Chapter

Biological Application and Disease of Oxidoreductase Enzymes

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Abstract

In biochemistry, oxidoreductase is a large group of enzymes that are involved in redox reaction in living organisms and in the laboratory. Oxidoreductase enzymes catalyze reaction involving oxygen insertion, hydride transfer, proton extraction, and other essential steps. There are a number of metabolic pathways like glycolysis, Krebs cycle, electron transport chain and oxidative phosphorylation, drug transformation and detoxification in liver, photosynthesis in chloroplast of plants, *etc*. that require the direct involvements of oxidoreductase enzymes. In addition, degradation of old and unnecessary endogenous biomolecules is catalyzed by a family of oxidoreductase enzymes, e.g., xanthine oxidoreductase. Oxidoreductase enzymes use NAD, FAD, or NADP as a cofactor and their efficiency, specificity, good biodegradability, and being studied well make it fit well for industrial applications. In the near future, oxidoreductase may be utilized as the best biocatalyst in pharmaceutical, food processing, and other industries. Oxidoreductase play a significant role in the field of disease diagnosis, prognosis, and treatment. By analyzing the activities of enzymes and changes of certain substances in the body fluids, the number of disease conditions can be diagnosed. Disorders resulting from deficiency (quantitative and qualitative) and excess of oxidoreductase, which may contribute to the metabolic abnormalities and decreased normal performance of life, are becoming common.

Keywords: biocatalyst, biological application, disease, metabolism, mutation, oxidoreductase

1. Introduction

Oxidoreductases, which includes oxidase, oxygenase, peroxidase, dehydrogenase, and others, are enzymes that catalyze redox reaction in living organisms and in the laboratory [1]. Interestingly, oxidoreductases catalyze reaction involving oxygen insertion, hydride transfer, proton extraction, and other essential steps. The substrate that is oxidized is considered as hydrogen or electron donor, whereas the substrate that is reduced during reaction as hydrogen/electrons acceptor. Most commonly, oxidoreductase enzymes use NAD, FAD, or NADP as a cofactor [2].

Organisms use this group of enzymes for synthesis of biomolecules, degradation and removal of molecules, metabolism of exogenous molecules like drugs, and so on [3–5]. Their biochemical property such as efficiency, specificity, good biodegradability, and being studied well make it fit well for industrial purposes. As a result, oxidoreductases are being utilized in nutrition, food processing, medicine, and other chemical synthesis. In the near future, oxidoreductase may be utilized as the best biocatalyst in pharmaceutical, food processing, and other industries [6, 7].

Enzymes like oxidoreductase play great and significant function in the field of disease diagnosis, prognosis, and treatment [8]. By analyzing the activities of enzymes and changes of certain substances in the body fluids, a number of disease conditions can be diagnosed [9, 10]. The determination of the activity of the oxidoreductases is helpful in understanding the metabolic activity of different organs [8, 11]. For example, the activity of oxidoreductase enzymes in Krebs cycle is significantly increased during skin infection [12].

There are different disease conditions resulting from deficiency (quantitative and qualitative) and excess of oxidoreductase, which may contribute to the metabolic abnormalities and decreased normal performance of life [13, 14]. For example, relative decreases in the activities of NADH dehydrogenase and ubiquinol-cytochrome c oxidoreductase are highly associated with the developments of peripheral arterial disease. Another best example is mutation of p450 oxidoreductase (POR) gene, which leads to insufficiency of P450 enzymes characterized by defective steroidogenesis. Similarly, deficiency of mitochondrial acetaldehyde dehydrogenase disturbs normal metabolism of alcohol and leads to accumulation of acetaldehyde [8, 15, 16]. These conditions in turn affect the normal development and reproduction.

