# Targeting mitochondrial oxidative stress: A novel therapeutic strategy for degenerative joint diseases (Review)

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**Abstract.** Degenerative joint diseases, such as osteoarthritis (OA), intervertebral disc degeneration (IVDD) and rheumatoid arthritis (RA), cause pain and disability worldwide. Globally, OA affects >500 million individuals, IVDD affects 40-60% of adults and RA affects 0.5-1% of the global population. Current treatments (such as non-steroidal anti-inflammatory drugs and corticosteroids for OA, conservative management and spinal surgery for IVDD, and disease-modifying anti-rheumatic drugs/biologics for RA) focus on symptom relief and inflammation control, but they do not prevent disease progression nor restore damaged tissue. Furthermore, these treatments are often associated with risks of systemic side effects (such as gastrointestinal bleeding, cardiovascular events and immunosuppression) or surgical complications (such as infection and implant failure). Although accumulating evidence implicates mitochondrial dysfunction and excessive reactive oxygen species (ROS) in the pathogenesis of these disorders, strategies that directly target mitochondrial oxidative stress are yet to be developed and translated into the clinic. In the present study this gap in the knowledge was addressed by systematically reviewing mitochondria-targeted antioxidant therapies and mitochondrial quality-control mechanisms due to their potential as novel, disease-modifying approaches for degenerative joint diseases. The preclinical efficacy of mitochondria-directed antioxidants (such as mitoquinone, MitoTEMPO, 10-(6'-plastoquinonyl) decyltriphenylphosphonium and Szeto-Schiller-31) in alleviating ROS-induced cellular damage, inhibiting apoptosis/pyroptosis and preserving extracellular matrix integrity in OA, IVDD and RA models were summarized. Additionally, strategies to enhance mitophagy (such as through PTEN-induced kinase 1/Parkin), rebalance mitochondrial dynamics (such as through the dynamin-related protein 1/mitofusin 1/2) and activate antioxidant signaling pathways (such as nuclear factor erythroid 2-related factor 2 and sirtuin 3) were highlighted. The present study identified key translational challenges (such as optimal delivery systems, long-term safety and clinical validation) and suggested integrated therapeutic frameworks that combine targeted antioxidants with advanced drug carriers and adjunctive treatments. Mitochondria-focused interventions may have potential as the next generation of disease-modifying treatments for OA, IVDD and RA.

**Contents**



## 1. Introduction

Degenerative joint diseases include osteoarthritis (OA), intervertebral disc (IVD) degeneration (IVDD) and rheumatoid arthritis (RA). The gradual structural and functional deterioration of articular cartilage, subchondral bone and surrounding joint tissues are common features, which lead to joint pain, stiffness and functional impairment (1-3). It is reported that degenerative joint diseases affect >250 million individuals worldwide (4). In OA, progressive degradation of the cartilage matrix occurs, with notable reductions in the main components of the extracellular matrix (ECM), such as type II collagen and proteoglycans; in later stages, osteophytes (which are outgrowths of bone at joint margins that develop in response to cartilage loss) often form, and joint deformities may develop (2,5). In IVDD, the nucleus pulposus (NP) cells

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and annulus fibrosus cells progressively lose their viability and function; over time, the intervertebral discs become dehydrated, collapse and deform, causing various clinical issues such as lower back pain (6). Furthermore, in RA, an autoimmune disease, chronic inflammation and synovial hyperplasia erode the articular cartilage and subchondral bone, typically manifesting as marked joint swelling, morning stiffness and cartilage destruction (7,8). Regardless of the specific form, inflammation and oxidative stress both serve roles in the pathogenesis of these diseases.

Oxidative stress is the excessive accumulation of reactive oxygen species (ROS) and reactive nitrogen species that surpass the scavenging capacity of endogenous antioxidant systems (such as superoxide dismutase, catalase, glutathione peroxidase and peroxiredoxins). Oxidative stress causes cellular damage and can lead to apoptosis or necrosis (9,10). In tissues such as articular cartilage and intervertebral discs, oxidative stress induces the expression of matrix-degrading enzymes [such as matrix metalloproteinases (MMPs; MMP-1, -3 and -13) and aggrecanases (such as a disintegrin and metalloproteinase with thrombospondin motifs-4 and -5)], which accelerates the degradation of the ECM (2,11,12). Moreover, oxidative stress can activate associated signaling pathways (such as the NLRP3 inflammasome), exacerbating local inflammation (13,14). With aging or disease progression, the capacity of joint cells to defend against free radical damage declines. This results in an increased likelihood that oxidative damage will accumulate, which further exacerbates joint or disc degeneration (2,15).

