reduced and oxidized coenzyme Q10- and 8-hydroxy-2'-deoxyguanosine in the cerebrospinal fluid of patients with living Parkinson’s disease demonstrate that mitochondrial oxidative damage and/or oxidative DNA damage contributes to the neurodegenerative process. Neurosci Lett 2010;469:159-63.

11. Littarru GP, Langsjøen P. Coenzyme Q10 and statins: Biochemical and clinical implications. Mitochondrion 2007;7 Suppl:S168-74.

12. Tauskela JS. MitoQ—a mitochondria-targeted antioxidant. I Drugs 2007;16:169-71.

13. Smith RA, Porteous CM, Coulter CV, Murphy MP. Selective targeting of an antioxidant to mitochondria. Eur J Biochem 1999;263:709-16.

14. Adlam VJ, Harrison JC, Porteous CM, James AM, Smith RA, Murphy MP, et al. Targeting an antioxidant to mitochondria decreases cardiac ischemia-reperfusion injury. FASEB J 2005;19:1088-95.

15. McChlatchlan J, Beattie E, Murphy MP, Koh-Tan CH, Olson E, Beattie W, et al. Combined therapeutic benefit of mitochondria-targeted antioxidant, MitoQ10, and angiotensin receptor blocker, losartan, on cardiovascular function. J Hypertens 2014;32:555-64.

16. Ng LF, Grootveld M, Shaw JK, Gao CK, Cheung WF, Shi G, et al. The mitochondria-targeted antioxidant MitoQ extends lifespan and improves healthspan of a transgenic Caenorhabditis elegans model of Alzheimer disease. Free Radic Biol Med 2014;71:390-401.

17. Trnka J, Bolognani F, Smith RA, et al. A mitochondria-targeted nitroxide is reduced to its hydroxylamine by ubiquinol in mitochondria. Free Radic Biol Med 2008;44:1406-19.

18. Dey S, DeMazumder D, Sidor A, Foster DB, O’Rourke B. Mitochondrial ROS drive sudden cardiac death and chronic proteome remodeling in heart failure. Circ Res 2018;123:356-71.

19. Choumar A, Tarhuni A, Lettéron P, Reyl-Desmars F, Dauhoo N, et al. Therapeutic targeting of mitochondrial reactive oxygen species to reduce healthspan. Antioxid Redox Signal 2011;15:2837-54.

20. Långarrus A, Wiklund M, Rosenqvist M, et al. Reduced and oxidized coenzyme Q-10 and 8-hydroxy-2'-deoxyguanosine in the cerebrospinal fluid of patients with living Parkinson’s disease demonstrate that mitochondrial oxidative damage and/or oxidative DNA damage contributes to the neurodegenerative process. Neurosci Lett 2010;469:159-63.

21. Lee KR, Lindsey JR, El-Hattab AW. Endothelial dysfunction and the effect of riboflavin in children with complex II deficiency. Combined therapeutic benefit of mitochondria-targeted antioxidants and heme oxygenase. Free Radic Biol Med 2007;43:720-9.

22. Khan NA, Auranen M, Paetau I, Pirinen E, Eksela T, Niskanen T. Targeting mitochondria-derived reactive oxygen species to reduce healthspan. Antioxid Redox Signal 2011;15:2837-54.

23. Priyanga SK, Vazirian A, Riedel R, Schwenger V, Wanner C, et al. Flavonoids in atherosclerosis: An overview of their mechanisms of action. Cardiovasc Drug Rev 2010;19:152-71.

24. Scoditti E, Calabriso N, Massaro M, Pellegrino M, Storelli M, et al. Effect of flavonoids in atherosclerosis: An overview of their mechanisms of action. Cardiovasc Drug Rev 2010;19:152-71.

25. Vavuranakis M, Steffen D, Thun MJ, et al. Flavonoids in atherosclerosis: An overview of their mechanisms of action. Cardiovasc Drug Rev 2010;19:152-71.

26. Aylett SB, Burdett LT, Rammaert K, et al. Mitochondrion: Role of citrulline and arginine supplementation in apolipoprotein E-knockout mice by alleviating inflammation and endothelial dysfunction. Arterioscler Thromb Vasc Biol 2015;30:749-57.

27. Priyanga SK, Vazirian A, et al. Mitochondria-targeted antioxidants: A new paradigm for cardioprotection. Life Sci 2015;135:68-76.

