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Review

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Targeting Mitochondrial Dysfunction for the Prevention and Treatment of Metabolic Disease by Bioactive Food Components

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ABSTRACT

Dysfunctional mitochondria have been linked to the pathogenesis of obesity-associated metabolic diseases. Excessive energy intake impairs mitochondrial biogenesis and function, decreasing adenosine-5'-triphosphate production and negatively impacting metabolically active tissues such as adipose tissue, skeletal muscle, and the liver. Compromised mitochondrial function disturbs lipid metabolism and increases reactive oxygen species production in these tissues, contributing to the development of insulin resistance, type 2 diabetes, and non-alcoholic fatty liver disease. Recent studies have demonstrated the therapeutic potential of bioactive food components, such as resveratrol, quercetin, coenzyme Q10, curcumin, and astaxanthin, by enhancing mitochondrial function. This review provides an overview of the current understanding of how these bioactive compounds ameliorate mitochondrial dysfunction to mitigate obesity-associated metabolic diseases.

Keywords: Mitochondrial dysfunction; Metabolic diseases; Obesity; Type 2 diabetes; NAFLD

INTRODUCTION

Bioactive compounds derived from foods and natural plants have been extensively utilized to prevent and manage metabolic disorders, such as obesity, type 2 diabetes, insulin resistance, non-alcoholic fatty liver disease (NAFLD), and cardiovascular disease (CVD) due to their various health benefits.[1] Moreover, a report by the World Health Organization in 2008 revealed that up to 80% of diabetic patients rely on natural products for the treatment of their condition.[2] Thus, consuming bioactive compounds in food is an effective strategy to reduce the risks of metabolic diseases.

Oxidative stress plays a pivotal role in the pathogenesis of metabolic disorders associated with obesity, including insulin resistance, type 2 diabetes, and NAFLD.[3] Excessive accumulation of reactive oxygen species (ROS), primarily generated during oxidative phosphorylation (OXPHOS) in mitochondria, damages proteins, DNA, lipids, and other cellular components.[4] Also, reduced adenosine-5'-triphosphate (ATP) synthesis due to impaired OXPHOS can contribute to the pathogenesis of metabolic disorders.[5,6]

Conflict of Interest
The authors have no conflicts of interest to declare.

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Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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The imbalance between ROS production and elimination leads to oxidative stress, damaging mitochondria and cells in metabolically active tissues, including adipose tissue, skeletal muscle, and the liver.[7] In adipose tissue, compromised mitochondrial function disturbs adipogenesis, lipolysis, fatty acid esterification, and adiponectin production, leading to insulin resistance.[8] In skeletal muscle, impaired mitochondrial function lowers ATP production while elevating ROS production, which has been linked to the pathogenesis of insulin resistance and type 2 diabetes.[4] Also, hepatic mitochondrial dysfunction disrupts lipid homeostasis and increases excessive ROS production, causing hepatocyte damage.[9] Additionally, oxidative stress in hepatocytes can trigger lipid peroxidation, inflammatory cytokine production, and cell death, further contributing to hepatic fibrosis by activating hepatic stellate cells.[9,10] As such, dysfunctional mitochondria in these metabolically active tissues are closely linked with type 2 diabetes and NAFLD.[5,6]

Since excessive ROS production causes mitochondrial defects, the antioxidant properties of bioactive food compounds may be suitable targets to improve mitochondrial function.[5,11] Dietary antioxidants, such as resveratrol, quercetin, coenzyme Q10, curcumin, and astaxanthin, are abundant in grapes and berries, vegetables and fruits, turmeric (*Curcuma longa Linn.*), salmon, and shrimp, respectively.[12-17] Also, these bioactives have demonstrated beneficial health effects, including antioxidant and anti-inflammatory effects that can reduce mitochondrial oxidative damage.[18-21] In particular, they are known to ameliorate mitochondrial dysfunction to mitigate obesity-associated metabolic diseases. Therefore, it is crucial to identify bioactive food components and natural products capable of maintaining mitochondrial integrity and function to prevent obesity-associated metabolic diseases. This review summarizes current knowledge on selected few bioactive components that can preserve mitochondrial homeostasis, thereby offering potential preventative and therapeutic avenues for mitochondria-related metabolic disorders.

REGULATION OF MITOCHONDRIAL FUNCTIONS

1. Mitochondrial structure and functions

Mitochondria are double-membrane organelles integral to energy production in cells.[5] They have five distinct components: the outer membrane, inner membrane, intermembrane space, mitochondrial cristae, and mitochondrial matrix.[22,23] The outer membrane acts as a barrier between the mitochondrion and the cytosol. It contains porins, which are voltage-dependent anion-selective channels that allow the passage of hydrophilic molecules up to 5 kDa while preventing the diffusion of larger molecules.[24] This membrane facilitates the entry and exit of various nutrients, ions, and energy molecules.[5,22,23,25] Unlike the outer membrane, the inner membrane is highly impermeable to most molecules because it lacks porins.[22] Thus, the inner membrane permits the passage of only a few compounds, such as water, carbon dioxide, oxygen, and ammonia.[22] The inner membrane envelops the mitochondrial matrix and houses electron transport chain (ETC) complexes facilitating OXPHOS for ATP generation.[5,23] Also, the inner membrane is compartmentalized into numerous folds called cristae, which increase the surface of the inner mitochondrial membrane, boosting ATP production, and the matrix contains DNA, RNA, and ribosomes.[26,27]

Mitochondria are often called the cellular power factories because they produce chemical energy and heat by metabolizing nutrients, as they are the site for the tricarboxylic acid (TCA) cycle, fatty acid β-oxidation, and OXPHOS.[28] The ETC system transfers electrons through

a series of redox reactions using reduced β-nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FAD) from glycolysis and TCA cycle to molecular oxygen, reducing it to form water.[28] Also, mitochondrial uncoupling proteins can dissipate the electrochemical gradient as heat, a process known as thermogenesis.[23,29]

2. Regulatory mechanisms for mitochondrial biogenesis

Mitochondrial biogenesis involves synthesizing and importing nuclear-encoded mitochondrial proteins and replicating mitochondrial DNA (mtDNA).[30] Several factors, including peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α), sirtuin 1 (SIRT1), adenosine monophosphate-activated protein kinase (AMPK), nuclear respiratory factor (NRF)-1, NRF-2, and estrogen-related receptor alpha (ERRα), are known to regulate mitochondrial biogenesis in response to cellular stress or environmental stimuli, e.g., calorie restriction and exercise.[5,31]

PGC-1α regulates mitochondrial biogenesis by functioning as a co-transcriptional regulator to activate transcription factors, such as NRF-1, NRF-2, and ERRα, required to induce genes involved in mitochondrial biogenesis.[32] Activating NRF-1 and NRF-2 stimulates the expression of nuclear genes encoding mitochondrial proteins and mitochondrial transcription factor A (TFAM) that regulates the replication of mtDNA.[32,33] PGC-1α also enhances mitochondrial fatty acid oxidation through the activation of peroxisome proliferator-activated receptor alpha (PPARα) and PPARδ, which induce the expression of genes for mitochondrial fatty acid β-oxidation.[34-36] Therefore, PGC-1α increases mitochondrial mass and substrate oxidation.