Mitochondria, the organelles responsible for oxidative phosphorylation and energy supply in cells, are the primary sites of endogenous ROS production (1,16). During oxidative phosphorylation in the mitochondrial electron transport chain, superoxide anions ($O_2^-$) are generated and then converted to $H_2O_2$, OH·, singlet oxygen and peroxynitrite by antioxidant systems such as superoxide dismutases (SODs; such as SOD2) (17). If the levels of the $O_2^-$ exceeds this regulatory capacity, damage on the mitochondrial proteins, membrane lipids and DNA may occur (16). Previous studies reveal that mitochondrial dysfunction and excess mitochondrial ROS production are involved in numerous degenerative diseases, including OA, RA and IVDD (5,8,18). Therefore, protecting mitochondria and improving redox homeostasis is a notable research focus and may be a strategy in the prevention and treatment of degenerative joint diseases.

Mitochondrial oxidative stress results in tissue damage in degenerative joint diseases; however, therapeutic strategies aimed at restoring the mitochondrial redox balance are scarce. Although conventional antioxidants (such as vitamin C, vitamin E and N-acetylcysteine) and anti-inflammatory drugs (for example, non-steroidal anti-inflammatory drugs such as ibuprofen and indomethacin, or corticosteroids such as prednisone) can transiently alleviate symptoms, they cannot mitigate the mitochondria-derived ROS at the source (2). Despite growing evidence that aberrant mitochondrial ROS contribute to cartilage degradation, NP cell senescence and synovial inflammation, only a small number of therapeutic strategies target mitochondrial oxidative stress. At present, the existing antioxidant approaches rely on non-mitochondria-specific compounds, such as vitamin C, vitamin E, N-acetylcysteine, glutathione and polyphenols (for example, resveratrol), and clinical translation is limited (2). Therefore, an evaluation of the mitochondria-targeted antioxidants and quality-control mechanisms was needed in order to assess this translational gap and highlight the novel disease-modifying treatments for OA, IVDD and RA.

## 2. Methods

*Literature search strategy*. A systematic search of PubMed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://www.webofscience.com/) and the Cochrane Library (https://www.cochranelibrary.com/) was carried out for articles published between 2000 and June 2025. Search terms included combinations of 'osteoarthritis' OR 'intervertebral disc degeneration' OR 'rheumatoid arthritis' with 'mitochondria', 'oxidative stress', 'mitophagy', 'MitoQ', 'SS-31' and 'mitochondrial antioxidant'. Boolean operators and Medical Subject Headings were used as appropriate. Reference lists of relevant reviews and clinical guidelines were also reviewed to identify additional studies.

The inclusion criteria used were as follows: i) Primary research or review articles written in English; ii) *in vitro*, *in vivo* or *ex vivo* models of OA, IVDD or RA; iii) interventions that directly targeted mitochondrial function or oxidative stress; and iv) quantifiable outcomes regarding the levels of ROS, cell survival, ECM integrity or functional scores.

The exclusion criteria used were as follows: i) Publications not written in English; ii) conference abstracts or editorials; iii) duplicate reports; or iv) studies with insufficient methodological detail.

## 3. Biological basis of mitochondria-targeted antioxidant strategies in degenerative joint diseases

*Production and scavenging of mitochondrial ROS*. Within mitochondria, 1-5% of the oxygen taken in by the cell may 'leak' in the form of ROS during the activity of the electron transport chain (19,20). Under normal conditions, SODs located in the mitochondria (such as SOD2, which is primarily located in the mitochondrial matrix), peroxiredoxins and glutathione peroxidases convert or remove these ROS, which keeps the levels of the ROS within a reasonable range (typically at nM to low $\mu$M concentrations, such as superoxide in the 10-100 nM range and hydrogen peroxide in the 1-10 $\mu$M range, which act as signaling molecules) and allows them to function in cell signal transduction and normal metabolic processes, such as MAPK (ERK, JNK and p38), NF-κB, PI3K-Akt, hypoxia-inducible factor-1α and Wnt/β-catenin signaling pathways (2,21) (Fig. 1). However, when mitochondrial function is impaired (due to exogenous harmful stimuli, aging or gene mutations that inactivate complexes involved in the electron transport chain) excessive levels of ROS can accumulate, resulting in lipid peroxidation, oxidative protein modifications and breaks in the DNA (16,22).

*Mechanisms linking mitochondrial dysfunction with degenerative changes in joints*. Mitochondrial dysfunction is associated with degenerative changes in joint tissues by promoting apoptosis, pyroptosis and inflammatory responses, as well as undermining cartilage matrix integrity and normal

