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Review Article

Role of Mitochondria and Mitochondrial Transplantation in Drug-induced Toxic Organ Injury

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Abstract

Mitochondria, which are one of the main organelles of the cell, have vital importance for the body. Mitochondrial mechanisms, which have critical roles in many physiological processes, are active in drug-induced toxic tissue damage as well as in diseases related to mitochondrial dysfunction. Mitochondrial dysfunction is a major mechanism by which various drugs can cause adverse effects in various tissues such as the liver, kidney and heart. Inhibiting respiratory complexes of the electron chain; disrupting cell bioenergetic mechanisms; inducing mitochondrial oxidative stress; inhibiting DNA replication, transcription, or translation; and reduction of protein synthesis are the most common ways drugs harm mitochondria. Mitochondrial transplantation has emerged as a promising area that has been studied more frequently in recent years. The importance of mitochondrial transplantation in a variety of mitochondrial dysfunction-related diseases such as cardiovascular diseases, neurodegenerative diseases, and ischemia has been emphasized. The purpose of this review article is to present current information on the role of mitochondria in toxic drug damage and the possible effects of mitochondrial transplantation on toxic damage.

Introduction

Mitochondria play a crucial role in the homeostasis of eukaryotic cells by generating adenosine triphosphate (ATP) via oxidative phosphorylation. Additionally, mitochondria are closely related to cell death pathways, such as apoptosis and necrosis, which are significant factors in toxic tissue damage. Moreover, mitochondria are the main base of reactive oxygen species (ROS) production, which occurs as a result of ATP production. The amount of mitochondrial ROS (mtROS) depends on the calcium load, metabolic status, and the use of substrates by mitochondria. When mitochondrial dysfunction occurs, an increase in mtROS production can cause oxidative damage to cellular structures. However, mtROS plays a role in important processes such as immune function, basic developmental processes, and antioxidant defense mechanisms.[1]

There are various mechanisms related to mitochondria that cause drug-induced toxic damage. Inhibition of the mitochondrial electron transport chain (ETC), ROS production, reduction of protein synthesis, cytochrome c secretion, and cell death are some of these mechanisms.[2] Apoptosis is the energy-dependent cell death pathway. Cytochrome c is released from the mitochondrial intermembrane space in the initial step of the mechanism (intrinsic pathway). It can also be initiated by apoptosis caspases (extrinsic pathway). Necrosis is an uncontrolled mechanism for cell death, caused by external factors such as hypoxia, trauma, and infection, which then cause swelling of the cell organelles, plasma membrane rupture, and cell lysis.[3,4] There is a close relationship between apoptosis and necrosis in terms of signaling pathways and regulatory mechanisms. For instance, some toxins can damage membrane structures and cause the release of cytochrome c and interrupt mitochondria processes. Some drugs target mitochondria as their area of therapeutic action. For example, a group of anticancer drugs can result in mitochondrial toxicity in cancer cells.[5] Mitochondrial damage that occurs in the mitochondria of healthy cells for this or

Keywords: Mitochondrion; Drug-induced toxic damage; Drug-induced mitochondrial toxicity; Mitochondrial transplantation.

Abbreviations: AKI, acute kidney injury; ALT, alanine transaminase; AMP, adenosine monophosphate; AMPK, 5′ adenosine monophosphate-activated protein kinase; APAP, acetaminophen; AST, aspartate aminotransferase; ATP, adenosine triphosphate; Ca2+, calcium ion; DILI, drug-induced liver injury; DNA, deoxyribonucleic acid; ETC, electron transport chain; GSH, glutathione; LDH, lactate dehydrogenase NAD+, oxidised nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide (NAD)+hydrogen (H); NRTIs, nucleotide reverse transcriptase inhibitors; MDA, malondialdehyde; mtDNA, mitochondrial DNA; mtROS, mitochondrial ROS; MPTP, mitochondrial permeability transition pore; OXPHOS, oxidative phosphorylation; PGC-1, peroxisome proliferator receptor gamma coactivator 1; ROS, reactive oxygen species.

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Table 1. Examples of the effects of drugs on mitochondria[6,7]

Inhibitors of the Respiratory Chain (Complex I)	Group I, NADH-flavin interface inhibitor (*e.g.,* rhein); Group II, quinol antagonists (*e.g.,* myxothiazol and quinolone aurachins); Group III, specific/potent complex I inhibitors (*e.g.,* rotenone)
Inhibitors of the Respiratory Chain (Complex III)	Group I occludes ubiquinol oxidation (*e.g.,* myxothiazol, strobilurins, and oudemansins); -Group II occludes electron transfer and prevents the reduction of cytochrome bL (*e.g.,* undecylhydroxydioxobenzothiazole and undecylhydroxynaphtoquinone); Group III prevents electron transfer between heme bH and quinone molecules (*e.g.,* antimycin A and funiculosin, quinolones)
Inhibitors of the Respiratory Chain (Complex IV and Cytochrome c Oxidase)	Group I inhibits heme-binding enzymes (*e.g.,* azide, cyanide, and sulfide); -Group II inhibits COX enzyme via oxygen competition (*e.g.,* carbon monoxide and nitric oxide); Group III inhibits COX enzyme via cytochrome c binding (*e.g.,* polycations); Group IV, other inhibitors not interacting with heme groups (*e.g.,* phosphate ions and alkaline pH)
Inhibitors of ATP-Synthase (H^+-ATP synthase (complex V)	Inhibits ATPase activity and occludes proton transmission (*e.g.,* mycotoxins, flavonoids and local anesthetics)
Uncouplers of Oxidative Phosphorylation	Affects routine mitochondrial energy production function: Lipophilic weak acids (*e.g.,* substituted phenols, trifluoromethyl benzimidazoles, salicylanilides, carbonyl cyanide phenylhydrazones); Other types of uncouplers (*e.g.,* ionophore gramicidin, cationic uncoupler pentamidine, membrane-active peptide mastoparan)
Targeting mtDNA	Interfere with mtDNA and mtDNA processes: Effects mitochondrial polymerase-γ (*e.g.,* menadione, antiviral drugs); Effects mitochondrial ribosomal RNA (*e.g.,* chloramphenicol, thiamphenicol); Effects mitochondrial topoisomerases (*e.g.,* amsacrine, etoposide, teniposide)

ATP, adenosine triphosphatase; COX, cytochrome c oxidase; cytochrome bL, cytochrome b subunit; NADH, nicotinamide adenine dinucleotide (NAD)+hydrogen (H); mtDNA, mitochondrial DNA; RNA, ribonucleic acid.

other reasons can lead to undesirable results and yield toxic effects.

This review aims to summarize the role of mitochondria in toxic organ damage and the therapeutic effects of mitochondrial transplantation. We provide an overview of the mitochondrial mechanisms of toxic organ damage, with a focus on some of the most commonly damaged organs such as liver and kidney, and the potential of mitochondrial transplantation.