Mitochondrial biogenesis is a physiological response to energy demand, such as increased AMP:adenosine diphosphate (ADP)/ATP and β-nicotinamide adenine dinucleotide (NAD^+):NADH ratios.[36,37] When cells are depleted of ATP with AMP accumulation, AMP activates AMPK.[38] Also, SIRT1, an NAD^+-dependent protein deacetylase, becomes activated and deacetylates target proteins to control essential metabolic functions, including preadipocyte hyperplasia, insulin sensitivity, inflammation, and lipid accumulation, by inhibiting PPARγ.[39] Notably, PGC-1α is activated by increased cellular AMP and NAD^+ via the activation of AMPK and SIRT1, respectively.[36,40] The complex interaction between SIRT1 and AMPK plays a crucial role in regulating the activity of PGC-1α, a central regulator of mitochondrial biogenesis and energy metabolism.[41] For instance, SIRT1 can directly deacetylate and activate liver kinase B1 (LKB1), a kinase upstream of AMPK, promoting the translocation of LKB1 from the nucleus to the cytosol, where it phosphorylates AMPK for activation.[40,42] Furthermore, AMPK increases PGC-1α activity, which then interacts with transcription factors that induce several key genes in mitochondrial respiration (e.g., NADH dehydrogenase and succinate dehydrogenase [*SDH*]), glucose transport (e.g., glucose transporter 1 [*GLUT1*] and *GLUT4*), and glycolysis (e.g., phosphoenolpyruvate carboxykinase and glucose-6-phosphatase).[37] PGC-1α activation also reduces cellular oxidative stress by increasing the activity of antioxidant enzymes, including superoxide dismutase 2 (*SOD2*), catalase, peroxiredoxin 5 (*PRDX5*), *PRDX3*, thioredoxin reductase 2, and thioredoxin 2.[36,43] Therefore, enhancing the PCG-1α/AMPK/SIRT1 axis to elevate mitochondrial biogenesis is a powerful tool to prevent and treat obesity-related metabolic diseases.

3. Mitochondrial proteostasis

Mitochondria harbor their genome encoding 13 ETC proteins, while they contain over 1,000 proteins.[44] Therefore, most mitochondrial proteins are of nuclear origin and must be imported and folded correctly to maintain their functionality in mitochondria.[44]

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The disruption of mitochondrial protein homeostasis, i.e., proteostasis, can lead to mitochondrial dysfunction. Mitochondrial unfolded protein response (UPR^{mt}) is a retrograde mitochondrial-to-nuclear signaling pathway that can increase the synthesis of mitochondrial chaperones and proteases for import, folding, and quality control of the mitochondrial proteome.[45,46] Mitochondrial chaperones help reduce misfolded proteins by folding newly imported proteins or refolding damaged proteins.[47,48] Key mitochondrial chaperone proteins include heat shock protein 60 (HSP60), HSP10, and HSP70.[47,48] Mitochondrial proteases, such as caseinolytic protease proteolytic (CLPP) and mitochondrial Lon protease-like 1 (LONP1), break down damaged or unnecessary proteins.[47,48]

Studies have shown the role of the UPR^{mt} pathway in regulating obesity-associated metabolic diseases. Male C57BL/6J mice fed a high-fat diet containing fish oil for 14 weeks exhibited higher expression of UPR^{mt} proteins, such as CLPP and HSP60, in epididymal white adipose tissue (eWAT) than mice fed a saturated fat-rich diet.[49] Deficiency in leptin-regulated *Hspd1* (gene encoding HSP60) in mice increased ROS production, hypothalamic insulin resistance, and diabetes, and type 2 diabetic patients had reduced *HSPD1* expression in the brain.[50] *LONP1* deficiency by small interfering RNA increased the protein expression of gluconeogenic enzymes, worsening hepatic insulin resistance, which was attenuated by *LONP1* overexpression in human liver SK-HEP-1 cells.[51] The UPR^{mt} pathway is also related to the protection against NAFLD. Nicotinamide riboside, a precursor of NAD^+, attenuated severe mitochondrial dysfunction in mice fed a long-term high-fat and high-sucrose diet, which was attributed to NAD^+-mediated induction of SIRT1 and SIRT3, triggering UPR^{mt} proteins, such as CLPP and HSP10.[52]

Thus, the UPR^{mt} pathway has been related to increased energy expenditure, improved hepatic insulin resistance, and decreased hepatic fat accumulation, which are beneficial to prevent obesity-associated metabolic diseases, such as obesity, type 2 diabetes, and NAFLD. However, our *in vivo* knowledge of the UPR^{mt} pathway is limited, and therefore, further investigations are needed to explore its therapeutic potential.

4. Mitochondrial dysfunction

Mitochondrial dysfunction is characterized by a decrease in the ability of the mitochondria to produce sufficient ATP through OXPHOS in response to energy demands.[53] This dysfunction may stem from reductions in mitochondrial biogenesis, mitochondrial membrane potential, and the activities of mitochondrial oxidative proteins due to ROS accumulation.[54] Mitochondria are the primary site of ROS generation in mammalian cells.[55] ROS, such as hydroxyl radicals (OH^-), hydrogen peroxide (H_2O_2), and superoxide anions (O_2^-), are natural by-products of oxygen metabolism during the OXPHOS process and they can damage mitochondrial and cellular components like DNA, proteins, lipids, and other molecules.[4] Loss of mitochondrial function is closely associated with insulin resistance in adipose tissue, liver, and skeletal muscle,[56,57] as discussed below.

5. Mitophagy

Mitophagy, a selective form of autophagy, is critical for maintaining cellular homeostasis by degrading damaged or superfluous mitochondria.[58] The dysregulation of mitophagy is increasingly recognized as a contributing factor to the pathogenesis of metabolic diseases, including obesity, insulin resistance, type 2 diabetes, and NAFLD.[59] Emerging evidence indicates that impaired mitophagy contributes to the accumulation of dysfunctional mitochondria in metabolically active tissues under conditions of excessive nutrient intake, leading to oxidative

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stress, inflammation, and insulin resistance.[60,61] In rodent models of diet-induced obesity (DIO), reduced mitophagy markers indicate a compromised ability of cells to remove damaged mitochondria, which can aggravate obesity and metabolic syndrome. For example, the deficiency of a mitophagy receptor FUN14 domain containing 1 impairs mitochondrial quality and aggravates dietary-induced obesity and metabolic syndrome in mice.[62] Therefore, enhancing mitophagy has been proposed as a therapeutic strategy to improve mitochondrial quality control, reduce oxidative stress, and restore metabolic homeostasis.