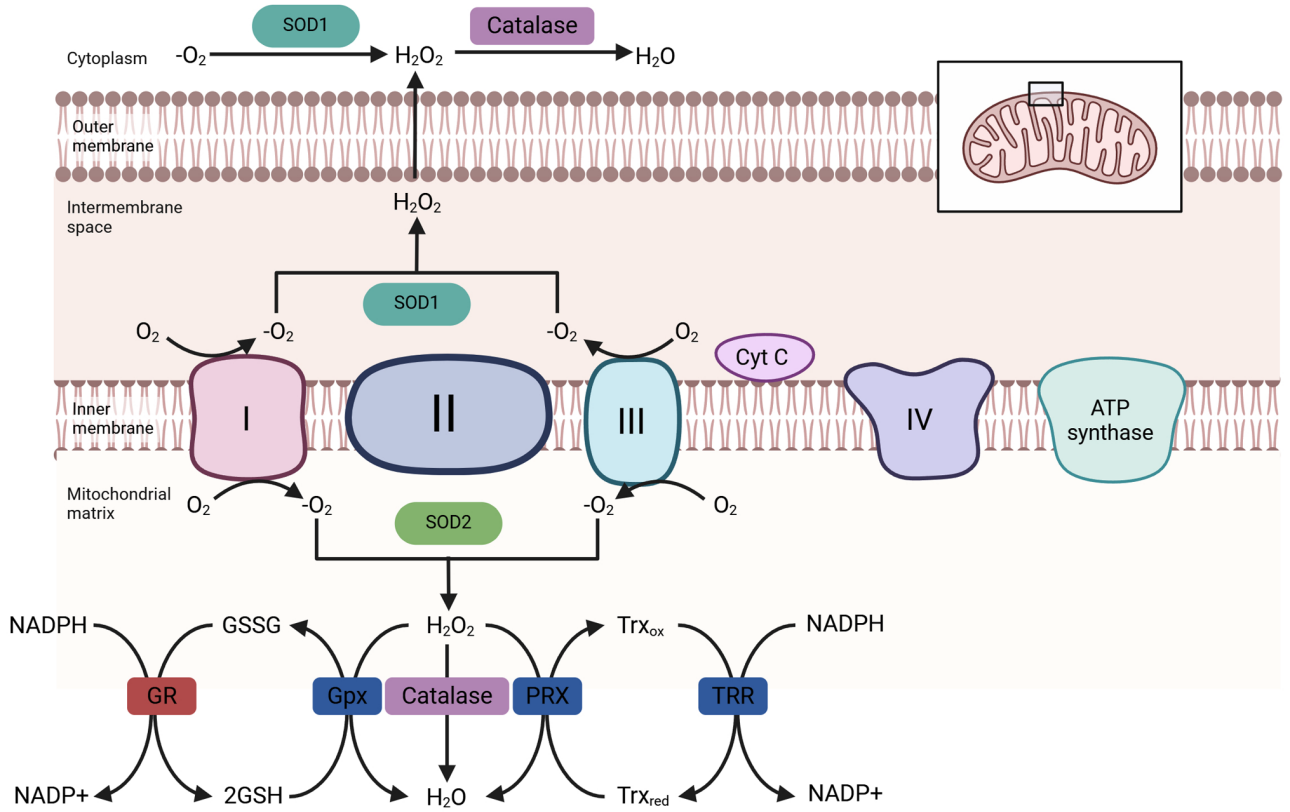


Figure 1. Schematic illustration of mitochondrial reactive oxygen species generation and the antioxidant defense systems. During mitochondrial respiration, electron leakage from the electron transport chain leads to the formation of superoxide anions, which are subsequently converted to hydrogen peroxide and hydroxyl radicals through enzymatic and non-enzymatic reactions. To counteract oxidative stress, mitochondria utilize several antioxidant mechanisms, such as SOD that catalyzes the dismutation of superoxide into $H_2O_2$, which is further detoxified by Gpx and PRX. The glutathione system, composed of reduced GSH, oxidized GSSG and GR, maintains redox homeostasis. In parallel, the Trx/TRR system reduces oxidized proteins and supports peroxiredoxin activity. Cyt C is also a key electron carrier and its release into the cytosol can trigger apoptotic signaling. Gpx, glutathione peroxidase; PRX, peroxiredoxin; SOD, superoxide dismutase; Cyt C, cytochrome c; GR, glutathione reductase; GSSG, glutathione disulfide; GSH, glutathione; TRR, thioredoxin reductase; Trx, thioredoxin; ox, oxidized; red, reduced.

cellular functions (23,24). The excessive generation of mitochondrial ROS and the loss of the mitochondrial membrane potential can cause a release of cytochrome c. This can lead to the subsequent activation of the caspase cascade, which induces apoptosis (13,25). Furthermore, elevated ROS levels can promote the assembly of the NLRP3 inflammasome, triggering pyroptosis and increasing the inflammatory damage within joint tissues (13,26).

In addition to the aforementioned direct mechanisms of cell death, oxidative stress activates inflammatory pathways such as NF-κB and MAPK. These inflammatory pathways increase the production of proinflammatory factors (such as IL-1β and TNF-α) and MMPs, which together accelerate cartilage matrix degradation (7,27).