2. Oxidoreductase in metabolism of foodstuff

Oxidoreductases are a family of enzymes that catalyze redox reactions. Oxidoreductases catalyze the transfer of electrons from oxidant to reductant [4]. Generally, oxidoreductases catalyze reactions which are similar to $A^- + B \rightarrow A + B^-$ where A is the oxidant and B is the reductant [17]. Oxidoreductases can be oxidases where a molecular oxygen acts as an acceptor of hydrogen or electrons and dehydrogenases which are enzymes that oxidize a substrate by transferring hydrogen to an acceptor that is either $NAD^+/NADP^+$ or a flavin enzyme. Other classes are oxidoreductases enzymes, peroxidases which are localized in peroxisomes and catalyze the reduction of hydrogen peroxide. Hydroxylases are involved in the addition of hydroxyl groups to their substrates, and oxygenases are key in the incorporation of oxygen from molecular oxygen into organic substrates. And reductase enzymes are involved in the catalysis of reduction reaction [2, 3, 18]. In general, oxidoreductase enzymes play an important role in both aerobic and anaerobic metabolism. They are involved in glycolysis, TCA cycle, oxidative phosphorylation, fatty acid, and amino acid metabolism [5, 19, 20].

3. Oxidoreductase in glycolysis

In glycolysis, the enzyme glyceraldehydes-3-phosphate dehydrogenase catalyzes the reduction of NAD + to NADH. In order to maintain the redox state of the cell, this NADH must be re-oxidized to NAD+, which occurs in the oxidative phosphorylation pathway [21].

$$\text{G-3-P} + \text{Pi} + \text{NAD}^+ \xleftrightarrow{\text{Glyceraldehyde-3-phosphate dehydrogenase}} \text{1, 3-BPG} + \text{NADH} + \text{H}^+ \quad (1)$$

$$\text{Pyruvate} + \text{NADH} + \text{H}^+ \xleftrightarrow{\text{lactate dehydrogenase}} \text{lactate} + \text{NAD}^+ \quad (2)$$

4. Oxidoreductase in TCA cycle

A high number of NADH molecules are produced in the TCA cycle. The product of glycolysis, pyruvate, enters the TCA cycle in the form of acetyl-CoA. Except leucine and lysine, all twenty of the amino acids can be degraded to TCA cycle intermediates. And most of the fatty acids are oxidized into acetyl coA through beta oxidation that enter TCA cycle [19, 22].

The precursor for the TCA cycle comes from lipids and carbohydrates, both of which produce the molecule acetyl-CoA. This acetyl-CoA enters the eight-step sequence of reactions that comprise the Krebs cycle, all of which occur inside mitochondria of eukaryotic cells. TCA or Krebs cycle produces NADH and FADH, and the reactions are catalyzed by classes of oxidoreductase enzymes [23].

$$\text{Pyruvate} + \text{NAD}^+ + \text{CoA} \xrightarrow{\text{pyruvate dehydrogenase}} \text{acetyl-CoA} + \text{NADH} + \text{H}^+ + \text{CO}_2 \quad (3)$$

$$\text{Isocitrate} + \text{NAD}^+ \xrightarrow{\text{isocitrate dehydrogenase}} \text{alfa-ketoglutarate} + \text{NADH} + \text{H}^+ + \text{CO}_2 \quad (4)$$

$$\alpha\text{-ketoglutarate} + \text{NAD}^+ + \text{CoA} \xrightarrow{\alpha\text{-ketoglutarate dehydrogenase}} \text{succinyl CoA} + \text{NADH} + \text{CO}_2 \quad (5)$$

$$\text{Succinate} + \text{FAD}^+ \xrightarrow{\text{succinate dehydrogenase}} \text{fumarate} + \text{FADH}_2 \quad (6)$$

5. Oxidoreductase in electron transport chain and oxidative phosphorylation

Living cells use electron transport chain to transfer electrons stepwise from substrates (NADH & FADH_2) to a molecular oxygen. The proton gradient which is generated through electron transport chain runs downhill to drive the synthesis of ATP. Electron transport chain and oxidative phosphorylation take place in the matrix of mitochondria, and there are oxidoreductase enzymes impregnated in the inner mitochondrial membrane, which catalyze these reactions and are engaged in energy production. NADH:quinone oxidoreductase, also called NADH dehydrogenase (complex I), is responsible for the transfer of electrons from NADH to quinones, coupled with proton translocation across the membrane. Succinate:quinone oxidoreductase, or succinate dehydrogenase (complex II), is an enzyme of the Krebs cycle, which oxidizes succinate and reduces quinones, in the absence of proton translocation. Quilon:cytochrome c oxidoreductase (complex III), which transfers electrons from quinols to cytochrome c and cytochrome c:oxygen oxidoreductase, an aa3-type enzyme (complex IV), which receives these electrons and transfers it to oxygen are both oxidoreductase enzymes involved in electron transport chain and oxidative phosphorylation [19, 24, 25] (**Figure 1**).