The PINK1-Parkin pathway primarily regulates mitophagy by recruiting Parkin, a cytosolic E3 ubiquitin-protein ligase, to damaged mitochondria, leading to their selective autophagic degradation.[63] In addition, mitophagy is modulated by several other pathways, including the receptor-mediated pathway involving BCL2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3) and BNIP3-like (NIX/BNIP3L).[64]

Several bioactive food compounds, such as resveratrol, quercetin, and curcumin, have been shown to activate the mitophagy pathway, suggesting their potential role in mitigating mitochondrial dysfunction associated with obesity and metabolic diseases, which is described below. Furthermore, interventions that promote physical activity and caloric restriction have also been shown to enhance mitophagy, highlighting the interplay between lifestyle factors, mitophagy, and metabolic health.[65]

MITOCHONDRIAL DYSFUNCTION AND DISEASES

1. Mitochondrial dysfunction in obesity

In adipose tissue, compromised mitochondrial function due to disturbed mitochondrial biogenesis leads to adipocyte hypertrophy, reduced lipolysis, increased triacylglycerol synthesis, and inflammatory cytokine production, decreasing insulin sensitivity.[8] Obesity-induced mitochondrial dysfunction decreases fatty acid oxidation and increases ROS production, triggering insulin resistance in skeletal muscle (**Fig. 1**).[66]

Studies have demonstrated that mitochondrial function is crucial in regulating adipocyte metabolism *in vitro* and *in vivo*. In 3T3-L1 adipocytes, excessive glucose and free fatty acids significantly increased ROS accumulation while reducing the mitochondrial membrane potential, resulting in impaired insulin-stimulated glucose uptake and decreased expression of mitochondrial biogenesis genes, such as *Ppargc1a* (gene encoding PGC-1α), *Ppargc1β* (gene encoding PGC-1β), and *Nrf1*.[67] Also, tumor necrosis factor α significantly decreased insulin-stimulated glucose uptake and decreased the mitochondrial membrane potential and intracellular ATP production, simultaneously increasing ROS production in 3T3-L1 adipocytes.[68] In obese/diabetic KKAy mice, lipid peroxidation and H_2O_2 production were significantly increased in WAT, accompanied by an increase in the gene expression of NADH phosphate oxidase subunits (such as $gp91^{phox}$ and $p22^{phox}$) and cytosolic components ($p47^{phox}$, $p67^{phox}$, and $p40^{phox}$) and a decrease in antioxidant enzyme expression.[69] Thus, increased ROS production in obesity leads to elevated systemic oxidative stress, which can disturb mitochondrial function.

During 3T3-L1 adipocyte differentiation, inhibition of mitochondrial OXPHOS using antimycin A, rotenone, stigmatellin, myxothiazol, or oligomycin induces adipocyte differentiation and consequently increases triglyceride accumulation.[70] Tricarboxylate

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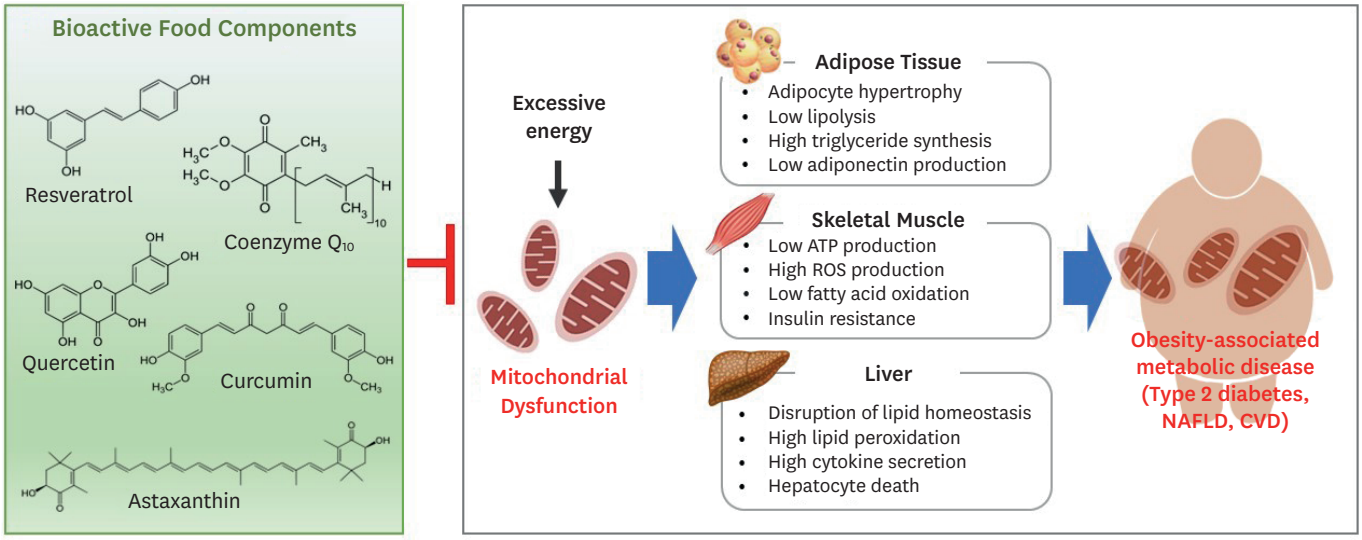

Fig. 1. Mechanisms of preventing and treating mitochondrial dysfunction in metabolic diseases by bioactive food components. This figure illustrates the inhibitory effects of bioactive food compounds, including resveratrol, coenzyme Q_{10}, quercetin, curcumin, and astaxanthin, on obesity-induced mitochondrial dysfunction and its metabolic consequences in adipose tissue, skeletal muscle, and the liver for the prevention of obesity-associated metabolic diseases, e.g., type 2 diabetes, NAFLD, and CVD.
NAFLD, non-alcoholic fatty liver disease; CVD, cardiovascular disease; ATP, adenosine-5'-triphosphate; ROS, reactive oxygen species.

carriers transport citrate from the mitochondria to the cytosol, while dicarboxylate carriers export malate from the mitochondria to the cytosol.[71] Treating 3T3-L1 mature adipocytes with specific inhibitors of mitochondrial dicarboxylate and tricarboxylate carriers of TCA intermediates inhibits adipocyte maturation, significantly reducing fat accumulation.[72] When 3T3-L1 preadipocytes are treated with mitochondrial inhibitors, such as antimycin A, cyclic AMP response element-binding (CREB), a transcriptional factor crucial for adipocyte differentiation, is activated to induce the differentiation of preadipocytes into adipocytes, which leads to triglyceride accumulation and excessive lipogenesis.[73] Increased mitochondrial protein expression and mitochondrial number within 4 days of adipogenesis in 3T3-L1 cells are associated with fatty acid metabolism, indicating mitochondrial composition changes occur during adipocyte differentiation.[74] Thus, mitochondrial dysfunction stimulates adipocyte differentiation in preadipocytes but disturbs lipid accumulation and excessive lipogenesis in mature adipocytes. This suggests that mitochondrial biogenesis and remodeling are inherent to adipose differentiation.