Drug induced mitochondrial toxicity

Various chemical agents, whether toxic or therapeutic, exert significant effects on mitochondrial bioenergetic mechanisms by interacting with the ETC and causing changes in oxidative phosphorylation processes. As a result of these effects, the electrochemical proton gradient and electron transport mechanisms may be disrupted, the effectiveness of ATP production may be decreased, and oxidative damage may occur. In addition, changes in deoxyribonucleic acid (DNA) replication and protein expression can also bring important results. Some of the main sites of action of various chemical agents are listed in the table below (Table 1).[6,7]

There are various mechanisms related to mitochondria that cause drug-induced toxic damage. Inhibition of the ETC is one of these mechanisms that can cause excessive ROS production and cytochrome c secretion. Many drugs and drug metabolites can inhibit the ETC. Metformin is used to control hyperglycemia in type 2 diabetes and inhibits complex I of the ETC.[8] The inhibition effect of metformin was shown in a study on complex I isolated from metformin-pretreated hepatocyte mitochondria. According to the result, metformin localized in complex I and inhibited the mitochondrial respiratory chain but did not affect the other oxidative phosphorylation mechanisms.[9] Although the mechanisms are not identified, it is reported that the binding of the hydrocarbon part of the biguanide molecule to the hydrocarbon molecules of the membrane phospholipids could be a mechanism.[2] Inhibition of complex I activity brings about a reduction of hepatic gluconeogenesis and an augmentation of glucose consumption in peripheral tissue.[10] Rotenone, widely used as a pesticide, is a toxic agent that inhibits mitochondrial respiratory complex I. Rotenone prevents electron transfer from iron-sulfur to ubiquinone, inhibits oxidative phosphorylation and ATP synthesis, as well as induces ROS production.[4] It is also reported that rotenone caused the death of HL-60 cells via apoptosis revealed by DNA fragmentation, cytochrome c release, and caspase 3 activation.[11] Another drug that acts on an ETC complex is antimycin A. Antimycin A is an antibiotic that binds to a domain of cytochrome b on complex III, blocking the electron transport from bH heme to ubiquinone. This can result in increased ROS production and cell death by releasing iron from ferritin.[12,13]

Drugs can bind membrane phospholipids and inhibit oxidative phosphorylation via changes in membrane permeability. 2,4-Dinitrophenol disrupts the mitochondrial membrane potential, transmits protons through the mitochondrial membrane into the mitochondrial matrix, and uncouples oxidative phosphorylation. As the proton gradient and complex V activities are disrupted, protons need to be transported through the enzyme to synthesize ATP which results in thermal energy production without ATP formation.[14] Although it is not legal today, it is used by bodybuilders because it causes an increase in metabolism and the loss of body fat. Tolcapone, an inhibitor of levodopa metabolism, is also a potential uncoupling drug that decreases cellular ATP.[8] In a study on isolated mitochondria, GABA receptor agonist propofol (2,6-diisopropylphenol) has been shown to reduce transmembrane potential.[15] Although it can cause an increase in oxygen uptake and glycolysis, it can decrease glucose synthesis and cause lactic acidosis.

Oxidative stress is a defined mechanism of drug toxicity. For instance, the antibiotic doxorubicin is used as a chemotherapeutic drug that arrests cell proliferation via induction of DNA damage. However, it can cause cardiotoxicity via oxidative stress, impairment of mitochondria, down-regulation of cardiac-specific genes, and myocyte apoptosis.[16] Semiquinone radicals generated by nicotinamide adenine dinucleotide (NAD)+hydrogen (H) (NADH):b5 reductase and complex I are reported as a cause of mitochondrial

dysfunction and impaired oxidative phosphorylation.[2] Moreover, semiquinone reacts with oxygen, generates superoxide and hydrogen peroxide, and forms a complex with iron molecules, producing hydroxyl radical, which is one of the most reactive free radical.[17] Oxidative stress is reported to be a mechanism behind the inhibition of adenine nucleotide translocase and the deterioration of calcium homeostasis in a study performed on isolated mitochondria.[18] These changes cause mitochondrial permeability transition, cytochrome c release, and caspase activation, resulting in apoptosis. Necrosis is another cell death mechanism by ATP loss in doxorubicin toxicity. Clofibrate, used for hyperlipidemia treatment, also increases ROS production and causes oxidative damage to mitochondria. The reason for ROS production is defined as the uncoupling of oxidative phosphorylation at either complex II or III.[19]

Some drugs can also affect mitochondrial DNA replication. Nucleoside and nucleotide reverse transcriptase inhibitors (NRTI; *e.g.,* Zidovudine) which are used to interrupt the replication of HIV can inhibit mitochondrial DNA polymerase γ activity. NRTI-induced mitochondrial toxicity is related to clinically hepatic steatosis, pancreatitis, lactic acidosis, nephrotoxicity, and peripheral neuropathy.[20] Inhibition of mitochondrial DNA replication may cause a decrease in mitochondrial DNA (mtDNA).[21] As mtDNA encodes some mitochondrial proteins, mitochondrial function is deleteriously affected. A NRTI-induced cytotoxic effect on human hepatoma cells was reported in a study in which increased levels of mitochondrial ROS, DNA oxidation, and complex I inhibition were revealed.[22]

Toxic organ damage

The liver, kidney, and heart are the organs where damage due to toxic dose drug intake is frequently encountered. Most drugs are metabolized and removed by the liver and kidney, making them the most susceptible to toxic damage. Drug-induced liver injury (DILI) is the most common reason for acute liver failure in the US and the foremost cause of liver-related death in Western countries.[23,24] DILI is reported as a reason for 10% of hospitalizations with abnormal liver function.[25] The kidney is an indispensable organ that executes numerous vital functions containing the preservation of homeostasis, regulation of the extracellular environment, and excretion of metabolites.[26] Exposure to drugs frequently results in drug-induced acute kidney injury (AKI).[27] The frequency of drug-induced nephrotoxicity is reported in approximately 14–26% of adults with AKI cases, but it can be as high as 60%.[28–30] In addition, drug-induced toxic damage is seen primarily in organs such as the heart, which uses aerobic pathways in energy production.

Mitochondrial functions are significantly dependent on maintaining the impermeable structure of the inner mitochondrial membrane and mitochondrial complex function. At the same time, mtDNA, which is unique to the mitochondria, should be healthy, and its replication and the interaction between mtDNA and cell DNA should be appropriate. Many drugs have been reported to cause toxic damage due to their damaging effects on mitochondrial function, mtDNA, and protein expression. These effects of drugs on mitochondria are important for the prevention and treatment of toxic drug damage as well as for the development of new drugs and the evaluation of drug efficacy, as reported by Dykens *et al.*[31]

Liver

Wide-ranging agents can cause liver damage, like antibiotics, nonsteroidal anti-inflammatory drugs, anesthetics, anticancer drugs, central nervous system agents, and antiretrovirals.[32,33] The toxic effects of these agents, that can cause tissue damage and liver failure leading to organ transplantation or death, are reported in plenty of studies.[34–40] The mechanisms of DILI are not fully described, but mitochondrial dysfunction containing membrane permeabilization, oxidative phosphorylation (OXPHOS) impairment, fatty acid oxidation inhibition, and mtDNA depletion are reported as significant mechanisms, besides many other events.[41,42] Drugs themselves or reactive metabolites of the drugs generated in the cell can cause mitochondrial dysfunction,[43,44] but the transformation of nontoxic active ingredients into a chemically reactive metabolite is the most common source of DILI. Conjugation of these metabolites with glutathione (GSH) and hepatic macromolecules (including mitochondrial membranes) harms the cell and causes hepatic damage.[44]

Drugs can cause impaired respiration and energy production through different mechanisms. OXPHOS uncoupling and inhibition of the mitochondrial respiratory chain activity (together or separately) are some of these mechanisms.[45–47] Blocking of electron flow decreases ATP formation and impairs OXPHOS which harms cell function and survival. Severe ATP depletion can impair calcium homeostasis and consecutively activate proteases, endonucleases, and phospholipases that take part in the devastation of cell structures.[48] It is reported that liver cell necrosis, cholestasis, and fibrosis can occur consequently in some cases.[49] Impairment of mitochondrial respiration gives rise to the accumulation of electrons in the mitochondrial respiratory chain which causes ROS formation, oxidative stress, and mtDNA damage. Blocking of electron flow can also result in lactic acidosis because of the insufficient reduction of pyruvate.[42] The event that led to this situation is a decrease in the reoxidation of NADH into oxidised nicotinamide adenine dinucleotide (NAD+). Oxidation of pyruvate by the pyruvate dehydrogenase complex decreases because of the relative deficiency of NAD+.