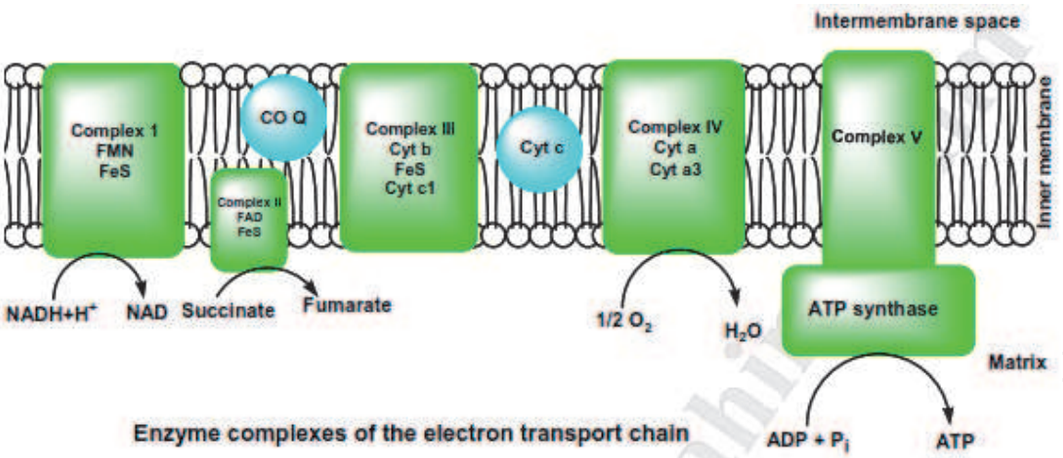

Figure 1.
Oxidoreductase enzymes involved in electron transport chain and oxidative phosphorylation [18].

6. Oxidoreductase in drug metabolism

Liver is the principal organ for drug metabolism. The body uses different strategies to metabolize drugs like oxidation, reduction, hydrolysis, hydration, conjugation, condensation, or isomerization. The main goal of drug metabolism is to make the drug more hydrophilic and excrete easily. Enzymes involved in drug metabolism are found in many tissues and organs but are more concentrated in the liver. Rates of drug metabolism may vary among individuals. Some individuals metabolize a drug so rapidly; in others, metabolism may be so slow and have different effects. Genetic factors, coexisting disorders (particularly chronic liver disorders and advanced heart failure), and drug interactions are responsible factors for variation of rate of drug metabolism among individuals [26].

Generally, drug metabolism can be in three phases. In phase I drug metabolism, oxidoreductase enzymes such as cytochrome P450 oxidases add polar or reactive groups into drugs (xenobiotics). In phase I reaction, drugs are introduced into new or modified functional group through oxidation, reduction, and hydrolysis. In Phase II reactions, modified compounds are in conjugation with an endogenous substance, e.g., glucuronic acid, sulfate, and glycine. Phase II reactions are synthetic, and compounds become more polar and thus, more readily excreted by the kidneys (in urine) and the liver (in bile) than those formed in nonsynthetic reactions. At the end, in phase III reaction, the conjugated drugs (xenobiotics) may be further processed, before being recognized by efflux transporters and pumped out of cells. The metabolism of drug often converts hydrophobic compounds into hydrophilic products that are more readily excreted [27].

In normal cases, human body wants to remove or detoxify any compounds that cannot be metabolized otherwise utilized to serve the needs of the body. This removal process is carried out mainly by the liver. The liver has classes of oxidoreductase enzymes that are extremely effective at detoxification and removal of drugs from the body [5, 18].