2. Mitochondrial dysfunction in type 2 diabetes

Diminished mitochondrial contents, evidenced by decreased citrate synthase (CS) activity, a surrogate marker of mitochondrial content, were observed in the skeletal muscles of type 2 diabetic patients, with diminished ATP production, oxidative capacity, and maximal oxygen consumption.[75,76] Insulin resistance, primarily caused by the accumulation of toxic lipid molecules, reduces the capacity of mitochondria for lipid oxidation by decreasing the ratio of glycolytic to oxidative enzyme activities, such as phosphofructokinase to CS, glyceraldehyde phosphate dehydrogenase to CS, hexokinase to CS, and glycogen phosphorylase to CS.[77] Also, triglyceride accumulation in the liver, skeletal muscle, and adipose tissue increases ROS levels and decreases mitochondrial oxidative capacity and ATP/ADP ratio, impairing insulin sensitivity.[78] As such, insulin resistance is closely associated with mitochondrial dysfunction.

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In C2C12 myotube cells, the induction of mitochondrial dysfunction using ethidium bromide (an inhibitor of mtDNA replication and transcription) or oligomycin (an inhibitor of mitochondrial ATP synthase) impairs insulin-stimulated phosphorylation of AKT and insulin receptor substrate 1, decreasing glucose uptake.[79] Also, excessive ROS production in mitochondria can contribute to the development of insulin resistance and, therefore, reduce glucose uptake in C2C12 myotube cells.[80] The *db/db* mice and C57BL/6J mice fed a high-fat diet showed lower expression of genes involved in mitochondrial ATP production, energy uncoupling, mitochondrial ribosomal proteins, translocases of the outer and inner membranes, and mitochondrial heat-shock proteins compared to control mice.[81] However, the expression of these genes was increased by rosiglitazone, a PPARγ agonist used as an anti-diabetic agent.[81] Also, patients with a family history of type 2 diabetes who consumed a short-term high-calorie diet displayed an increase in oxidative stress markers and a transient increase in OXPHOS enzymes, resulting in mitochondrial dysfunction.[82] In the skeletal muscle of type 2 diabetic patients, mitochondrial function and ATP synthesis were decreased, coupled with increased ROS production and insulin resistance.[83] When type 2 diabetic patients were administered thiazolidinediones, such as pioglitazone, for 12 weeks at a daily dose of 45 mg, mitochondrial copy number and expression of genes related to mitochondrial biogenesis, such as *PPARGC1A* and *TFAM*, in the subcutaneous adipose tissue, were increased along with elevated fatty acid β-oxidation.[84] Thus, excessive ROS production due to lipid accumulation can induce insulin resistance via impairment of mitochondrial function.

3. Mitochondrial dysfunction in NAFLD

NAFLD encompasses a spectrum of liver diseases ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis.[85] Hepatic mitochondrial dysfunction is a key factor in the pathogenesis of NAFLD, leading to disrupted intrahepatic lipid homeostasis, lipid peroxidation, inflammatory cytokine secretion, ROS production, and hepatocyte death, which contribute to the progression of NAFLD by inducing hepatic inflammation and fibrosis.[85,86] Mitochondrial dysfunction in NAFLD is characterized by mitochondrial swelling, cristae disorientation and breakage, mtDNA depletion, reduced mitochondrial respiratory chain complex activity, and impaired mitochondrial β-oxidation.[87]

Oxidative stress triggers the production of inflammatory cytokines, resulting in hepatic inflammatory and fibrogenic responses.[88] Hepatic PGC-1α expression is known to decrease by up to 40% in NAFLD patients, associated with increased mitochondrial ROS production.[88] When mice with liver-specific *Ppargc1a* deletion were fed a high-fat and high-fructose diet for 25 weeks, mitochondrial ROS production was increased concomitantly with decreased hepatic expression of ROS detoxification enzymes, such as *Prdx5* and *Sod2*.[89] These mice also displayed more body weight and fat mass with exacerbated NASH features, including hepatic lipid content, serum alanine transaminase (ALT) levels, and hepatic expression of pro-fibrogenic and inflammatory genes than wild-type mice.[89] Also, leptin-receptor deficient mice fed a high-fat diet for 10 weeks developed NASH, which was attributed to hepatic mitochondrial dysfunction, as evidenced by decreased expression of mitochondrial biogenesis genes, e.g., *Ppargc1a*, *Ppargc1β*, *Tfam*, and *Nrf1*, and protein levels of LKB1 and phosphorylated AMPKα.[90] In male albino mice, a high-fat diet feeding for 60 days significantly increased serum liver injury markers, such as ALT and aspartate transaminase (AST), while reducing the expression of mitochondrial complexes I, II, and IV in the liver.[78] Additionally, NASH patients showed decreased expression of mtDNA-encoded polypeptides[91] and low activity of mitochondria respiratory chain complexes I, III, IV, and V in the liver.[92] Thus, evidence suggests that correcting mitochondrial dysfunction may be an effective tool to prevent and treat NAFLD.

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4. Mitochondrial dysfunction in CVD

CVD refers to the disorders affecting the heart and blood vessels, including coronary heart disease, cerebrovascular disease, rheumatic heart disease, and other related conditions.[93] Elevated mtDNA damage due to excessive ROS production is recognized as one of the major factors in the pathogenesis of CVD, causing metabolic abnormalities, energy deficit, endoplasmic reticulum (ER) stress, autophagy dysregulation, and activation of apoptosis.[94] Mitochondrial dysfunction in CVD, in particular, is characterized by impairment of cellular respiration and energy production, oxidative stress due to ROS generation, apoptosis, cell damage, and death.[95]

CVD patients exhibit higher levels of mtDNA damage, caused by oxidative stress, in the heart and aorta compared to healthy subjects.[96,97] In failing hearts of mice, overexpression of thioredoxin-dependent peroxide reductase, a mitochondrial antioxidant enzyme, ameliorated the decline in mtDNA copy number.[98] Also, the mitochondria isolated from failing cardiac myocytes showed higher ROS production at the complex I site, suggesting that the heart generates the majority of ROS through uncoupling mitochondrial ETC complexes I and II.[99] Mouse models of myocardial infarction displayed reduced mitochondrial activity concomitantly with decreased mtDNA copy number and enzyme activities for complexes I, III, and IV.[100] Additionally, deficits in mitochondrial antioxidant proteins accelerated the onset of CVD in mice, supporting that oxidants produced in the mitochondria can contribute to the development of atherosclerosis.[101,102] Tumor necrosis factor-α increased ROS production in neonatal rat ventricular myocytes, which interfered with mitochondrial biogenesis, damaged the mtDNA, and changed the structure of mitochondria.[103] These factors contribute to the development and progression of heart diseases, such as heart failure and cardiac dysfunction. Thus, mounting evidence suggests that preventing oxidative stress can be a crucial means to maintain mitochondrial function in preventing and treating CVD.