Some drugs can inhibit the mitochondrial fatty acid oxidation and consequently induce microvesicular steatosis.[50] The existence of cytoplasmic lipid droplets is presented in liver pathology.[51] This was reported as a potential severe liver lesion that can be associated with liver failure.[52] Antiestrogenic tamoxifen which is used to treat breast cancer accumulates electrophoretically in mitochondria, inhibits OXPHOS and mitochondrial β-oxidation, and can cause steatosis as well.[53,54] Tamoxifen can also lead to progressive hepatic mtDNA depletion and inhibits mitochondrial ATPase.[55,56] Another mechanism that leads to steatosis is the activation of 5′ adenosine monophosphate-activated protein kinase (AMPK). Inhibition of mitochondrial respiration causes a decrease in ATP and an increase in adenosine diphosphate and adenosine monophosphate (AMP). When AMP increases, AMPK activates, and ATP-consuming pathways shift to ATP-producing catabolic pathways.[57] AMPK activation stimulates fatty acid uptake via the fatty acid transporter and enhances fatty acid oxidation. In case of a lack of NAD+, efficient β-oxidation might be prevented and contributes to fat accumulation in hepatic cells.[58]

Another cause of cell death and liver damage is mitochondrial permeability transition pore (MPTP) opening. MPTP opening is one of the important mechanisms of mitochondrial membrane disruption that can be a result of toxicity activated by reactive drug metabolites. Some of the mechanisms of MPTP opening are oxidation of MPTP components, increased levels of mitochondrial calcium, and activation of c-Jun N-terminal kinase or other endogenous MPTP inducers.[46,59,60] Opening of MPTP causes proton and fluid accumulation within the organelle, causing both loss of func-

tion and activating cell death pathways.[61] It has been reported that some drugs like salicylate, benzarone, and valproic acid can uncouple mitochondrial respiration and trigger MPTP opening.[62–66] Excessive intake of acetaminophen can also cause MPTP opening throughout hepatic GSH depletion, mitochondria damage, ROS formation, and c-Jun N-terminal kinase activation.[67,68]

Kidney

Toxic dose drug intake can cause a group of renal diseases including acute renal injury, altered intraglomerular hemodynamics, interstitial nephritis, acid-base and electrolyte disorders, and inflammatory changes in tubular cells that cause AKI and renal scarring.[30] The kidney is highly dependent on ATP to sustain its function, such as secretion and reabsorption of solutes.[69] For this reason, mitochondrial ATP production is crucial for the kidney, and ATP production in mitochondria is oxygen-dependent. Principally, the proximal and distal tubular cells are rich in mitochondria.[70] Moreover, the proximal tubular cells also have plenty of transporters (*e.g.,* solute carrier and ATP binding cassette pumps) which carry drugs between peritubular blood and the urine.[71]

The damage to mitochondrial membranes, mitochondrial complexes, and mitochondrial DNA, the disruption of protein synthesis and ATP production, and the increase of MPTP are some of the toxic damage mechanisms.[72] Inhibition of protein synthesis and mitochondrial DNA replication has been demonstrated in drug-related acute kidney injury experiments. One study reported that streptozotocin damaged mitochondrial DNA in a dose-dependent manner in rat insulinoma cell lines.[73] Another study on four different cell lines (HEK293, HeLa, Hepa 1-6, and GT1-7) found that tetracyclines caused mitonuclear protein imbalance by influencing nuclear gene expression and mitochondrial translation as well as changing mitochondrial dynamics and function.[74] Inhibition of DNA polymerase γ (responsible for replication of the mitochondrial genome) activity is a mechanism of acyclic nucleotide analog-induced acute kidney injury.[75] Covalent modifications of mtDNA might result in the inhibition of mitochondrial DNA replication. Additionally, cisplatin shows toxic effects via the covalent binding of the platinum derivates to mtDNA.[76] Mitochondria are considered an endosymbiotic organelle of bacterial origin. Therefore, mitochondrial protein synthesis is the target of some antibiotics.[77]

Mitochondrial complexes especially, complex I and complex II, are the target for a wide range of drugs.[78] Ifosfamide, a chemotherapeutic, was reported as a cause of tubular dysfunction.[79] Activation of complex I of rat renal cortex mitochondria was found to decrease in a study after ifosfamide treatment.[80] Antibiotic gentamicin can directly interact with complex II, and it can inhibit mitochondrial protein synthesis.[81,82] Moreover, it was reported that antibiotic vancomycin inhibited complex I activity and depolarized the mitochondrial membrane of the Lilly Laboratories Culture-Porcine Kidney 1 cells.[83]

Mitochondrial damage can be related to the direct interaction of taxane or platinum with the permeability transition pore. The platinum-containing drug cisplatin can generate crosslinks with the voltage-dependent anion channel and ease membrane permeabilization. As a consequence, cytochrome c releases, and apoptotic cell death occurs.[84] Paclitaxel is another drug that induces mitochondrial permeability transition pore opening and alters mitochondrial dynamics and function.[85,86] It induces an abrupt fall of the mitochondrial membrane potential and a loss of mitochondrial calcium ions (Ca^{2+}). The renal tubule epithelial lining and brush border membranes diminish because of necrosis and apoptosis.[87] Furthermore, aristolochic acid causes ATP depletion, depolarization of the mitochondrial membrane, the release of cytochrome c, activation of caspase 3 in HK-2 cells, and inhibition of the mitochondrial adenine nucleotide translocase in isolated mitochondria.[88–90]

Mitochondrial transplantation

Mitochondria play an important role in damage mechanisms due to toxic dose drug intake. Against this damage, protective mechanisms in mitochondria and adaptation of mitochondria to changed conditions gain importance.[91] For example, the production of mitochondrial antioxidants increases in response to augmented oxidative stress.[92] Additionally, heat shock proteins, peroxisome proliferator receptor gamma coactivator 1 (PGC-1), nuclear factor-kappa, and mitochondrial biogenesis also increase.[92,93] Because PGC-1 controls mitochondrial biogenesis via induction of nuclear respiratory factors 1 and 2, synthesis of respiratory chain polypeptides and induction of mitochondrial transcription factors rise.[94] Although mtDNA has many copies, it also has its weaknesses, such as the lack of a nucleotide excision repair mechanism. However, they can provide the elimination of damaged mtDNA through mechanisms such as mitochondrial fusion, fission, and autophagy.[1]