As mitochondrial damage worsens, cells face an energy deficit. An overabundance of ROS further impairs proteoglycans and collagen, increasing the breakdown of the ECM in the cartilage (15,28). For example, in RA, mitochondrial dysfunction in fibroblast-like synoviocytes increases both local inflammation and synovial hyperplasia (7). Moreover, the accumulation of ROS may lead to cell cycle arrest, reduced chondrocyte proliferation and the emergence of cellular senescence phenotypes (such as increased p16 and p21 expression levels), which are observed in conditions such as osteoporosis, OA and IVDD (29-31).

## 4. Research progress on mitochondria-targeted antioxidants in degenerative joint diseases

*Mitoquinone (MitoQ).* MitoQ is a mitochondria-targeted antioxidant formed by conjugating a ubiquinone analog with triphenylphosphonium (TPP) through an alkyl chain. It demonstrates certain protective effects in models of both OA and IVDD (2,32) (Table I).

*Research in OA. In vitro* studies, using chondrocyte models induced with oxidative stress, demonstrate that MitoQ mitigates mitochondrial damage and ECM degradation, while enhancing the expression of anti-inflammatory genes, such as *IL-10* and *TGF-β*, as well as antioxidant genes including *SOD2*, *catalase*, *glutathione peroxidase 1* and *NAD(P)H:quinone oxidoreductase 1* (2,31). *In vivo*, MitoQ alleviates cartilage degeneration and reduces the levels of inflammatory cytokines, which slows the progression of OA (32,33).

*Research in IVDD.* Studies indicate that under mechanical overload or inflammatory stimulation, intervertebral disc tissue exhibits notable accumulation of ROS, elevated apoptosis and impaired ECM synthesis (34,35). MitoQ inhibits the activation of inflammatory signaling pathways such as the NLRP3 inflammasome and NF-κB, and prevents the excessive secretion of key cytokines, such as IL-1β, TNF-α

Table I. Comparison of mitochondria-targeted antioxidants in degenerative joint diseases.

| Antioxidant | Structure and targeting | Mechanism of action | Evidence in OA | Evidence in IVDD | Evidence in RA |
|---|---|---|---|---|---|
| MitoQ | Ubiquinone and $TPP^+$ | Scavenges mtROS, stabilizes the mitochondrial membrane and downregulates NF-κB/NLRP3 | Reduces cartilage damage and inflammation (demonstrated in *in vitro* studies and models of mice with OA) (25,32) | Reduces NP cell apoptosis and increases ECM stability (demonstrated in rat models) (8,40) | Limited |
| MitoTEMPO | TEMPO and $TPP^+$ | Removes mitochondrial superoxide, inhibits the expression of JNK/AP-1 and NF-κB, and promotes mitophagy | Reduces MMPs expression levels and cartilage degeneration (demonstrated in mice with OA) | Reduces caspase-induced pyroptosis and increases PINK1/Parkin-induced mitophagy (demonstrated in NP cell models) | Reduces synovial inflammation and ROS (demonstrated *in vitro*) |
| SkQ1 | Plastoquinone and $TPP^+$ | Induces apoptosis in neutrophils, and reduces synovial oxidative stress | Not reported | Not reported | Reduces joint damage and the levels of cytokines (demonstrated in a rat model of RA) |
| SS-31 (Elamipretide) | Peptide binding to cardiolipin | Stabilizes the ETC, reduces lipid peroxidation and preserves mitochondrial dynamics | Increases the synthesis of the ECM by chondrocytes and reduces senescence (demonstrated in *in vitro* cellular models) | Reduces NP apoptosis and increases mitochondrial stability (demonstrated in *in vitro* LPS- and oxidative stress-induced cellular models) | Limited |

OA, osteoarthritis; IVDD, intervertebral disc degeneration; RA, rheumatoid arthritis; AP-1, activator protein-1; PINK1, PTEN-induced kinase 1; ROS, reactive oxygen species; MitoQ, mitoquinone; SkQ1, plastoquinonyl-decyl-triphenylphosphonium; SS-31, Szeto-Schiller-31; LPS, lipopolysaccharide; $TPP^+$, triphenylphosphonium cation; mtROS, mitochondrial ROS; NP, nucleus pulposus; ECM, extracellular matrix; ETC, electron transport chain; MMP, matrix metalloproteinase.

and IL-6 (30,32,36). In a rat IVDD model, MitoQ administration maintains disc height and hydration; therefore, delaying degenerative changes (6,30,36).

These findings suggest that MitoQ confers protective effects on both articular cartilage and intervertebral discs, potentially due to its ability to reduce mitochondrial oxidative damage and stabilize energy metabolism.

*MitoTEMPO*. MitoTEMPO is a mitochondria-targeted antioxidant formed by coupling the superoxide scavenger TEMPO with the $TPP^+$ cationic group, which removes mitochondrial superoxide radicals (37,38). Multiple *in vivo* and *in vitro* studies highlight its beneficial role in counteracting oxidative stress and apoptosis in joint cells (27,37).