POTENTIAL OF BIOACTIVE FOOD COMPOUNDS: TARGETING MITOCHONDRIAL DYSFUNCTION IN METABOLIC DISEASES

1. Resveratrol

Resveratrol is a natural phytoalexin compound found abundantly in grapes and berries.[12] It is known for activating SIRT1 and SIRT3, enhancing mitochondrial biogenesis and function.[104] SIRT1 activates PGC-1α, leading to its translocation to the nucleus, where deacetylated PGC-1α enhances the transcriptional activity of NRF-1 and -2.[105] NRF-1 and -2, then, bind to the promoters of their responsive genes involved in mitochondrial biogenesis, energy production, and OXPHOS.[105] In contrast to SIRT1, SIRT3 not only directly activates key enzymes in the TCA cycle (e.g., SDH), fatty acid oxidation (e.g., long chain acyl-CoA dehydrogenase), and OXPHOS (e.g., complex I-IV, including NADH dehydrogenase, SDH, ubiquinol–cytochrome c oxidoreductase, cytochrome c oxidase, and ATP synthase membrane subunit c locus 1) through deacetylation but also indirectly activates PGC-1α and AMPK.[105]

In adipocytes, resveratrol exerts an anti-adipogenic effect by inducing the expression of SIRTs. Resveratrol inhibited pig preadipocyte proliferation and differentiation, attributed to the upregulation of *Sirt1* expression.[106] Also, resveratrol suppressed lipid accumulation during adipogenesis in 3T3-L1 adipocytes by increasing the expression of *Sirt3*, uncoupling

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protein 1 (*Ucp1*), and mitofusin 2 (*Mfn2*), a mitochondrial membrane protein essential for mitochondrial fusion.[107] In C57BL/6J mice on a high-fat diet, resveratrol supplementation at a dose of 400 mg/kg/day for 15 weeks increased mitochondrial size and mtDNA content in brown adipose tissue (BAT) by activating SIRT1 and PGC-1α, thereby increasing energy expenditure.[108] Zucker diabetic rats on a diet supplemented with resveratrol (200 mg/kg body weight) for 6 weeks showed increased uncoupled mitochondrial respiration, complex I and II-supported respiration, and mitochondrial content in WAT, leading to an increase in glyceroneogenesis and adiponectin secretion.[109]

In skeletal muscle, both *in vivo* and *in vitro* studies have demonstrated the beneficial effect of resveratrol on mitochondrial functions. In C57BL/6J mice on a high-fat diet, resveratrol supplementation at a dose of 400 mg/kg/day for 15 weeks significantly increased exercise capacity and prevented the development of insulin resistance, attributed to increases in mitochondrial size, mtDNA copy number, CS activity, and enzymes such as SDH in skeletal muscle.[108] The effects of resveratrol were mediated through SIRT1 activation, which boosted the expression of genes related to mitochondrial biogenesis, including *Ppargc1a*, *Nrf1*, and *Tfam*, in skeletal muscle. When wild-type and *Sirt1* knockout mice were fed a high-fat diet, resveratrol supplementation at 25–30 mg/kg per day for 8 months significantly increased mtDNA content, mitochondrial area, phosphorylated AMPK, and NAD^+ levels dependent on SIRT1 through LKB1 deacetylation in the gastrocnemius muscle.[40] In mouse myoblast C2C12 cells infected with SIRT1 short hairpin RNA, resveratrol increased mitochondrial biogenesis and function, as evidenced by increases in cellular ATP content, mtDNA copy number, and the expression of mitochondrial ETC genes, in a SIRT1-dependent manner.[40] Also, resveratrol supplementation increased mitochondrial biogenesis in a SIRT1-independent manner, as evidenced by the increased mitochondrial biogenesis in resveratrol-treated *Sirt1* knockdown mice.[110]

In HepG2 cells, resveratrol activates complex I, facilitating NADH oxidation and electron transfer along the respiratory chain, increasing respiration. The increase in NADH oxidation by complex I occurs through SIRT3 activation.[111] The study demonstrated that resveratrol significantly enhanced both isolated NADH: flavin mononucleotide (FMN) dehydrogenase and complex I activities in mitochondrial membranes of HepG2 cells and mouse liver.[111] The effect of resveratrol was more significant on NADH-ferricyanide reductase activity than on NADH ubiquinone reductase activity, suggesting that resveratrol targets the NADH dehydrogenase part of complex I, which binds FMN.[111] Also, resveratrol mitigated arachidonic acid- and iron-induced oxidative stress and mitochondrial dysfunction in HepG2 cells.[112] The protective effects of resveratrol on oxidative stress and mitochondrial dysfunction were mediated through the activation of the LKB1/AMPK pathway, enhancing mitochondrial biosynthesis.[112] In the liver of mice fed a high-fat diet, resveratrol supplementation attenuated increases in weight, lipid accumulation, and apoptosis by elevating mitochondrial number, AMPK phosphorylation, and SIRT1 activity.[113] Therefore, resveratrol enhances liver function and provides hepato-protective effects by activating SIRTs and AMPK, promoting mitochondrial biogenesis, and elevating mitochondrial NAD^+/NADH ratios.

2. Quercetin

Quercetin is a polyphenolic flavonoid found abundantly in vegetables, fruits, and tea, and studies have demonstrated its effects on mitochondrial functions. In DIO mice, quercetin supplementation at 0.05% by weight for 18 weeks notably suppressed macrophage accumulation and decreased the ratio of $CD4^+$ helper T cells to $CD8^+$ killer T-cells, contributing to the recruitment and activation of macrophages in eWAT.[13] Concomitantly,

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mtDNA content and the expression of genes associated with mitochondrial OXPHOS were significantly increased, indicating that quercetin might prevent immune cell activation and, therefore, chronic inflammation.[13] ER stress contributes to mitochondrial dysfunction through calcium (Ca^{2+}) signaling in adipocytes, as Ca^{2+} released from the ER to the cytoplasm stimulates ROS production, causing mitochondrial swelling, i.e., breakage of the outer mitochondrial membrane.[114] In 3T3-L1 adipocytes treated with tunicamycin for the induction of ER stress, quercetin significantly reduced ROS production while increasing mitochondrial membrane potential and mass.[115] Interestingly, a combination of quercetin and resveratrol reduced lipid accumulation in mature 3T3-L1 adipocytes by suppressing adipocyte differentiation-related proteins, such as PPARγ and CCAAT/enhancer binding protein α (C/EBPα), and induced apoptosis via the mitochondria pathway.[115] Recent studies have revealed that the anti-cancer effects of quercetin are attributed to its ability to inhibit growth and promote apoptosis across various cancer cell models.[116-118] The suppression of cancer cell proliferation by quercetin has been linked to inhibiting key intracellular signaling pathways, including phosphatidylinositol 3-kinase, epidermal growth factor receptor, and human epidermal growth factor receptor-2.[119-122] Furthermore, quercetin is known to trigger apoptosis in cancer cells by modulating survival signaling pathways such as Akt, nuclear factor-κB or by affecting regulatory molecules involved in cell apoptosis, including p53, the B-cell lymphoma 2 family, and Fas ligand.[118,121,123,124]