Mitochondria serve an important role in research, particularly in the process of drug-induced toxic damage and the time after the damage. Positive effects of mitochondrial transplantation have been reported not only in drug intoxication but also in many disease models such as ischemic tissue damage and neurodegenerative diseases. In this context, it has been discussed in more detail in our review articles.[95,96] In contrast, there are few studies on the effects of mitochondrial transplantation on tissue damage caused by the intake of toxic dose drugs (Table 2).[82,97–100] Kubat *et al.* investigated the effects of mitochondrial transplantation isolated from mesenchymal stem cells on a doxorubicin-mediated nephrotoxicity model within rats and its mechanism of action. They carried out kidney injury with an intraperitoneal injection of 6 mg/kg doxorubicin and transplanted the isolated mitochondria to the renal cortex of rats via direct injection. Histopathological (hematoxylin-eosin staining), immunohistochemical (Bcl-2 and caspase-3), biochemical (urea, creatinine, and blood urea nitrogen), and oxidative stress analysis (lipid peroxidation, total superoxide dismutase, and glutathione peroxidase) were performed in the study. It was reported that mitochondrial transplantation improved the cellular antioxidant capacity and the regeneration of tubular cells. Protein accumulation in tubular cells and renal deficits were decreased. Moreover, Bcl-2 levels increased while caspase-3 levels decreased. As a result of this study, mitochondrial dysfunction and doxorubicin-mediated nephrotoxicity were interrelated, and transplanting isolated mitochondria to damaged tissue had therapeutic effects.[97]

Shi *et al.* studied an acetaminophen (APAP) toxicity model applied by intraperitoneal injection of 250 mg/kg APAP on mice.[98] They demonstrated *in vivo* distribution of transplanted mitochondria via systemic injection and reported that the injected mitochondria were internalized by several tissues, such as the brain, lung, liver, kidney, and muscle. They reported the reduction of serum transaminase, histopathological damage, mitochondrial swelling, ROS production, and promotion of hepatic GSH and ATP levels after mitochondrial transplantation. The results were reported as indicators of the therapeutic effects of transplanted exogenous mitochondria.[98]

Ulger *et al.* examined the effects of transplanted mitochondria on APAP-induced toxic liver damage. 8.2×10^6 isolated mitochondria were transplanted to the liver after induction of tissue damage

Table 2. Summary of the effect of mitochondrial transplantation in different drug toxicity methods

Target cell/ tissue	Toxic damage method	Toxic effects of drugs	Application route and dose	Effects of transplanted mitochondria	Ref.
a. Liver	a. Intraperitoneal injection of 250 mg/kg APAP	a. Liver damage and cell swelling, increased transaminase activities and ROS production, decreased ATP and GSH levels	a. Intravenous injection of 10^{12} mitochondria	a. Reduced hepatotoxicity, decreased transaminase activities, increased ATP and GSH levels, and reduced ROS production	98
b. Hepatocyte cell culture	b. Incubation of 10 mM APAP for 2 h	b. Decreased cell viability	b. Coincubation of 10 µg/mL mitochondria	b. Increased cell viability, increased, ATP and GSH levels, decreased ROS production, and anti-apoptotic effects	98
Kidney	Intraperitoneal injection of 6 mg/kg DOX	Increased tubular dilatation and tubular protein accumulation, increased caspase-3, and decreased Bcl-2 levels	Direct injection of 8×10^6/ml mitochondria into the kidney	Increased tubular cell regeneration, improved renal deficits, reduced apoptosis, and oxidative stress	97
Liver	Subcutaneous injection of 1 µl/kg 20% carbon tetrachloride 1 time over 3 days for 3 weeks	Decreased cell viability, increased MDA, reduced antioxidants and ATP levels, enhanced serum ALT and AST levels, impaired tissue morphology, mitochondrial swelling, broken mitochondrial membrane, irregular crista arrangement, and vacuolar structure	Systemic injection of 0.2 or 0.4 mg/kg/day mitochondria for 7 days	Higher cell viability, increased anti-oxidants and ATP levels, reduced ROS production, decreased serum ALT and AST levels, improved tissue morphology and reduced fibrotic area, and improved mitochondrial ultrastructure and membrane potential	100
Liver	Oral administration of 1 g/kg APAP	Increased hepatocyte necrosis, ballooning degeneration, and inflammatory and apoptotic cell levels, elevated serum AST, ALT, and LDH levels, and increased oxidant levels	Injection into the subcapsular region of the spleen of 8.2×10^6 mitochondria	No evidence of tissue damage, reduced apoptotic cells, normal AST, ALT, and LDH levels, and decreased oxidant levels	99
Renal proximal tubular cells	Incubation of 1.5 mM gentamicin for 2 h	Increased cytotoxicity, ROS production, MMP collapse, LPO content, GSSG levels, and caspase-3 activity and reduced levels of ATP and GSH	Coincubation of 0.5 mg of mitochondrial protein/ml	Decreased cytotoxicity, ROS production, MMP collapse, LPO content, GSSG levels, and caspase-3 activity and increased levels of ATP and GSH	82

ALT, alanine transaminase; APAP, acetaminophen; AST, aspartate aminotransferase; ATP, adenosine triphosphate; DOX, doxorubicin; GSH, glutathione; GSSG, oxidized glutathione; LDH, lactate dehydrogenase; LPO, lipid peroxidation; MDA, malondialdehyde; MMP, mitochondrial membrane potential; ROS, reactive oxygen species.

with 1 g/kg APAP administered by oral gavage to the rats. They investigated multiple effects of the transplanted mitochondria. These were hepatocyte necrosis, ballooning, and degeneration, and the presence of inflammatory cells as shown by histological analysis; apoptosis as shown by terminal deoxynucleotidyl transferase dUTP nick end labeling assay; AST, ALT, lactate dehydrogenase (LDH) levels in blood samples; and malondialdehyde (MDA), superoxide dismutase, total antioxidant status, total oxidant status, and GSH levels as shown by oxidative stress analysis. According to the results, histological structures of damaged liver tissue improved to a similar level with healthy rats. Additionally, plasma ALT levels, apoptotic cells, and total oxidant levels decreased. It was reported that mitochondrial transplantation was very effective in terms of histological and functional improvement.[99]

Future directions

Mitochondrial transplantation is an emerging research area that draws attention with significant results in current studies and attracts more attention day by day. Ischemic tissue injuries and neurodegenerative diseases are frequently studied models of disease. In addition, as explained in the previous section, there are successful results in experimental studies on drug-induced toxic damage. Considering the mechanisms of action of drugs on mitochondria, it can be thought that, by transplanting healthy mitochondria to damaged tissues, eminent progress can be made in this area where significant problems are experienced during treatment. However, there are some limitations and problems that need to be resolved before the mitochondrial transplantation method can be used most effectively. For example, it has been reported that the presence of isolated mitochondria in a medium containing Ca^{2+} may adversely affect mitochondrial function and energy production. It is claimed that Ca^{2+} will accumulate in the mitochondria and increase membrane permeability. In this case, it is thought that osmotic balance agents in the mitochondrial medium may enter into the mitochondria and cause organelle edema. In addition, the fate of mitochondria after penetrating the target cell (how many mitochondria can pass into the cell and how they maintain their integrity and functions) is another question. Moreover, it is necessary to determine what the consequences will be when the mitochondrial genetic

material interacts with the cell nucleus and how the immune reactions will respond following mitochondrial transplantation.[95,101] For the clinical application of mitochondrial transplantation, these questions should be answered and issues, such as the route of administration and dosing, should be investigated with multi-faceted studies, and protocols should be clearly stated.