28. Roncali L, Weiss J, Sequeira JM, et al. The mitochondria-targeted antioxidant MitoQ extends lifespan and improves healthspan of Caenorhabditis elegans model of Alzheimer disease. Free Radic Biol Med 2014;71:390-401.

29. Nicolson GL. Metabolic syndrome and mitochondrial function: Molecular replacement and antioxidant supplements to prevent membrane peroxidation and restore mitochondrial function. J Cell Mol Med 2007;11:159-65.

30. Nicolson GL, Eilthorpe R. Lipid replacement and antioxidant nutritional therapy for reducing mitochondrial function and reducing fatigue in chronic fatigue syndrome and other fatiguing illnesses. J Chronic Fatigue Syndr 2006;13:57-68.

31. Reuter SE, Evans AM. Carnitine and acylcarnitines: Pharmacokinetic, pharmacological and clinical aspects. Clin Pharmacokinet 2012;51:553-72.

32. Rizos I. Three-year survival of patients with heart failure caused by dilated cardiomyopathy and L-carnitine administration. Am Heart J 2003;145:1102-6.

33. Serati AR, Motamedi MR, Mani A, Vakili A, Movahed MR. L-carnitine treatment in patients with mild diastolic heart failure is associated with improvement in diastolic function and symptoms. Cardioiology 2010;116:178-82.

34. Siasos G, Tousoulis D, Tsikou V, Kokkou E, Oikonomou E, Varvarunakis M, et al. Flavonoids in atherosclerosis: An overview of their mechanisms of action. Cardiovasc Drug Rev 2010;19:152-71.

35. Vavuranakis M, Sarkisian H, et al. Mitochondria-targeted antioxidants: A new paradigm for cardioprotection. Life Sci 2015;135:68-76.

36. Bahadorani S, Ramezanzadeh A, et al. Mitochondria-targeted antioxidants: A new paradigm for cardioprotection. Life Sci 2015;135:68-76.

37. Ali Jamsi F, Al Zaaeb N, Al Tenisi AM, et al. Follow-up of folinic acid in inborn errors of metabolism. Int J Mol Sci 2020;21:3847.

38. Khan NA, Auranen M, Paetau I, Pirinen E, Eksela T, Niskanen T. Targeting mitochondria-derived reactive oxygen species to reduce healthspan. Antioxid Redox Signal 2011;15:2837-54.

39. Nicolson GL, Eilthorpe R. Lipid replacement and antioxidant nutritional therapy for reducing mitochondrial function and reducing fatigue in chronic fatigue syndrome and other fatiguing illnesses. J Chronic Fatigue Syndr 2006;13:57-68.

40. Reuter SE, Evans AM. Carnitine and acylcarnitines: Pharmacokinetic, pharmacological and clinical aspects. Clin Pharmacokinet 2012;51:553-72.

41. Priyanga SK, Vazirian A, et al. Mitochondria-targeted antioxidants: A new paradigm for cardioprotection. Life Sci 2015;135:68-76.

42. Rizos I. Three-year survival of patients with heart failure caused by dilated cardiomyopathy and L-carnitine administration. Am Heart J 2003;145:1102-6.

43. Serati AR, Motamedi MR, Mani A, Vakili A, Movahed MR. L-carnitine treatment in patients with mild diastolic heart failure is associated with improvement in diastolic function and symptoms. Cardioiology 2010;116:178-82.

44. Siasos G, Tousoulis D, Tsikou V, Kokkou E, Oikonomou E, Varvarunakis M, et al. Flavonoids in atherosclerosis: An overview of their mechanisms of action. Cardiovasc Drug Rev 2010;19:152-71.

45. Testai L. Flavonoids and mitochondrial pharmacology: A new paradigm for cardioprotection. Life Sci 2015;135:68-76.

46. Vavuranakis M, Sarkisian H, et al. Mitochondria-targeted antioxidants: A new paradigm for cardioprotection. Life Sci 2015;135:68-76.

47. Ali Jamsi F, Al Zaaeb N, Al Tenisi AM, et al. Follow-up of folinic acid in inborn errors of metabolism. Int J Mol Sci 2020;21:3847.

48. Khan NA, Auranen M, Paetau I, Pirinen E, Eksela T, Niskanen T. Targeting mitochondria-derived reactive oxygen species to reduce healthspan. Antioxid Redox Signal 2011;15:2837-54.