Quercetin is also known to enhance mitochondrial function in skeletal muscle. Daily quercetin consumption (50 μg) for 8 weeks in DIO mice prevented obesity-induced mitochondrial dysfunction by increasing the expression of *Ppargc1a* in skeletal muscle, likely contributing to increased energy expenditure and reduced insulin resistance.[125] Quercetin supplementation in mice fed a high-fat diet for 9 weeks prevented high-fat diet-induced hypermethylation in the promoter of *Ppargc1a* and stimulated expression of an N-terminal truncated splice variant of *Ppargc1a* in skeletal muscle, resulting in the improvement of fatty acid β-oxidation for the prevention of high-fat DIO and insulin resistance.[126]

Studies have shown that quercetin boosts hepatic mitochondrial biogenesis *in vitro* and *in vivo*. In HepG2 cells, quercetin significantly increased the expression of mitochondrial biogenesis genes, such as *Ppargc1a*, *Nrf1*, and *Tfam*, as well as mtDNA content.[127] Also, in DIO mice, quercetin supplementation enhanced hepatic mitochondrial oxidative metabolism by inducing the mitochondrial biogenesis genes (*Pparα*, *Ppargc1a*, *Nrf1*, and *Tfam*) and oxidative metabolism protein (cytochrome c oxidase subunit 4; COX4), accompanied by increased antioxidant enzyme *Nfe2l2* (gene encoding nuclear factor erythroid 2-related factor 2 [NRF2]) expression.[128] This suggests the preventive effect of quercetin on obesity-induced hepatic lipid accumulation is mediated through the NRF2 pathway. Mitophagy is another protective mechanism in NAFLD that regulates the quality and quantity of mitochondria in hepatocytes by removing defective mitochondria.[129] Quercetin protected high-fat diet-induced hepatic steatosis and mitochondrial damage by increasing LC3II, PINK1, mitochondria Parkin, and Beclin1 protein expressions and decreasing p62 levels in the liver.[130] Also, quercetin has been demonstrated to activate the PINK1-Parkin pathway, promoting the clearance of damaged mitochondria and improving mitochondrial function in hepatocytes exposed to high-fat diet conditions.[131] This suggests the protective effects of quercetin on hepatic lipid accumulation and mitochondrial dysfunction are mediated through the activation of the PINK1/Parkin mitophagy pathway.

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Quercetin improves mitochondrial function by activating mitochondrial membrane potential and mass, mitochondrial oxidative metabolism, and mitophagy in WAT, skeletal muscle, and liver. These biological functions of quercetin poise it as a bioactive food component that may be used to prevent insulin resistance and metabolic disorders linked to mitochondrial dysfunction by increasing mitochondrial biogenesis and function.

3. Coenzyme Q10 (CoQ_{10})

CoQ_{10} is crucial for mitochondrial electron transport as a cofactor.[14,15] It is mainly located in the inner mitochondrial membrane, facilitating electron transfer from complexes I and II to complex III of the ETC complex.[132] CoQ exists in several forms — CoQ_6 to CoQ_{10} — with CoQ_{10} and CoQ_9 being the predominant forms in humans and rodents, respectively.[133] In diabetic/obese KKAy mice, supplementation of $CoQ_{10}H_2$, an enzymatically reduced form of CoQ_{10}, prevented lipid droplet accumulation and increased expression of thermogenesis-related genes, e.g., *Ucp1* and *Ppargc1a*, and also genes crucial for mitochondrial function, including AMPK, SIRT1, and PGC-1α in BAT, enhancing mitochondrial biogenesis and thermogenesis.[14] Similarly, in *ob*/*ob* mice fed a combination of CoQ_{10} and rosiglitazone, body weight was reduced, which was attributed to the upregulation of genes associated with mitochondrial biogenesis and function, such as *Ppargc1a*, *Cox4*, carnitine palmitoyl transferase 1B (*Cpt1b*), and *Ucp1*, and increased palmitic acid oxidation rates in inguinal WAT.[134] CoQ_{10} deficiency induced by a high-fat, high-sucrose diet for 14 days in C57BL/6J mice led to insulin resistance by increasing mitochondrial superoxide/hydrogen peroxide production.[135] However, supplementing with CoQ_{10} improved insulin sensitivity and, therefore, increased glucose uptake in adipose tissue, suggesting the role of CoQ_{10} in preventing insulin resistance in adipose tissue by inhibiting mitochondrial ROS production.[135]

CoQ_{10} deficiency reduced mitochondrial respiration in skeletal muscle, suggesting the therapeutic potential of CoQ_{10} supplementation for muscle disorders.[136] Treatment with CoQ_{10} normalized serum creatine kinase and lactate levels, indicators of myopathy, and was associated with improved activities of the enzymes in the ETC in patients with muscle weakness.[137] Statins inhibit CoQ_{10} synthesis, decreasing intramuscular CoQ_{10} levels and impairing mitochondrial energy production and function in skeletal muscle, leading to statin-induced myopathies.[138] Thus, CoQ_{10} supplementation can help patients with muscle disorders by restoring mitochondrial function in muscle.

Studies have shown that CoQ_{10} and its derivatives can improve mitochondrial biogenesis in the liver. Ubiquinone-10, an oxidized form of CoQ_{10}, prevented age-related decline of mitochondrial activity by increasing the hepatic expression of *Sirt1*, *Sirt3*, and *Ppargc1a* in mice that displayed early signs of aging and hepatocyte mitochondrial dysfunction.[139] $CoQ_{10}H_2$ enhanced mitochondrial function in the liver of KKAy mice by increasing protein levels of AMPK and PGC-1α, inhibiting fatty acid synthesis and promoting fatty acid β-oxidation.[14] Furthermore, CoQ_{10} restored hepatic mitochondrial dysfunction in statin-treated rats, improving mitochondrial bioenergetic parameters, including SDH activity, mitochondrial membrane potential, ATP levels, and mitochondrial permeability transition pore, a transmembrane protein residing in the mitochondrial inner membrane.[140] Mitochondrial permeability transition pore remains typically closed, but opens when triggered by factors such as Ca^{2+} accumulation, adenine nucleotide depletion, phosphate concentration increase, or oxidative stress.[141]

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Overall, CoQ_{10} is critical for mitochondrial ETC and, therefore, plays a pivotal role in cellular energy production. CoQ_{10} supplementation enhances mitochondrial function, thermogenesis, and insulin sensitivity. Statins, the most prescribed drugs for hypercholesterolemia, reduce CoQ_{10} levels and impair mitochondrial function, potentially leading to muscle disorders. However, CoQ_{10} supplementation can counteract the adverse effects of statins, offering therapeutic potential for statin-induced myopathies.