Studies have been conducted in different research areas based on the role of mitochondria in drug-induced toxic organ damage. In this context, mitohormesis is a phenomenon that interests scientists. While stress normally has detrimental effects, mitohormesis refers to the potential of stress to be beneficial at low levels. For instance, although exercise increases ROS production, it can have curative effects on mitochondrial function and patients. In addition to exercise, the mitohormetic effects of different manipulations such as dietary restriction, genetic manipulation, and reduction of ROS levels are emphasized. It has been reported that the severe genetic knockdown of ETC components decreases lifespan in *Caenorhabditis elegans*, but mild genetic knockdown increases viability.[1,102] It is an extremely important and necessary issue for today's world to conduct research on effective treatment by using this and other research methods and to support such research.

Conclusions

Nowadays, the increase in the number of prescriptions and the upsurge in the use of over-the-counter drugs has led to more exposure to toxic-dose drug usage. Although mitochondria are components for many physiological mechanisms in cells, they have a significant role in toxic organ damage mechanisms. The large number of drugs that cause mitochondrial dysfunction increasingly attracts the attention of researchers. Many drug failures or withdrawals have been reported related to mitochondrial toxicity. For this reason, some of the cellular damage mechanisms might be blocked via reorganizing the mitochondrial processes by transplantation of isolated healthy mitochondria to the damaged tissue. In light of the data obtained from studies on mitochondria transplantation, more research is needed on this method, which has the potential to have significant effects on toxic drug damage.

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Author contributions

Concept/design (OU and GBK). Drafting of the manuscript (GBK and OU). All authors read and approved the final manuscript.

References

[1] Meyer JN, Hartman JH, Mello DF. Mitochondrial Toxicity. Toxicol Sci 2018;162(1):15–23. doi:10.1093/toxsci/kfy008, PMID:29340618.

[2] Chan K, Truong D, Shangari N, O'Brien PJ. Drug-induced mitochondrial toxicity. Expert Opin Drug Metab Toxicol 2005;1(4):655–669. doi:10.1517/17425255.1.4.655, PMID:16863431.

[3] Fink SL, Cookson BT. Apoptosis, pyroptosis, and necrosis: mechanistic description of dead and dying eukaryotic cells. Infect Immun 2005;73(4):1907–1916. doi:10.1128/iai.73.4.1907-1916.2005, PMID:15784530.

[4] Khalid N, Azimpouran M. Necrosis. Treasure Island (FL): StatPearls Publishing; 2022.

[5] Jeena MT, Kim S, Jin S, Ryu JH. Recent Progress in Mitochondria-Targeted Drug and Drug-Free Agents for Cancer Therapy. Cancers (Basel) 2019;12(1):4. doi:10.3390/cancers12010004, PMID:31861339.

[6] Wallace KB, Starkov AA. Mitochondrial targets of drug toxicity. Annu Rev Pharmacol Toxicol 2000;40:353–388. doi:10.1146/annurev.pharmtox.40.1.353, PMID:10836141.

[7] Olszewska A, Szewczyk A. Mitochondria as a pharmacological target: magnum overview. IUBMB Life 2013;65(3):273–281. doi:10.1002/iub.1147, PMID:23441041.

[8] Hargreaves IP, Al Shahrani M, Wainwright L, Heales SJ. Drug-Induced Mitochondrial Toxicity. Drug Saf 2016;39(7):661–674. doi:10.1007/s40264-016-0417-x, PMID:26992920.

[9] El-Mir MY, Nogueira V, Fontaine E, Avéret N, Rigoulet M, Leverve X. Dimethylbiguanide inhibits cell respiration via an indirect effect targeted on the respiratory chain complex I. J Biol Chem 2000;275(1):223–228. doi:10.1074/jbc.275.1.223, PMID:10617608.

[10] Owen MR, Doran E, Halestrap AP. Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain. Biochem J 2000;348(Pt 3):607–614. PMID:10839993.

[11] Caboni P, Sherer TB, Zhang N, Taylor G, Na HM, Greenamyre JT, *et al*. Rotenone, deguelin, their metabolites, and the rat model of Parkinson's disease. Chem Res Toxicol 2004;17(11):1540–1548. doi:10.1021/tx049867r, PMID:15540952.

[12] Siraki AG, Pourahmad J, Chan TS, Khan S, O'Brien PJ. Endogenous and endobiotic induced reactive oxygen species formation by isolated hepatocytes. Free Radic Biol Med 2002;32(1):2–10. doi:10.1016/s0891-5849(01)00764-x, PMID:11755311.

[13] Jaeschke H, Kleinwaechter C, Wendel A. NADH-dependent reductive stress and ferritin-bound iron in allyl alcohol-induced lipid peroxidation *in vivo*: the protective effect of vitamin E. Chem Biol Interact 1992;81(1-2):57–68. doi:10.1016/0009-2797(92)90026-h, PMID:1730148.

[14] Pinchot GB. The mechanism of uncoupling of oxidative phosphorylation by 2,4-dinitrophenol. J Biol Chem 1967;242(20):4577–4583. PMID:4964808.

[15] Branca D, Roberti MS, Vincenti E, Scutari G. Uncoupling effect of the general anesthetic 2,6-diisopropylphenol in isolated rat liver mitochondria. Arch Biochem Biophys 1991;290(2):517–521. doi:10.1016/0003-9861(91)90575-4, PMID:1656882.

[16] Johnson-Arbor K, Dubey R. Doxorubicin. Treasure Island (FL): StatPearls Publishing; 2022.

[17] Hasinoff BB, Schnabl KL, Marusak RA, Patel D, Huebner E. Dexrazoxane (ICRF-187) protects cardiac myocytes against doxorubicin by preventing damage to mitochondria. Cardiovasc Toxicol 2003;3(2):89–99. doi:10.1385/ct:3:2:89, PMID:14501028.

[18] Zhou S, Starkov A, Froberg MK, Leino RL, Wallace KB. Cumulative and irreversible cardiac mitochondrial dysfunction induced by doxorubicin. Cancer Res 2001;61(2):771–777. PMID:11212281.

[19] Qu B, Li QT, Wong KP, Tan TM, Halliwell B. Mechanism of clofibrate hepatotoxicity: mitochondrial damage and oxidative stress in hepatocytes. Free Radic Biol Med 2001;31(5):659–669. doi:10.1016/s0891-5849(01)00632-3, PMID:11522451.

[20] Kakuda TN. Pharmacology of nucleoside and nucleotide reverse transcriptase inhibitor-induced mitochondrial toxicity. Clin Ther 2000;22(6):685–708. doi:10.1016/s0149-2918(00)90004-3, PMID:10929917.

[21] Caron M, Auclair M, Lagathu C, Lombès A, Walker UA, Kornprobst M, *et al*. The HIV-1 nucleoside reverse transcriptase inhibitors stavudine and zidovudine alter adipocyte functions *in vitro*. AIDS 2004;18(16):2127–2136. doi:10.1097/00002030-200411050-00004, PMID:15577645.