*Research in OA*. Under high-glucose conditions or inflammatory stimulation, ROS levels in chondrocytes increase. Previous studies report that MitoTEMPO blocks the JNK/activator protein-1 and NF-κB pathways that are activated by ROS, leading to a reduction in the expression of MMPs compared with the expression of MMPs without MitoTEMPO treatment (27,37). Furthermore, intra-articular injection of

MitoTEMPO in mice with cholesterol-induced OA reduces MMP-13 gene expression levels compared with vehicle-treated OA controls. Additionally, this intervention alleviates cartilage lesions and leads to a notable reduction in cartilage degeneration (2).

*Research in IVDD*. MitoTEMPO also demonstrates protective effects in IVDD. In NP cells with IL-1β exposure or endplate chondrocytes with $H_2O_2$ exposure, MitoTEMPO notably reduces the pathological increase in mitochondrial ROS compared with the stressor-only groups without MitoTEMPO treatment. This suppresses the activation of the caspase cascade and pyroptosis (25,39). When mitochondrial ROS are suppressed, PTEN-induced kinase 1 (PINK1)/Parkin-mediated mitophagy is maintained, reducing the accumulation of damaged mitochondria in cells (25,39). This process improves the function of NP cells and the homeostasis of the ECM, exerting an interventional effect on IVDD.

*Research in RA*. Although the research on MitoTEMPO in RA is limited, studies in synovial cell models suggest that exogenous mitochondrial ROS scavenging can attenuate the inflammatory cascade and ROS bursts (7,40). Therefore, MitoTEMPO exhibits broad-spectrum antioxidant protection by targeting mitochondria in various degenerative joint diseases.

*Plastoquinonyl-decyl-triphenylphosphonium (SkQ1)*. SkQ1 is a mitochondria-targeted antioxidant derived from plastoquinone linked to TPP (8). In a RA model, low doses of SkQ1 (on the nM scale) suppresses the progression of arthritis and reduces the pathological damage to cartilage and the synovium (8). Its mechanism is associated with inducing neutrophil apoptosis, alleviating oxidative stress and improving the joint microenvironment. Although direct evidence in OA and IVDD is scarce, the robust mitochondrial antioxidant properties of SkQ1 and its efficacy in autoimmune arthritis models suggest it may hold potential value for degenerative joint diseases as well.

*Szeto-Schiller-31 (SS-31)*. SS-31 (also known as Elamipretide) is a mitochondria-targeting short peptide that binds to cardiolipin on the inner mitochondrial membrane. This helps to stabilize the electron transport chain and reduce the generation of ROS (41). Studies demonstrate that SS-31 improves the mitochondrial membrane potential, inhibits inflammation and promotes the synthesis of the ECM in both intervertebral disc cells and chondrocytes (6,42).

Additionally, SS-31 reduces mitochondrial lipid peroxidation, a key factor in oxidative damage, and partially reverses stress-induced cellular senescence phenotypes (43). Its ability to ameliorate mitochondrial function also contributes to mitigating inflammatory signaling and promoting the stability of the ECM, which is critical for preventing tissue degeneration (44).

## 5. Other strategies targeting mitochondrial regulatory molecules in degenerative joint diseases

Apart from the direct use of mitochondria-targeted antioxidants, recent studies increasingly focus on mitochondrial dynamics, mitophagy and mitochondrial biogenesis as indirect methods for reducing mitochondrial ROS accumulation, which may offer a therapeutic potential in degenerative joint diseases (Fig. 2) (45,46).

*Regulation of PINK1/Parkin-mediated mitophagy*. The PINK1/Parkin pathway is an essential cellular mechanism for clearing damaged mitochondria. When the mitochondrial membrane potential decreases, PINK1 accumulates on the outer mitochondrial membrane, recruiting Parkin to the mitochondrial surface. Parkin then ubiquitinates several outer mitochondrial membrane substrates, including mitofusins 1/2, voltage-dependent anion channel 1 and translocase of outer mitochondrial membrane 20, which facilitates the recognition and clearance of damaged mitochondria through autophagy. Enhancing PINK1/Parkin-mediated mitophagy can reduce the release of mitochondrial ROS, which protects cells from damage (47). Previous studies demonstrate that inhibition of leucine-rich repeat kinase 2 can restore Parkin-mediated mitophagy and alleviate IVDD (48,49). Taurine, a naturally occurring amino acid derivative, promotes mitophagy by activating the PINK1/Parkin pathway, which ameliorates IVDD (50). Additionally, knocking down the expression of early growth response protein 1 activates PINK1-Parkin-dependent mitophagy, which suppresses NP cell senescence and mitochondrial damage, and slows disc degeneration (51). Furthermore, a recent study reveals that cellular repressor of E1A-stimulated genes 1 can alleviate NP cell pyroptosis through the PINK1/Parkin-associated mitophagy pathway, which improves IVDD (52).