49. Nicolson GL, Eilthorpe R. Lipid replacement and antioxidant nutritional therapy for reducing mitochondrial function and reducing fatigue in chronic fatigue syndrome and other fatiguing illnesses. J Chronic Fatigue Syndr 2006;13:57-68.

50. Reuter SE, Evans AM. Carnitine and acylcarnitines: Pharmacokinetic, pharmacological and clinical aspects. Clin Pharmacokinet 2012;51:553-72.
Toxicol 2012;31:355-63.
54. Hernanz R, Martín A, Pérez-Girón JV, Palacios R, Briones AM, Miguel M, et al. Preglizzone treatment increases COX-2-derived prostacyclin production and reduces adavit stress in hypertensive rats: Role in vascular disease. Br J Pharmocol 2012;166:1303-19.
55. Sharov VG, Todor A, Khanal S, Imam M, Sabbah HN. Cyclosporine A attenuates mitochondrial permeability transition and improves mitochondrial respiratory function in cardiomycocytes isolated from dogs with heart failure. J Mol Cell Cardiol 2007;42:150-8.
56. Zhang WH, Wang H, Wang X, Narayanan MV, Stavrovskaya IG, Kristal BS, et al. Nortriptyline protects mitochondria and reduces cerebral ischemia/hypoxia injury. Stroke 2008;39:455-62.
57. Lombard DB, Tishkoff DX, Bao J. Mitochondrial sirtuins in the regulation of mitochondrial activity and metabolic adaptation. Handb Exp Pharmacol 2011;206:163-88.
58. Osborne B, Bentley NL, Montgomery MK, Turner N. The role of mitochondrial sirtuins in health and disease. Free Radic Biol Med 2016;100:164-74.
59. Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, et al. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. Cell 2006;127:1109-22.
60. Saiko P, Szakmany A, Jaeger W, Szekeres T. Resveratrol and its analogs: Defense against cancer, coronary disease and neurodegenerative maladies or just a fad? Mutat Res 2008;658:68-94.
61. Parikh S, Saneto R, Falk MJ, Anselm I, Cohen BH, Haas R, et al. A modern approach to the treatment of mitochondrial disease. Curr Treat Options Neurol 2009;11:414-9.
62. Ungvari Z, Sonntag WE, de Cabo R, Baur JA, Csiszar A. Mitochondrial protection by resveratrol. Exerc Sport Sci Rev 2011;39:128-32.
63. Csiszar A, Labinskyn N, Pinto JT, Ballabbi P, Zhang H, Losonczy G, et al. Resveratrol induces mitochondrial biogenesis in endothelial cells. Am J Physiol Heart Circ Physiol 2009;297:H13-20.
64. Wang H, Guan Y, Widlund AL, Becker LB, Baur JA, Reilly PM, et al. Resveratrol ameliorates mitochondrial dysfunction but increases the risk of hypoglycemia following hemorrhagic shock. J Trauma Acute Care Surg 2014;77:926-33.
65. Bellever B, Boudreau LD, Souza DG, Rodrigues MD, de Assis WM, Wajner M, et al. Signaling mechanisms underlying the glioprotective effects of resveratrol against mitochondrial dysfunction. Biochim Biophys Acta 2016;1862:1827-38.
66. Augustyniak J, Lenart J, Gaj P, Kolanowska M, Jazdzewski K, Augustyniak J, et al. Defective mitochondrial tRNA biogenesis and influence neural differentiation of human-induced pluripotent stem cells. Mol Neurobiol 2019;56:4346-63.
67. Steele H, Gomez-Duran A, Pyle A, Hopton S, Newman J, Stefanetti A, et al. Beazafibrate upregulates mitochondrial biogenesis and influence neural differentiation of human-induced pluripotent stem cells. Mol Neurobiol 2019;56:4346-63.
68. EMBO Mol Med 2020;12:e11589.
69. Khajuria et al. Asian J Pharm Clin Res, Vol 14, Issue 5, 2021, 24-30
70. male-derived Hmc1 expressing Saccharomyces cerevisiae. EMBO Mol Med 2020;12:e11589.
71. Oliveira AN, Hoo DA. Exercise is mitochondrial medicine for muscle. Sports Med Health Sci 2019;1:118-86.