6.1 Metabolism of drugs through cytochrome P450 monooxygenase

Oxidation and metabolism of a high number of drugs and endogenous molecules are catalyzed by a class of oxidoreductase enzymes called cytochrome P450 monooxygenases. Even though they are distributed throughout the body, cytochrome

P450 enzymes are primarily concentrated in liver cells. The CYP2D6 isozymes play a great role in metabolizing certain opioids, neuroleptics, antidepressants, and cardiac medications. Currently it is going to be understood that difference in the genes for CYP450 enzymes play to inter-individual differences in the serum concentrations of drug metabolites, resulting in interpatient variability in drug efficacy and safety [28].

6.2 Metabolism of drugs with flavin-containing monooxygenase (FMO) system

Flavin-containing monooxygenases (FMOs) (EC 1.14.13.8) are a family of microsomal NADPH-dependent oxidoreductase, responsible for oxygenation of nucleophilic nitrogen, sulfur, phosphorus, other drugs, and endogenous molecules. Different variants of mammalian FMOs play a significant role in the oxygenation of nucleophilic xenobiotics. FMO utilizes NADPH as a cofactor and contains one FAD as a prosthetic group. FMOs have a broad substrate specificity and their activity is maximal at or above pH 8.4. FMO is a highly abundant enzyme in the liver endoplasmic reticulum and participates in drug metabolism (activation and detoxification) [29].

Before FMOs bind to a substrate, they activate molecular oxygen. First, flavin adenine dinucleotide (FAD), the prosthetic group of FMO, is reduced by NADPH to form FADH, then oxygen is added into the FAD, and hydro-peroxide FADH-4α-OOH is produced. And then, one oxygen atom is transferred to the substrate [30, 31].

6.3 Metabolism of drugs through alcohol dehydrogenase and aldehyde dehydrogenase

Alcohol dehydrogenase (ADH) and mitochondrial aldehyde dehydrogenase (ALDH) are another family of oxidoreductase responsible for metabolizing ethanol. These enzymes are highly expressed in the liver but at lower levels in many tissues and play a great role in detoxification and easy removal of alcohols. Liver is the main organ for ethanol metabolism. Oxidation of ethanol with these enzymes can become a major energy source especially in the liver, and it can interfere metabolism of other nutrients [32].

The first step in ethanol metabolism is its oxidation to acetaldehyde, and this reaction is catalyzed by enzymes called alcohol dehydrogenases (ADHs). The second reaction in ethanol metabolism is oxidation of acetaldehyde into acetate catalyzed by aldehyde dehydrogenase (ALDH) enzymes. There are different ADH and ALDH enzymes encoded by different genes occurring in several alleles and enzymes that have different alcohol metabolizing capacity; thereby, they influence individuals' alcoholism risk. These are either through rapid oxidation of ethanol to acetaldehyde where there is more active ADH or slower oxidation of acetaldehyde into acetate where there are less active ALDH enzymes. Excess accumulation of acetaldehyde is toxic, which results in different adverse reactions and produces nausea, skin rash, rapid heartbeat, etc. Most commonly, single-nucleotide polymorphisms (SNPs) are responsible for ADH and ALDH gene variants, and these may occur on both coding and non-coding regions of the gene [33, 34].

6.4 Metabolism of drugs by monoamine oxidase (MAO)

Monoamine oxidase is a very important oxidoreductase enzyme mainly responsible for degradation of amine neurotransmitters like norepinephrine, epinephrine, serotonin, and dopamine. Oxidation of different endogenous and exogenous biogenic amines may produce other active or inactive metabolites. Monoamine oxidase (MAO) is found in two isozyme forms: monoamine oxidase A (MAO-A)

preferentially deaminates serotonin, norepinephrine, epinephrine, and dietary vasopressors such as tyramine, and MAO-B preferentially deaminates dopamine and phenethylamine. They are integral flavoproteins components of outer mitochondrial membranes in neurons and glia cell. The two isozymes of MAO differ based on substrate specificity and sensitivity to different inhibitors [35].

Monoamine oxidase enzymes catalyze the primary catabolic pathway for 5-HT oxidative deamination. Serotonin is converted into 5-hydroxy-indoleacetaldehyde, and this product is further oxidized by a NAD-dependent aldehyde dehydrogenase to form 5-hydroxyindoleacetic acid (5-HIAA). Immunohistochemical techniques and in situ hybridization histochemistry techniques are used to study the neuroanatomical localization and biochemical nature of the two forms of MAO [36].