4. Curcumin

Curcumin, a natural flavonoid found in turmeric (*Curcuma longa* Linn.), promotes the browning of WAT by enhancing mitochondrial biogenesis.[16] It increased mitochondrial density and elevated protein expression of PGC-1α, CPT-1, and cytochrome C in 3T3-L1 and primary white adipocytes, along with induction of brown fat-like phenotype by upregulating *Ucp1* expression through AMPK activation.[142] Curcumin also increased mtDNA and the expression of brown fat-specific genes, such as *Ucp1*, PR domain containing 16 and deiodinase type 2, and cell death-inducing DNA fragmentation factor alpha-like effector A, in inguinal WAT of mice.[143] Also, curcumin elevated fatty acid oxidation and the expression of mitochondrial enzymes, including ATP synthase F1 subunit beta, malate dehydrogenase 2, and *Ucp1*, likely promoting β-oxidation and energy expenditure by trans-differentiation of white adipocytes into brown adipocytes in rat primary white adipocytes.[144]

Curcumin supplementation at 50 mg/kg body weight for 16 weeks reduced the levels of ROS and malondialdehyde and reversed the high-fat diet-induced reduction in total and nuclear NRF2 levels in the skeletal muscle of male C57BL/6J mice fed a high-fat diet.[145] The curcumin effect is attributed to its protective role against oxidative stress and mitochondrial redox imbalance. The intraperitoneal injection of curcumin at doses of 50 and 100 mg/kg body weight with endurance training for 28 days promoted mitochondrial biogenesis, evidenced by increased COX4 and OXPHOS subunits expression, mtDNA content, and CS enzyme activity, through the activation of AMPK and SIRT1 in gastrocnemius and soleus muscles of rats.[146] AMPK and SIRT1 were activated by elevated intracellular cyclic AMP and NAD^+ levels, promoting phosphorylation of CREB and LKB1 involved in mitochondrial biogenesis in skeletal muscle.[146]

Curcumin can also inhibit hepatic mitochondrial dysfunction. It decreased malondialdehyde in isolated hepatic mitochondria and hepatic cellular ROS levels, increasing mitochondrial membrane potential and antioxidant enzyme activities in the liver of mice with D-galactosamine/lipopolysaccharide-induced liver injury.[147] In *ob*/*ob* mice, curcumin supplementation (1% or 3%, *w*/*w*) enhanced the expression of mitochondrial biogenesis genes, such as *Nrf1* and *Tfam*, with a concomitant increase in mitochondrial respiratory chain complex I activity and ATP levels, thereby preventing liver steatosis.[148] Additionally, in diabetic *db*/*db* mice, oral curcumin administration at a dose of 60 mg/kg/day for 4 weeks ameliorated mitochondrial dysfunction by decreasing lipid peroxidation and nitric oxide synthesis while enhancing mitochondrial ATPase activity in mitochondria isolated from liver.[149] Curcumin also countered free fatty acid-induced mitochondrial dysfunction in rat primary hepatocytes, possibly by enhancing mitochondria biogenesis via the increase in *Nrf1* and *Tfam* gene expression and PGC-1α and SIRT1 protein levels, elevating cellular ATP levels and mtDNA copy number.[150]

Therefore, curcumin significantly enhances mitochondrial health by promoting mitochondrial biogenesis and function and inhibiting oxidative stress in WAT, skeletal

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muscle, and the liver. By boosting mitochondrial function, curcumin helps mitigate insulin resistance, enhances fatty acid oxidation, and prevents liver steatosis, showcasing its potential as a therapeutic agent for metabolic and mitochondrial disorders.

5. Astaxanthin (ASTX)

ASTX is a xanthophyll carotenoid found in marine animals, such as salmon and shrimp. Studies have demonstrated that ASTX exhibits antioxidant, anti-inflammatory, anti-diabetic, anti-cardiovascular, and hepato-protective effects.[17] In C57BL/6J mice with high-fat diet-induced hepatic steatosis, ASTX consumption (6 or 30 mg/kg body weight) for 8 weeks upregulated the expression of fatty acid oxidation genes, such as *Cpt1α* and acyl-CoA oxidase 1 (*Acox1*), and enhanced the protein expression of *Ppara*, reducing hepatic lipid accumulation.[151] Additionally, ASTX stimulated the expression of thermogenic genes, such as *Ucp2* in the liver of DIO mice.[151] This study suggests ASTX as a promising preventive and therapeutic agent for treating liver diseases associated with mitochondrial dysfunction.

In the skeletal muscle of DIO mice, ASTX increased the expression of mitochondrial and peroxisomal fatty acid β-oxidation genes, such as *Cpt1α* and *Acox1*, and enhanced *Ppara* and *Ppargc1a* mRNA levels.[152] The results indicate the role of ASTX in boosting mitochondrial fatty acid β-oxidation, thereby ameliorating obesity-associated mitochondria dysfunction in skeletal muscle. Liu et al.[153] reported that ASTX improved mitochondrial function in skeletal muscle under aerobic exercise conditions. Mice fed ASTX and also engaged in aerobic exercise displayed higher levels of protein expression of PGC-1α along with increased cytochrome c and fibronectin type III domain-containing 5 protein, when compared to control mice.[153] This study suggests that ASTX can improve fatty acid β-oxidation and mitochondrial biogenesis under obesity and aerobic exercise conditions.

Thus, ASTX shows promise in treating metabolic disorders by boosting mitochondrial biogenesis, reducing oxidative stress, and enhancing fatty acid β-oxidation, offering a therapeutic approach for diseases linked to mitochondrial dysfunction, such as NAFLD and obesity.

CONCLUSION

Mitochondrial dysfunction plays a pivotal role in the etiology of obesity-associated metabolic diseases, where excessive fat triggers oxidative stress, damaging cellular components like DNA, proteins, lipids, and other molecules and inducing mtDNA mutations. This disrupts energy metabolism, leading to impaired lipid metabolism and ROS generation, which ultimately induces insulin resistance in adipose tissue, skeletal muscle, and the liver. Studies have highlighted that bioactive food compounds, including resveratrol, quercetin, CoQ_{10}, curcumin, and ASTX, target various cellular processes in adipocytes, myoblasts, and hepatocytes to attenuate mitochondrial dysfunction via regulating ROS generation, inflammation, adipocyte differentiation, insulin sensitivity, and fatty acid oxidation (**Fig. 1**, **Table 1**).[13,14,40,106-113,115,125-128,134-140,142-154] While promising, further research is needed to elucidate their bioavailability, optimal dosages, and efficacy in humans. Furthermore, to develop therapeutic agents that target mitochondria, it is necessary to have a deeper understanding of the molecular mechanisms and pharmacokinetics of food bioactive components in relation to mitochondrial dysfunction-related diseases.