*Maintenance of mitochondrial dynamics balance (fission and fusion)*. An imbalance in mitochondrial fission and fusion also leads to the excessive generation of ROS (36). Under pathological stimuli such as mechanical compression, excessive mitochondrial fission (mediated by dynamin-related protein 1) separates damaged mitochondrial segments; however, impaired fusion processes (mediated by mitofusin 1/2 and optic atrophy 1) result in the accumulation of fragmented and dysfunctional mitochondria, causing a persistent elevation of ROS (36). Antioxidants such as MitoQ not only reduce ROS levels but also attenuate excessive fission and promote fusion of functionally intact mitochondria (36,53). Therefore, the modulation of proteins involved in mitochondrial dynamics or the combined use with mitochondrial antioxidants may be a future therapeutic direction for joint degeneration.

*Nuclear factor erythroid 2-related factor 2 (Nrf2)-Kelch-like ECH-associated protein 1 (Keap1) antioxidant signaling pathway and mitochondria*. Nrf2, a central transcription factor for cellular antioxidant responses, induces the expression of antioxidant genes including *heme oxygenase-1* (*HO-1*), *NAD(P)H quinone dehydrogenase 1* and SOD2 (32). When mitochondrial ROS levels increase, oxidative modification of Keap1 leads to the stabilization and nuclear translocation of Nrf2, which then activates antioxidant gene expression to alleviate oxidative stress and maintain cellular homeostasis (54). A recent study demonstrates that both pharmacological and genetic activation of the Nrf2 pathway serves a crucial role in mitigating inflammatory responses and apoptosis in joint cartilage and IVD tissues (49). For example, Kartogenin-loaded hydrogel