Different antidepressant drugs like phenelzine and tranylcypromine inhibit the activity of monoamine oxidase. These are a result of MAO metabolizes biogenic amines such as 5-HT, DA, and NE. In addition, different dopaminergic neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) are metabolized by MAO [37].

6.5 NADPH-cytochrome P450 reductase (CPR) in drug metabolism

Another essential class of oxidoreductase enzyme is NADPH-cytochrome P450 reductase (CPR). It is a membrane-bound protein localized in the ER membrane. PR involves in the detoxification and activation of a number of xenobiotics. CPR uses FAD and FMN as cofactors, and it transfers the hydride ion of NADPH to FAD, and then FAD transfers electrons to FMN and other oxidases. Finally, it reduces the P450 enzyme heme center to activate molecular oxygen. Thus, electrons transfer from NADPH to the P450 heme center by CPR, which is central for P450-catalyzed metabolism. Flow of electron can be expressed as follows:

$$\text{NADPH} \rightarrow \text{FAD} \rightarrow \text{FMN} \rightarrow \text{P450} \rightarrow \text{O}_2 \quad (7)$$

Human cytochrome P450 reductase is encoded by the POR gene. It is a 78-kDa multi domain diflavin reductase that binds both FMN and FAD and is attached to the cytoplasmic side of the endoplasmic reticulum via a transmembrane segment at its N-terminus [5, 15, 38].

7. Industrial application of oxidoreductase enzymes

Several industries such as pharmaceutical, foods, biofuel production, natural gas conversion, and others have used enzyme catalysis at commercial scale [39]. Classes of oxidoreductase enzymes are becoming a target by a number of industries. The family of oxidoreductase like heme-containing peroxidases and peroxygenases, flavin-containing oxidases and dehydrogenases, and different copper-containing oxidoreductases is involved in synthesis and degradation of interested products by the above industries and they are biocatalysts of interest for establishing a bio-based economy. Oxidoreductase enzymes have the highest potential in the production of polymer building blocks, sustainable chemicals, and materials from plant biomass within lignocellulose biorefineries [6, 7, 40].

7.1 Oxidoreductase enzymes in pharmaceutical industries

Enzymes are biological catalysts and have great specificity, efficiency, and selectivity in the reaction they catalyze [39]. Oxidoreductase enzymes have

different redox-active centers for doing their functions. These unique features of oxidoreductase enzymes make it valuable targets of pharmaceutical and chemical industries. Advancement in recombinant DNA technology, protein engineering, and bioinformatics is a critical event in the application of enzymes in different industries. A number of dug synthesis processes require the involvement of oxidoreductase enzymes [6].

An oxidoreductase is involved in the synthesis of 3,4-dihydroxylphenyl alanine (DOPA), and 3,4-dihydroxylphenyl alanine is a drug used for treatment of Parkinson's disease [41]. Similarly, a class of oxidoreductase called monoamine oxidase (MAO) catalyzes enantiomeric desymmetrization of bicyclic proline intermediate, which is an important precursor in the synthesis of boceprevir. Boceprevir is a NS3 protease inhibitor that is used for the treatment of chronic hepatitis C infections. Using MAO in this reaction reduces time and waste product generation and is economically cost-competitive and profitable [42]. Its coenzyme specificity makes oxidoreductase an effective biocatalyst in protein engineering [43]. In vitro different oxidoreductase enzymes are involved in regeneration of coenzymes, pyridine nucleotides, NAD(H) and NADP(H). Alcohol dehydrogenase and format dehydrogenase are frequently used enzymes for recycling of coenzymes, and the intermediate products are useful in the synthesis of pharmaceutical drugs such as mevinic acid [44, 45].

7.2 Oxidoreductase enzymes in agricultural sector

Enzymes are biological catalysts and have a number of applications in agricultural fields. Using enzymes has great efficacy and efficiency over chemical catalysts with respect to their productivity, time, cost, quality, and quantity products. There are different classes of oxidoreductase enzymes nowadays involved in fertilizer production, dairy processing, and other food processing in agricultural sector, and their cost-effectiveness and quality product were confirmed by a number of researches [3].