[22] Velsor LW, Kovacevic M, Goldstein M, Leitner HM, Lewis W, Day BJ. Mitochondrial oxidative stress in human hepatoma cells exposed to stavudine. Toxicol Appl Pharmacol 2004;199(1):10–19. doi:10.1016/j.taap.2004.03.005, PMID:15289086.
[23] Ostapowicz G, Fontana RJ, Schiødt FV, Larson A, Davern TJ, Han SH, *et al*. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med 2002;137(12):947–954. doi:10.7326/0003-4819-137-12-200212170-00007, PMID:12484709.
[24] Hoofnagle JH, Björnsson ES. Drug-induced liver injury - types and phenotypes. N Engl J Med 2019;381(3):264–273. doi:10.1056/NEJMra1816149, PMID:31314970.
[25] Sistanizad M, Peterson GM. Drug-induced liver injury in the Australian setting. J Clin Pharm Ther 2013;38(2):115–120. doi:10.1111/jcpt.12039, PMID:23350857.
[26] Ferguson MA, Vaidya VS, Bonventre JV. Biomarkers of nephrotoxic acute kidney injury. Toxicology 2008;245(3):182–193. doi:10.1016/j.tox.2007.12.024, PMID:18294749.
[27] Kim SY, Moon A. Drug-induced nephrotoxicity and its biomarkers. Biomol Ther (Seoul) 2012;20(3):268–272. doi:10.4062/biomolther.2012.20.3.268, PMID:24130922.
[28] Moffett BS, Goldstein SL. Acute kidney injury and increasing nephrotoxic-medication exposure in noncritically-ill children. Clin J Am Soc Nephrol 2011;6(4):856–863. doi:10.2215/cjn.08110910, PMID:21212419.
[29] Perazella MA. Pharmacology behind Common Drug Nephrotoxicities. Clin J Am Soc Nephrol 2018;13(12):1897–1908. doi:10.2215/cjn.00150118, PMID:29622670.
[30] Ghane Shahrbaf F, Assadi F. Drug-induced renal disorders. J Renal Inj Prev 2015;4(3):57–60. doi:10.12861/jrip.2015.12, PMID:26468475.
[31] Dykens JA, Will Y. The significance of mitochondrial toxicity testing in drug development. Drug Discov Today 2007;12(17-18):777–785. doi:10.1016/j.drudis.2007.07.013, PMID:17826691.
[32] David S, Hamilton JP. Drug-induced liver injury. US Gastroenterol Hepatol Rev 2010;6:73–80. PMID:21874146.
[33] Francis P, Navarro VJ. Drug Induced hepatotoxicity. Treasure Island (FL): StatPearls Publishing; 2022.
[34] Larrey D. Drug-induced liver diseases. J Hepatol 2000;32(Suppl 1):77–88. doi:10.1016/s0168-8278(00)80417-1, PMID:10728796.
[35] Zimmerman HJ, Ishak KG. Valproate-induced hepatic injury: analyses of 23 fatal cases. Hepatology 1982;2(5):591–597. doi:10.1002/hep.1840020513, PMID:6811394.
[36] Arnaudo E, Dalakas M, Shanske S, Moraes CT, DiMauro S, Schon EA. Depletion of muscle mitochondrial DNA in AIDS patients with zidovudine-induced myopathy. Lancet 1991;337(8740):508–510. doi:10.1016/0140-6736(91)91294-5, PMID:1671889.
[37] David Josephy P. The molecular toxicology of acetaminophen. Drug Metab Rev 2005;37(4):581–594. doi:10.1080/03602530500205200, PMID:16393886.
[38] Davidson DG, Eastham WN. Acute liver necrosis following overdose of paracetamol. Br Med J 1966;2(5512):497–499. doi:10.1136/bmj.2.5512.497, PMID:5913083.
[39] Smith DA, Schmid EF. Drug withdrawals and the lessons within. Curr Opin Drug Discov Devel 2006;9(1):38–46. PMID:16445116.
[40] Nash E, Sabih AH, Chetwood J, Wood G, Pandya K, Yip T, *et al*. Drug-induced liver injury in Australia, 2009-2020: the increasing proportion of non-paracetamol cases linked with herbal and dietary supplements. Med J Aust 2021;215(6):261–268. doi:10.5694/mja2.51173, PMID:34272737.
[41] Labbe G, Pessayre D, Fromenty B. Drug-induced liver injury through mitochondrial dysfunction: mechanisms and detection during preclinical safety studies. Fundam Clin Pharmacol 2008;22(4):335–353. doi:10.1111/j.1472-8206.2008.00608.x, PMID:18705745.
[42] Pessayre D, Mansouri A, Berson A, Fromenty B. Mitochondrial involvement in drug-induced liver injury. Handb Exp Pharmacol 2010;196:311–365. doi:10.1007/978-3-642-00663-0_11, PMID:20020267.
[43] Yuan L, Kaplowitz N. Mechanisms of drug-induced liver injury. Clin Liver Dis 2013;17(4):507–518. doi:10.1016/j.cld.2013.07.002, PMID:24099014.
[44] Burcham PC, Harman AW. Acetaminophen toxicity results in site-specific mitochondrial damage in isolated mouse hepatocytes. J Biol Chem 1991;266(8):5049–5054. PMID:2002047.
[45] Berson A, Cazanave S, Descatoire V, Tinel M, Grodet A, Wolf C, *et al*. The anti-inflammatory drug, nimesulide (4-nitro-2-phenoxymethane-sulfoanilide), uncouples mitochondria and induces mitochondrial permeability transition in human hepatoma cells: protection by albumin. J Pharmacol Exp Ther 2006;318(1):444–454. doi:10.1124/jpet.106.104125, PMID:16617166.
[46] Berson A, Descatoire V, Sutton A, Fau D, Maulny B, Vadrot N, *et al*. Toxicity of alpidem, a peripheral benzodiazepine receptor ligand, but not zolpidem, in rat hepatocytes: role of mitochondrial permeability transition and metabolic activation. J Pharmacol Exp Ther 2001;299(2):793–800. PMID:11602696.
[47] Berson A, Schmets L, Fisch C, Fau D, Wolf C, Fromenty B, *et al*. Inhibition by nilutamide of the mitochondrial respiratory chain and ATP formation. Possible contribution to the adverse effects of this antiandrogen. J Pharmacol Exp Ther 1994;270(1):167–176. PMID:8035313.
[48] Pessayre D, Haouzi D, Fau D, Robin MA, Mansouri A, Berson A. Withdrawal of life support, altruistic suicide, fratricidal killing and euthanasia by lymphocytes: different forms of drug-induced hepatic apoptosis. J Hepatol 1999;31(4):760–770. doi:10.1016/s0168-8278(99)80360-2, PMID:10551404.
[49] Bioulac-Sage P, Parrot-Roulaud F, Mazat JP, Lamireau T, Coquet M, Sandler B, *et al*. Fatal neonatal liver failure and mitochondrial cytopathy (oxidative phosphorylation deficiency): a light and electron microscopic study of the liver. Hepatology 1993;18(4):839–846. doi:10.1002/hep.1840180414, PMID:8406357.
[50] Fromenty B, Pessayre D. Inhibition of mitochondrial beta-oxidation as a mechanism of hepatotoxicity. Pharmacol Ther 1995;67(1):101–154. doi:10.1016/0163-7258(95)00012-6, PMID:7494860.
[51] Hautekeete ML, Degott C, Benhamou JP. Microvesicular steatosis of the liver. Acta Clin Belg 1990;45(5):311–326. doi:10.1080/17843286.1990.11718105, PMID:2177300.
[52] Geneve J, Hayat-Bonan B, Labbe G, Degott C, Letteron P, Freneaux E, *et al*. Inhibition of mitochondrial beta-oxidation of fatty acids by pirprofen. Role in microvesicular steatosis due to this nonsteroidal anti-inflammatory drug. J Pharmacol Exp Ther 1987;242(3):1133–1137. PMID:3116197.
[53] Bruno S, Maisonneuve P, Castellana P, Rotmensz N, Rossi S, Maggioni M, *et al*. Incidence and risk factors for non-alcoholic steatohepatitis: prospective study of 5408 women enrolled in Italian tamoxifen chemoprevention trial. BMJ 2005;330(7497):932. doi:10.1136/bmj.38391.663287.E0, PMID:15746106.
[54] Unten Y, Murai M, Koshitaka T, Kitao K, Shirai O, Masuya T, *et al*. Comprehensive understanding of multiple actions of anticancer drug tamoxifen in isolated mitochondria. Biochim Biophys Acta Bioenerg 2022;1863(2):148520. doi:10.1016/j.bbabio.2021.148520, PMID:34896079.
[55] Larosche I, Lettéron P, Fromenty B, Vadrot N, Abbey-Toby A, Feldmann G, *et al*. Tamoxifen inhibits topoisomerases, depletes mitochondrial DNA, and triggers steatosis in mouse liver. J Pharmacol Exp Ther 2007;321(2):526–535. doi:10.1124/jpet.106.114546, PMID:17277197.
[56] Nadanaciva S, Bernal A, Aggeler R, Capaldi R, Will Y. Target identification of drug induced mitochondrial toxicity using immunocapture based OXPHOS activity assays. Toxicol In Vitro 2007;21(5):902–911. doi:10.1016/j.tiv.2007.01.011, PMID:17346924.
[57] Pessayre D, Fromenty B. NASH: a mitochondrial disease. J Hepatol 2005;42(6):928–940. doi:10.1016/j.jhep.2005.03.004, PMID:15885365.
[58] Blas-García A, Apostolova N, Ballesteros D, Monleón D, Morales JM, Rocha M, *et al*. Inhibition of mitochondrial function by efavirenz increases lipid content in hepatic cells. Hepatology 2010;52(1):115–125. doi:10.1002/hep.23647, PMID:20564379.
[59] Balakirev MY, Zimmer G. Mitochondrial injury by disulfiram: two different mechanisms of the mitochondrial permeability transition. Chem Biol Interact 2001;138(3):299–311. doi:10.1016/s0009-2797(01)00283-6, PMID:11714485.
[60] Sohn JH, Han KL, Kim JH, Rukayadi Y, Hwang JK. Protective Effects of macelignan on cisplatin-induced hepatotoxicity is associated with JNK activation. Biol Pharm Bull 2008;31(2):273–277. doi:10.1248/bpb.31.273, PMID:18239286.
[61] Feldmann G, Haouzi D, Moreau A, Durand-Schneider AM, Bringuier A,