72. Vivodtzev I, Robert D, Gómez-Duran A, Pyle A, Hopton S, Newman J, Stefanetti A, et al. Mitochondrial energy production correlates with the age-related BMI. Pediatr Res 2009;65:103-8.
73. Cormer J, Wolters J, Smit E, Schroders Y, Kleinjans J, van den Beucken T. Valproic acid promotes mitochondrial dysfunction in primary human hepatocytes in vitro; impact of CEBPα-controlled expression. Arch Toxicol 2020;94:3463-73.
74. Silva MF, Aries CC, Louis PB, Ruiter JP, Iljst L, Duran M, et al. Valproic acid metabolism and its effects on mitochondrial fatty acid oxidation: A review. J Inherit Metab Dis 2008;31:205-16.
75. Kakuda TN. Pharmacology of nucleoside and nucleotide reverse transcriptase inhibitor-induced mitochondrial toxicity. Clin Ther 2000;22:685-708.
76. Kohler JJ, Lewis M. A brief overview of mechanisms of mitochondrial toxicity from NRTIs. Environ Mol Mutagen 2007;48:166-72.
77. Dalakas MC. Peripheral neuropathy and antiretroviral drugs. J Peripher Nerv Syst 2001;6:14-20.
78. Scraggs ER, Dukx Naylor AJ. Mechanisms of zidovudine-induced mitochondrial toxicity and myopathy. Pharmacology 2008;82:83-8.
79. Pinti M, Salomoni P, Cossarizza A. Anti-HIV drugs and the mitochondria. Biochim Biophys Acta 2006;1757:700-7.
80. Broniarek I, Jarmuszkiewicz W. Statins and mitochondria. Postepy Biochem Genet 2007;27:125-37.
81. Ramachandran R, Wierzbiicki AS. Statins, muscle disease and mTORC1 as a regulator of mitochondrial functions and a therapeutic target in cancer. Front Oncol 2019;9:1373.
82. Tachibana M, Sparman M, Sritanudomchai H, Ma H, Clopper L, Woodward J, et al. Mitochondrial gene replacement in primate ESCs and embryonic stem cells. Nature 2009;461:367-72.
83. DiMauro S, Mancuso M. Mitochondrial diseases: Therapeutic approaches. Biosci Rep 2007;27:125-37.
84. Doyle SR, Chan CK. Mitochondrial gene therapy: An evaluation of strategies for the treatment of mitochondrial DNA disorders. Hum Gene Ther 2008;19:1335-48.
85. Agresti CA, Hallikadakis PN, Tolias P. MERRF and MELAS: Current gene therapy trends and approaches. J Transl Genet Genom 2018;2:9.
86. Tanaka M, Borgeld HJ, Zhang J, Muramatsu S, Gong JS, Yoneda M, et al. Gene therapy for mitochondrial disease by delivering restriction endonuclease Smal into mitochondria. J Biomed Sci 2002;9:534-41.
87. Menshikova EV, Ritov VB, Fairfull L, Ferrell RE, Kelley DE, Goodpaster BH. Effects of exercise on mitochondrial content and function in aging human skeletal muscle. J Gerontol A Biol Sci Med Sci 2006;61:534-40.
88. Ramachandran R, Wierzbiicki AS. Statins, muscle disease and mTORC1 as a regulator of mitochondrial functions and a therapeutic target in cancer. Front Oncol 2019;9:1373.
104. Burke AS, MacMillan-Crow LA, Hinson JA. Reactive nitrogen species in acetaminophen-induced mitochondrial damage and toxicity in mouse hepatocytes. Chem Res Toxicol 2010;23:1286-92.
105. Jaeschke H, Duan L, Nguyen N, Ramachandran A. Mitochondrial damage and biogenesis in acetaminophen-induced liver injury. Liver Res 2019;3:150-6.
106. Chrois KM, Larsen S, Pedersen JS, Rygg MO, Boilsen AE, Bendtsen F, et al. Acetaminophen toxicity induces mitochondrial complex I inhibition in human liver tissue. Basic Clin Pharmacol Toxicol 2019; 126:86-91.
107. Hinson JA, Roberts DW, James LP. Mechanisms of acetaminophen-induced liver necrosis. Handb Exp Pharmacol 2010;196:369-405.
108. Spiller HA, Sawyer TS. Toxicology of oral antidiabetic medications. Am J Health Syst Pharm 2006;63:929-38.