Manipulation of gene cod for different oxidoreductase in plants can also change the characters of plants in a way that it increases productivity and resists adverse effects of herbicide and environmental changes. For example, modification of DNA for glyphosate oxidoreductase (GOX) enzyme that catalyzes the oxidative cleavage of the C—N bond on the carboxyl side of glyphosate, resulting in the formation of aminomethylphosphonic acid (AMPA) and glyoxylate thereby augmented expression of GOX plants, results in glyphosate herbicide side effect tolerance [46, 47]. Some families of oxidoreductase like xanthine dehydrogenase in plants are used to metabolize reactive oxygen species associated with plant-pathogen and protect plants from stress-induced oxidative damage. Upregulation of xanthine dehydrogenase expression in plants is helpful to increase productivity [48, 49].

Classes of oxidoreductase are also involved in dairy processing. Glucose oxidase produced by fungal species acts as preservatives in dairy products and other foods. The intermediate and end product of glucose oxidase have antimicrobial effect [50]. Isozyme of xanthine oxidoreductase in bovine milk, which catalyzes reduction of oxygen to generate reactive metabolite is used as an anti-microbial agent in the neonatal gastrointestinal tract [51]. Similarly, peroxidases which are a family of oxidoreductase found in higher plants catalyze the oxidation of many compounds including phenolics, in the presence of hydrogen peroxide responsible in browning or darkening of noodles and pasta and associated with a grain quality defect [52]. Protochlorophyllide oxidoreductase (POR), which exists in two isozymes POR A and POR B, plays a vital role in plant chlorophyll synthesis, and manipulation on these genes can induce plant development [53]. In general, there are a number of

oxidoreductase enzymes found in plants, and their normal activity is crucial for qualitative and quantitative productivity of crops, and these were confirmed by a number of active researches. Different interventions are also going on at gene level to control the expression of oxidoreductase enzymes in plant as needed [3].

8. Disease related with oxidoreductase enzyme disorder

Oxidoreductase enzymes are involved in a number of valuable biochemical reactions in the living organism, and their qualitative and quantitative normality is essential. For example, one important class of oxidoreductase is xanthine oxidoreductase (XOR) that catalyzes oxidative hydroxylation of hypoxanthine to xanthine then to uric acid and over activity XOR leads to hyperuricemia and concomitant production of reactive oxygen species. In turn, hyperuricemia is confirmed as an independent risk factor for a number of clinical conditions such as gout, cardiovascular disease, hypertension, and others. Different urate-lowering drugs or XOR inhibitors are nowadays implemented to prevent and manage hyperuricemia disorder [9].

Another important class of oxidoreductase enzyme is cytochrome P450 oxidoreductase (POR) that is essential for multiple metabolic processes. Cytochrome P450 enzymes are involved in metabolism of steroid hormones, drugs, and xenobiotics. Nowadays, more than 200 different mutations and polymorphisms in POR gene have been identified and cause a complex set of disorders. Deficiency of cytochrome P450 oxidoreductase affects normal production of hormone; specifically, it affects steroid hormones, which are needed for normal development and reproduction. This is highly linked with the reproductive system, skeletal system, and other functions. Signs and symptoms can be seen from birth to adult age with different severities. Individuals with moderate cytochrome P450 oxidoreductase deficiency may have ambiguous external genitalia and have a high chance of infertility but a normal skeletal structure [5, 16, 18].

Aldehyde dehydrogenase 2 (ALDH2) deficiency known as Asian glow or alcohol flushing syndrome is a common genetic health problem that interferes with alcohol metabolism, and ALDH2 is a classical family of oxidoreductase enzymes. It was confirmed that ALDH2 deficiency results in the accumulation acetaldehyde, which is a toxic metabolite of alcohol metabolism and responsible for a number of health challenges like esophageal, head, and neck cancer. A number of researches conclude that acetaldehyde is a group 1 carcinogenic metabolite [33, 54]. Similarly, monoamine oxidase deficiency, which is a family oxidoreductase enzyme, affects the normal metabolism of serotonin and catecholamines. It is a rare X-linked disorder characterized by mild intellectual disability, and behavioral challenges appear at earlier age. Monoamine oxidase-A deficiency that occurs almost exclusively in males has episodes of skin flushing, excessive sweating, headaches, and diarrhea. Monoamine oxidase-A deficiency can be diagnosed by finding an elevated urinary concentration of the monoamine oxidase-A substrates in combination with reduced amounts of the monoamine oxidase products [36, 55].