Berson A, *et al*. Opening of the mitochondrial permeability transition pore causes matrix expansion and outer membrane rupture in Fas-mediated hepatic apoptosis in mice. Hepatology 2000;31(3):674–683. doi:10.1002/hep.510310318, PMID:10706558.
[62] Trost LC, Lemasters JJ. The mitochondrial permeability transition: A new pathophysiological mechanism for Reye's syndrome and toxic liver injury. J Pharmacol Exp Ther 1996;278(3):1000–1005. PMID:8819478.
[63] Kaufmann P, Török M, Hänni A, Roberts P, Gasser R, Krähenbühl S. Mechanisms of benzarone and benzbromarone-induced hepatic toxicity. Hepatology 2005;41(4):925–935. doi:10.1002/hep.20634, PMID:15799034.
[64] Smith BK, Ford RJ, Desjardins EM, Green AE, Hughes MC, Houde VP, *et al*. Salsalate (Salicylate) Uncouples Mitochondria, Improves Glucose Homeostasis, and Reduces Liver Lipids Independent of AMPK-β1. Diabetes 2016;65(11):3352–3361. doi:10.2337/db16-0564, PMID:27554471.
[65] Mihajlovic M, Vinken M. Mitochondria as the target of hepatotoxicity and drug-induced liver injury: molecular mechanisms and detection methods. Int J Mol Sci 2022;23(6):3315. doi:10.3390/ijms23063315, PMID:35328737.
[66] Salsaa M, Pereira B, Liu J, Yu W, Jadhav S, Hüttemann M, *et al*. Valproate inhibits mitochondrial bioenergetics and increases glycolysis in Saccharomyces cerevisiae. Sci Rep 2020;10(1):11785. doi:10.1038/s41598-020-68725-5, PMID:32678210.
[67] Bajt ML, Knight TR, Farhood A, Jaeschke H. Scavenging peroxynitrite with glutathione promotes regeneration and enhances survival during acetaminophen-induced liver injury in mice. J Pharmacol Exp Ther 2003;307(1):67–73. doi:10.1124/jpet.103.052506, PMID:12954812.
[68] Jaeschke H, Duan L, Nguyen N, Ramachandran A. Mitochondrial damage and biogenesis in acetaminophen-induced liver injury. Liver Res 2019;3(3-4):150–156. doi:10.1016/j.livres.2019.10.002, PMID:32655976.
[69] Soltoff SP. ATP and the regulation of renal cell function. Annu Rev Physiol 1986;48:9–31. doi:10.1146/annurev.ph.48.030186.000301, PMID:3010834.
[70] Clark AJ, Parikh SM. Mitochondrial metabolism in acute kidney injury. Semin Nephrol 2020;40(2):101–113. doi:10.1016/j.semnephrol.2020.01.002, PMID:32303274.
[71] Fisel P, Renner O, Nies AT, Schwab M, Schaeffeler E. Solute carrier transporter and drug-related nephrotoxicity: the impact of proximal tubule cell models for preclinical research. Expert Opin Drug Metab Toxicol 2014;10(3):395–408. doi:10.1517/17425255.2014.876990, PMID:24397389.
[72] Gai Z, Gui T, Kullak-Ublick GA, Li Y, Visentin M. The role of mitochondria in drug-induced kidney injury. Front Physiol 2020;11:1079. doi:10.3389/fphys.2020.01079, PMID:33013462.
[73] Pettepher CC, LeDoux SP, Bohr VA, Wilson GL. Repair of alkali-labile sites within the mitochondrial DNA of RINr 38 cells after exposure to the nitrosourea streptozotocin. J Biol Chem 1991;266(5):3113–3117. PMID:1825207.
[74] Moullan N, Mouchiroud L, Wang X, Ryu D, Williams EG, Mottis A, *et al*. Tetracyclines disturb mitochondrial function across eukaryotic models: A call for caution in biomedical research. Cell Rep 2015;10(10):1681–1691. doi:10.1016/j.celrep.2015.02.034, PMID:25772356.
[75] Leowattana W. Antiviral drugs and acute kidney injury (AKI). Infect Disord Drug Targets 2019;19(4):375–382. doi:10.2174/1871526519666190617154137, PMID:31288730.
[76] Olivero OA, Semino C, Kassim A, Lopez-Larraza DM, Poirier MC. Preferential binding of cisplatin to mitochondrial DNA of Chinese hamster ovary cells. Mutat Res 1995;346(4):221–230. doi:10.1016/0165-7992(95)90039-x, PMID:7753115.
[77] Wang X, Ryu D, Houtkooper RH, Auwerx J. Antibiotic use and abuse: a threat to mitochondria and chloroplasts with impact on research, health, and environment. Bioessays 2015;37(10):1045–1053. doi: 10.1002/bies.201500071, PMID:26347282.
[78] Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P. Molecular biology of the cell (4th edn). Ann Bot 2003;91(3):401. doi:10.1093/aob/mcg023.
[79] Arjmand A, Mashhadi M, Kaveh A, Kamranfar F, Seydi E, Pourahmad J. Mitochondrial transplantation therapy against ifosfamide induced toxicity on rat renal proximal tubular cells. Drug Res (Stuttg) 2023;73(2):113–120. doi:10.1055/a-1967-2066, PMID:36395822.
[80] Nissim I, Horyn O, Daikhin Y, Nissim I, Luhovyy B, Phillips PC, *et al*. Ifosfamide-induced nephrotoxicity: Mechanism and prevention. Cancer Res 2006;66(15):7824–7831. doi:10.1158/0008-5472.can-06-1043, PMID:16885387.
[81] O'Reilly M, Young L, Kirkwood NK, Richardson GP, Kros CJ, Moore AL. Gentamicin affects the bioenergetics of isolated mitochondria and collapses the mitochondrial membrane potential in cochlear sensory hair cells. Front Cell Neurosci 2019;13:416. doi:10.3389/fncel.2019.00416, PMID:31572129.
[82] Arjmand A, Shiranirad S, Ameritorzani F, Kamranfar F, Seydi E, Pourahmad J. Mitochondrial transplantation against gentamicin-induced toxicity on rat renal proximal tubular cells: the higher activity of female rat mitochondria. In Vitro Cell Dev Biol Anim 2023;59:31–40. doi:10.1007/s11626-022-00743-1, PMID:36630058.
[83] Arimura Y, Yano T, Hirano M, Sakamoto Y, Egashira N, Oishi R. Mitochondrial superoxide production contributes to vancomycin-induced renal tubular cell apoptosis. Free Radic Biol Med 2012;52(9):1865–1873. doi:10.1016/j.freeradbiomed.2012.02.038, PMID:22401854.
[84] Yang Z, Schumaker LM, Egorin MJ, Zuhowski EG, Guo Z, Cullen KJ. Cisplatin preferentially binds mitochondrial DNA and voltage-dependent anion channel protein in the mitochondrial membrane of head and neck squamous cell carcinoma: possible role in apoptosis. Clin Cancer Res 2006;12(19):5817–5825. doi:10.1158/1078-0432.ccr-06-1037, PMID:17020989.
[85] Kidd JF, Pilkington MF, Schell MJ, Fogarty KE, Skepper JN, Taylor CW, *et al*. Paclitaxel affects cytosolic calcium signals by opening the mitochondrial permeability transition pore. J Biol Chem 2002;277(8):6504–6510. doi:10.1074/jbc.M106802200, PMID:11724773.
[86] Zhou X, Li R, Chen R, Liu J. Altered mitochondrial dynamics, biogenesis, and functions in the paclitaxel-resistant lung adenocarcinoma cell line A549/Taxol. Med Sci Monit 2020;26:e918216. doi:10.12659/msm.918216, PMID:32129321.
[87] Rabah SO. Acute Taxol nephrotoxicity: Histological and ultrastructural studies of mice kidney parenchyma. Saudi J Biol Sci 2010;17(2):105–114. doi:10.1016/j.sjbs.2010.02.003, PMID:23961065.
[88] Qi X, Cai Y, Gong L, Liu L, Chen F, Xiao Y, *et al*. Role of mitochondrial permeability transition in human renal tubular epithelial cell death induced by aristolochic acid. Toxicol Appl Pharmacol 2007;222(1):105–110. doi:10.1016/j.taap.2007.03.029, PMID:17521691.
[89] Bernardi P. The permeability transition pore. Control points of a cyclosporin A-sensitive mitochondrial channel involved in cell death. Biochim Biophys Acta 1996;1275(1-2):5–9. doi:10.1016/0005-2728(96)00041-2, PMID:8688451.
[90] Liu X, Wu J, Wang J, Feng X, Wu H, Huang R, *et al*. Mitochondrial dysfunction is involved in aristolochic acid I-induced apoptosis in renal proximal tubular epithelial cells. Hum Exp Toxicol 2020;39(5):673–682. doi:10.1177/0960327119897099, PMID:31884831.
[91] Pessayre D, Fromenty B, Berson A, Robin MA, Lettéron P, Moreau R, *et al*. Central role of mitochondria in drug-induced liver injury. Drug Metab Rev 2012;44(1):34–87. doi:10.3109/03602532.2011.604086, PMID:21892896.
[92] Cox AG, Winterbourn CC, Hampton MB. Mitochondrial peroxiredoxin involvement in antioxidant defence and redox signalling. Biochem J 2009;425(2):313–325. doi:10.1042/bj20091541, PMID:20025614.
[93] St-Pierre J, Drori S, Uldry M, Silvaggi JM, Rhee J, Jäger S, *et al*. Suppression of reactive oxygen species and neurodegeneration by the PGC-1 transcriptional coactivators. Cell 2006;127(2):397–408. doi:10.1016/j.cell.2006.09.024, PMID:17055439.
[94] Wu Z, Puigserver P, Andersson U, Zhang C, Adelmant G, Mootha V, *et al*. Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. Cell 1999;98(1):115–124. doi:10.1016/s0092-8674(00)80611-x, PMID:10412986.
[95] Ulger O, Kubat GB. Therapeutic applications of mitochondrial transplantation. Biochimie 2022;195:1–15. doi:10.1016/j.biochi.2022.01.002, PMID:35026361.
[96] Kubat GB, Ulger O, Akin S. Requirements for successful mitochondrial transplantation. J Biochem Mol Toxicol 2021;35(11):e22898. doi:10.1002/jbt.22898, PMID:34435410.
[97] Kubat GB, Ozler M, Ulger O, Ekinci O, Atalay O, Celik E, *et al*. The