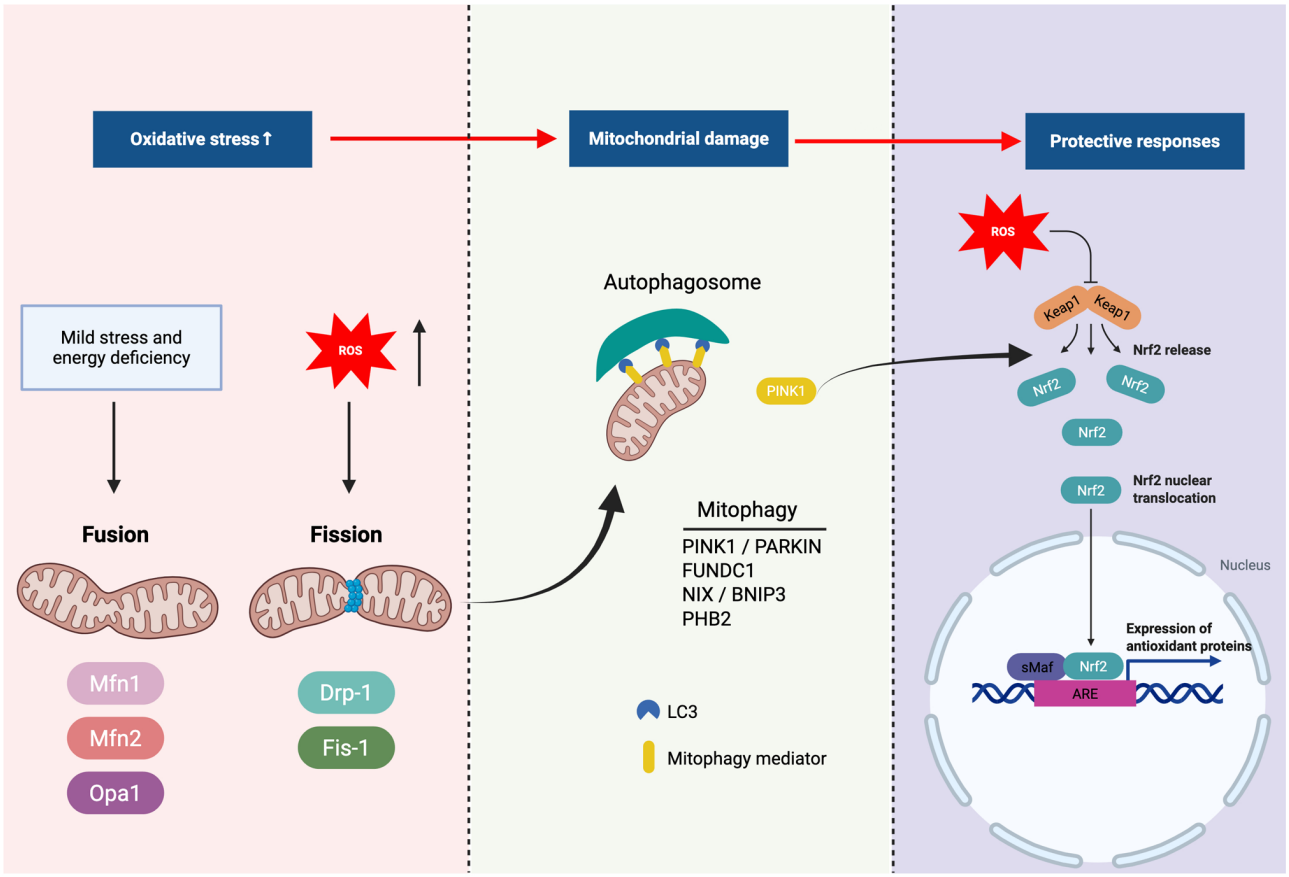


Figure 2. Mitochondrial stress responses following ROS-induced damage and the protective signaling pathways that maintain mitochondrial quality. ROS overproduction disrupts mitochondrial dynamics, leading to altered fusion (mediated by Mfn1 and 2, and Opa1) and fission (promoted by Drp1 and Fis1). Damaged mitochondria activate mitophagy, in which PINK1 accumulates on the outer mitochondrial membrane to recruit PARKIN, an E3 ubiquitin ligase, facilitating ubiquitination of outer membrane proteins. Receptors such as FUNDC1, NIX and BNIP3 interact with LC3 to promote autophagosome formation, while PHB2 functions as an inner membrane mitophagy receptor. Additionally, the Keap1-Nrf2-ARE signaling axis provides antioxidant defense, with sMaf proteins serving as transcriptional partners of Nrf2 in activating antioxidant response elements. These pathways together coordinate mitochondrial turnover and cytoprotective responses. ROS, reactive oxygen species; Mfn1, mitofusin 1; Mfn2, mitofusin 2; Opa1, optic atrophy 1; Drp1, dynamin-related protein 1; Fis1, fission protein 1; PINK1, PTEN-induced kinase 1; PARKIN, E3 ubiquitin ligase involved in mitophagy; FUNDC1, FUN14 domain-containing protein 1; NIX, BCL2/adenovirus E1B 19 kDa protein-interacting protein 3-like; BNIP3, BCL-2/adenovirus E1B 19 kDa protein-interacting protein 3; LC3, microtubule-associated protein 1 light chain 3; Nrf2, nuclear factor erythroid 2-related factor 2; sMaf, small musculoaponeurotic fibrosarcoma oncogene homologs that dimerize with Nrf2; Keap1, Kelch-like ECH-associated protein 1; ARE, antioxidant response element; PHB2, prohibitin 2.

promotes IVD repair by protecting mesenchymal stem cells from oxidative stress via the Nrf2/Thioredoxin-interacting protein/NLRP3 axis, which reduces inflammation and cellular apoptosis (55). Additionally, astaxanthin activates the Nrf2/HO-1 pathway, which suppresses oxidative stress and prevents cartilage endplate degeneration by inhibiting apoptosis and the degradation of the ECM (56).

*Other regulatory molecules or bioactive substances*

*Deacetylases [such as sirtuin (SIRT)3 and 1].* SIRT family proteins serve essential roles in mitochondrial homeostasis, redox balance and the regulation of energy metabolism (25,28). For example, SIRT3, localized in mitochondria, deacetylates and activates key antioxidant enzymes such as manganese superoxide dismutase (SOD2), isocitrate dehydrogenase 2 and catalase, which enhances mitochondrial ROS detoxification (28). Upregulation of SIRT3 suppresses cellular senescence and inflammation in joint cells.

A study by Guo *et al* (57) reveals that dysregulation of SIRT3 and its metabolic network, including downstream effectors such as isocitrate dehydrogenase 2 and manganese SOD, serves a role in mitochondrial oxidative stress and cartilage degradation in OA. This suggests that restoring the activity of SIRT3 may serve as a therapeutic approach to delay joint degeneration (57).

*AMP-activated protein kinase (AMPK)-peroxisome proliferator-activated receptor γ coactivator 1-α (PGC-1α) pathway.* The AMPK-PGC-1α signaling axis promotes mitochondrial biogenesis and the expression of antioxidant enzymes. A study by Yang *et al* (58) demonstrates that exposure to advanced glycation end-products represses the AMPKα-SIRT1-PGC-1α pathway in osteoarthritic chondrocytes, with reductions in PGC-1α expression levels compared with untreated control cells, resulting in impaired mitochondrial biogenesis and antioxidant defense. However, the study by Li *et al* (59) demonstrates that adipokine omentin-1 can activate the AMPK-PGC-1α pathway, promoting mitochondrial biogenesis in chondrocytes and slowing OA progression. The study by Yang *et al* (58) demonstrates that advanced glycation end products inhibit the AMPK-SIRT1-PGC-1α pathway,

which induces mitochondrial dysfunction and inflammation in chondrocytes. This suggests the antioxidant and anti-aging properties of the AMPK-SIRT1-PGC-1α pathway (58).