Mitochondria generate huge amounts of energy (ATP) to eukaryotic cells through oxidation of fats and sugars; and fatty acid β-oxidation and oxidative phosphorylation are two metabolic pathways that are central to this process. Qualitative and quantitative normality of oxidoreductase enzymes involved in oxidative phosphorylation and fatty acid oxidations are essential to get sufficient energy (ATP) form metabolism. Deficiency of a complex I (NADH-CoQ oxidoreductase) is common, and a well-characterized mitochondrial problem causes reduced ATP production [56]. Complex I (NADH-CoQ oxidoreductase) is responsible for

recycling of NADH to NAD^+, and in turn, this is essential to sustain Krebs cycle and glycolysis. Mutations in both nuclear and mitochondrial DNA for Complex I gene are responsible for mitochondrial disease. Individuals with mitochondrial diseases suffer from an energy insufficiency characterized by myopathies, neuropathy, delayed development, cardiomyopathy, lactic acidosis, and others. Furthermore, since mitochondria are a hub of metabolism, mitochondrial dysfunctions are highly associated with metabolic diseases like hypertension, obesity, diabetes, neurodegenerative diseases, and even aging. Deficiency of complex I leads to elevation of NADH levels in the mitochondria that inhibit pyruvate dehydrogenase and α-ketoglutarate dehydrogenase. This condition completely inhibits Krebs cycle, and it is measured by CO_2 evolution from [^{14}C] labeled precursors. Similarly, complex II (succinate:ubiquinone oxidoreductase) deficiency affects both fatty acid oxidation and electron transport chain, and it induces retinopathies and encephalopathies [57, 58].

Deficiency of the pyruvate dehydrogenase complex (PDHC), another class of oxidoreductase enzymes, causes similar clinical and biochemical alteration in energy production with complex I (NADH-CoQ oxidoreductase) [59]. Both TCA cycle and respiratory chain can be affected by succinate dehydrogenase deficiency. Deficiency of oxidoreductase enzymes involved in Krebs cycle affects all carbohydrate, protein, fat, and nucleic acid metabolism as it is a common pathway for metabolism of the above macromolecules [60].

Oxidoreductase enzymes are also involved in bile acid synthesis. Classes of oxidoreductase enzymes called 3beta-hydroxy-Delta (5)-C (27)-steroid oxidoreductase catalyze an early step of bile acids synthesis from cholesterol and are encoded by HSD3B7 gene on chromosome 16p11.2-12. Mutations of HSD3B7 gene affect bile acids synthesis, cause development of progressive liver disease characterized by cholestatic jaundice, malabsorption of lipids, and lipid-soluble vitamins from the gastrointestinal tract, and finally progress to cirrhosis and liver failure [61].

One important biomolecule that acts as a precursor for other molecules and a component of cell membrane is cholesterol. Mammalian cells can get cholesterol from de novo biosynthesis or uptake of exogenously derived cholesterol associated with plasma low-density lipoprotein (LDL). 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which is a class of oxidoreductase, catalyzes the rate-limiting steps of de novo cholesterol biosynthetic pathway and target for manipulation pharmacologically. Under or over activity of HMG-CoA reductase can disturb cholesterol homeostasis and lead to either hypercholesterolemia or hypocholesterolemia. And disturbed cholesterol level associated with number serious clinical problem like atherosclerosis [62, 63].

Conflict of interests

The authors declare that they have no competing interests.

Authors' contributions

Mezgeu Legesse Habte drafted the paper and write the literature review.

Etsegenet Assefa assisted in guidance, critical assessment and peer review of the writing. Both authors have given their final approval of this version to be published. Both authors read and approved the final manuscript.

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