effects of mesenchymal stem cell mitochondrial transplantation on doxorubicin-mediated nephrotoxicity in rats. J Biochem Mol Toxicol 2021;35(1):e22612. doi:10.1002/jbt.22612, PMID:32870571.

[98] Shi X, Bai H, Zhao M, Li X, Sun X, Jiang H, *et al*. Treatment of acetaminophen-induced liver injury with exogenous mitochondria in mice. Transl Res 2018;196:31–41. doi:10.1016/j.trsl.2018.02.003, PMID:29548626.

[99] Ulger O, Kubat GB, Cicek Z, Celik E, Atalay O, Suvay S, *et al*. The effects of mitochondrial transplantation in acetaminophen-induced liver toxicity in rats. Life Sci 2021;279:119669. doi:10.1016/j.lfs.2021.119669, PMID:34081988.

[100] Zhao Z, Hou Y, Zhou W, Keerthiga R, Fu A. Mitochondrial transplantation therapy inhibit carbon tetrachloride-induced liver injury through scavenging free radicals and protecting hepatocytes. Bioeng Transl Med 2021;6(2):e10209. doi:10.1002/btm2.10209, PMID:34027095.

[101] Chernyak BV. Mitochondrial transplantation: A critical analysis. Biochemistry (Mosc) 2020;85(5):636–641. doi:10.1134/s0006297920050132, PMID:32571194.

[102] Rea SL, Ventura N, Johnson TE. Relationship between mitochondrial electron transport chain dysfunction, development, and life extension in Caenorhabditis elegans. PLoS Biol 2007;5(10):e259. doi:10.1371/journal.pbio.0050259, PMID:17914900.