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Table 1. Summary for regulating mitochondrial dysfunction of bioactive food compounds in metabolic diseases

Bioactive components	Mitochondrial regulation	Metabolic effect	Experimental models	Ref.
Resveratrol	Upregulation of *Sirt1* expression	Inhibition of proliferation and differentiation	Pig preadipocyte	106
	Increase in *Sirt3*, *Ucp1*, and *Mfn2* expression	Suppression of lipid accumulation	3T3-L1 adipocytes	107
	Increase in mitochondrial size and mtDNA content by activating SIRT1 and PGC-1α in BAT and skeletal muscle	Increase in energy expenditure and prevention of insulin resistance	High-fat diet-fed C57BL6J mice	108
	Increase in mitochondrial respiration and content in WAT	Increase in glyceroneogenesis and adiponectin secretion	Zucker diabetic rats	109
	Activation of SIRT1 and AMPK in gastrocnemius muscle	Increase in mitochondrial biogenesis and function	High-fat diet-induced *Sirt1* knockout mice and C2C12 cells	40,110
	Increase in NADH oxidation and respiration rate through SIRT3 activation	Increase in liver mitochondrial biogenesis	HepG2 cells and C57BL/6J mice	111
	Increase in mitochondrial number, AMPK phosphorylation, and SIRT1 enzymatic activity	Attenuation of increased liver weight, lipid accumulation, and apoptosis	High-fat diet-fed C57BL/6NIA mice	113
	Prevention of oxidative stress and mitochondrial dysfunction through LKB1/AMPK activation	Increase in mitochondrial biosynthesis	Arachidonic acid- and iron-induced HepG2 cells	112
Quercetin	Increase in mtDNA content and mitochondrial OXPHOS gene in eWAT	Prevention of immune cell activation	DIO mice	13
	Increase in mitochondrial membrane potential and mass and reduction of ROS production	Reduction of lipid accumulation	ER stress-induced 3T3-L1 adipocytes	115
	Increases in the expression of *Ppargc1α* and prevention of *Ppargc1* hypermethylation in skeletal muscle	Increase in energy expenditure and fatty acid β-oxidation, and reduction of insulin resistance	DIO mice, High-fat diet-fed C57BL6J mice	125,126,154
	Increase in mitochondrial biogenesis genes and hepatic mitochondrial oxidative metabolism through the NRF2 pathway	Prevention of obesity-induced hepatic lipid accumulation	HepG2 cells and DIO mice	127,128
CoQ_{10}	Enhancement of mitochondrial biogenesis by increasing AMPK and PGC-1α in the BAT	Suppression of lipid accumulation and increase in thermogenesis	Diabetic/obese KKAy mice	14
	Increase in mitochondrial biogenesis genes and function in inguinal WAT	Reduction of body weight	*ob/ob* mice	134
	Inhibition of mitochondrial ROS production in adipose tissue	Prevention of insulin sensitivity	High fat and high sucrose diet fed C57BL/6J mice	135
	Improvement of activities of the enzymes in the ETC in patients with muscle weakness	Normalized serum creatine kinase and lactate levels	Myopathy and muscle weakness patients	136-138
	Increase in the hepatic expression of *Sirt1*, *Sirt3*, and *Ppargc1α* in mice	Prevention of age-related decline of mitochondrial activity in the liver	Senescence-accelerated mice	139
	Increase in protein levels of AMPK and PGC-1α	Inhibition of fatty acid synthesis and promotion of fatty acid β-oxidation	Diabetic/obese KKAy mice	14
	Increase in mitochondrial biogenesis parameters in the liver	Restoration of hepatic mitochondrial dysfunction	Statin treated rats	140
Curcumin	Increase in mitochondrial density and protein expression of PGC-1α, CPT-1	Browning of WAT	3T3-L1 and primary white adipocytes	142
	Increase in mtDNA and the expression of brown fat-specific genes in the inguinal WAT	Browning of WAT	C57BL/6 mice	143
	Increases in expression of mitochondrial enzymes	Promotion of β-oxidation and energy expenditure by browning of primary WAT	Sprague-Dawley rats	144
	Reduction of ROS and malondialdehyde levels by activating NRF2 in skeletal muscle	Protection of against oxidative stress and mitochondrial redox imbalance	High-fat diet-fed C57BL6J mice	145
	Increase in mitochondrial biogenesis by increasing cAMP and NAD^+ levels in skeletal muscle	Increase in mitochondrial biogenesis in skeletal muscle	Wistar rats	146
	Decrease of mitochondrial and ROS levels and increase in mitochondrial membrane potential in the liver	Decrease of hepatic oxidative stress	D-galactosamine/LPS-induced liver injury in mice	147
	Increase in the expression of mitochondrial biogenesis genes with a concomitant increase in mitochondrial respiratory activity and ATP levels in the liver	Prevention of liver steatosis	*ob/ob* mice	148
	Enhancement of mitochondrial ATPase activity in the liver mitochondria	Decrease of lipid peroxidation and nitric oxide synthesis	*db/db* mice	149
	Increase in *Nrf1* and *Tfam* gene expression and PGC-1α and SIRT1 protein levels	Increase in cellular ATP levels and mtDNA copy number	Primary rat hepatocytes	150

(continued to the next page)

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Table 1. (Continued) Summary for regulating mitochondrial dysfunction of bioactive food compounds in metabolic diseases

Bioactive components	Mitochondrial regulation	Metabolic effect	Experimental models	Ref.
ASTX	Upregulation of mitochondrial β-oxidation gene expression in the liver	Reduction of hepatic lipid accumulation and mitochondria-derived ROS	High-fat diet-induced hepatic steatosis C57BL/6J mice	151
	Prevention of obesity-associated mitochondria dysfunction in skeletal muscle	Prevention of obesity-associated mitochondria dysfunction	DIO mice	152
	Increase in protein expression of PGC-1α and cytochrome C and fibronectin type III domain-containing 5 in skeletal muscle	Improvement of lipid metabolism through activation of mitochondrial aerobic metabolism.	ICR mice	153

SIRT1 (gene encoding *Sirt1*), sirtuin 1; *Ucp1*, uncoupling protein 1; *Mfn2*, mitofusin 2; mtDNA, mitochondrial DNA; PGC-1α (gene encoding *Ppargc1a*), peroxisome proliferator-activated receptor-gamma coactivator-1 alpha; BAT, brown adipose tissue; WAT, white adipose tissue; NADH, β-nicotinamide adenine dinucleotide reduced; AMPK, adenosine monophosphate-activated protein kinase; LKB1, liver kinase B; eWAT, epididymal white adipose tissue; OXPHOS, oxidative phosphorylation; DIO, diet-induced obesity; ER, endoplasmic reticulum; NRF2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; CPT-1, carnitine palmitoyl transferase-1; cAMP, cyclic adenosine monophosphate; NAD^+, β-nicotinamide adenine dinucleotide; ATP, adenosine-5'-triphosphate; *Nrf1*, nuclear respiratory factor 1; *Tfam* mitochondrial transcription factor A, ICR mice, institute of cancer research mice, CoQ_{10}, coenzyme Q10; ASTX, astaxanthin.

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