Additionally, the study by Guo *et al* (57) reveals that activation of the AMPK-PGC-1α pathway not only restores energy metabolism but also reduces the accumulation of ROS and the expression of proinflammatory cytokines, including IL-1β, IL-6 and TNF-α, in degenerative joint diseases. This demonstrates its potential role as a therapeutic axis (57).

*Itaconate derivatives (such as 4-octyl itaconate).* A previous study indicates that exogenous itaconate reduces inflammatory responses and inhibits the generation of mitochondrial ROS (54). Zinc-based metal-organic super containers, such as 4-octyl itaconate (4-OI)@Zn-NH-pyr, demonstrates enhanced mitochondrial targeting and ROS-scavenging activity compared with free 4-OI alone, which alleviates proinflammatory states in arthritis models (54).

Additionally, novel mitochondria-targeted nanomedicines such as $Mn_3O_4$/UIO-TPP nanozymes scavenge mitochondrial ROS and restore mitochondrial function in OA cartilage, demonstrating potential therapeutic effects in rat models with anterior cruciate ligament transection induced OA (60,61). These nanozymes represent a promising material-based extension of mitochondrial antioxidant therapy and support the feasibility of precision mitochondria-targeted intervention (62).

*Crosstalk between mitochondria and the endoplasmic reticulum (ER) in joint degeneration.* Mitochondria and the ER are functionally connected via mitochondria-associated membranes, which coordinate calcium signaling, lipid exchange and cellular stress responses. In degenerative joint diseases, this interplay becomes dysregulated, which contributes to oxidative injury and inflammation (63).

ER stress promotes the release of $Ca^{2+}$ through inositol 1,4,5-trisphosphate receptors, while excessive uptake of $Ca^{2+}$ by the mitochondria via the mitochondrial calcium uniporter leads to the overproduction of ROS, mitochondrial dysfunction and apoptosis (14). Furthermore, ER stress activates proapoptotic pathways (such as protein kinase R-like ER kinase-activating transcription factor 4-CHOP) and promotes the activation of the NLRP3 inflammasome (64).

In addition, ion channels (such as transient receptor potential cation channel, subfamily V, member 4) participate in mechano-oxidative signaling in joint cells, and their dysregulation may further exacerbate mitochondrial stress (65). Targeting ER-mitochondria interactions or associated $Ca^{2+}$ channels may offer new therapeutic avenues in OA, IVDD and RA.

## 6. Crosstalk in immunometabolism: Mitochondrial oxidative stress and the immune system in degenerative joint diseases

Mitochondrial oxidative stress not only contributes to direct tissue damage but also serves a role in modulating immune responses, which are involved in the pathogenesis of OA, IVDD and RA. Both innate immune cells, such as macrophages, dendritic cells, neutrophils and natural killer cells, and adaptive immune cells, including T cells and B cells, respond to and are regulated by mitochondrial metabolism and ROS signaling, forming an interconnected immunometabolic axis (66,67).

*Innate immunity and mitochondrial ROS.* Innate immune cells, such as macrophages and neutrophils, are sensitive to mitochondrial ROS. In RA and IVDD, macrophages polarize toward a proinflammatory (M1-like) phenotype under oxidative stress conditions, leading to an enhanced production of TNF-α, IL-1β and IL-6, which further exacerbates tissue inflammation and matrix degradation (68). Mitochondrial ROS act as secondary messengers to activate the NLRP3 inflammasome, a key inflammatory complex that promotes caspase-1 activation and IL-1β/IL-18 maturation, which accelerates pyroptosis in disc and synovial tissues (69).

Neutrophils also exhibit enhanced respiratory bursts and NETosis in the presence of mitochondrial ROS, which contributes to synovial inflammation and cartilage degradation in RA (70). Toll-like receptors (TLRs), especially TLR2 and 4, recognize damage-associated molecular patterns (such as mitochondrial DNA and cardiolipin) that are released from stressed mitochondria. This activates the myeloid differentiation primary response protein 88-dependent signaling pathway and NF-κB-induced transcription of proinflammatory cytokines, including TNF-α, IL-1β and IL-6 (71,72).

*Adaptive immunity and oxidative microenvironment.* T cell differentiation and function are dependent on metabolism. Under elevated ROS conditions, mitochondrial dysfunction promotes a T helper 17 phenotype in $CD4^+$ T cells, promoting proinflammatory responses in RA and OA synovium (73,74). Regulatory T cells, which rely on oxidative phosphorylation for their function, are suppressed in oxidative microenvironments, which further amplifies inflammation (73).

B cells are also influenced by mitochondrial metabolism, with mitochondrial ROS promoting autoantibody production and immune complex deposition in RA (75). Mitochondria-targeted antioxidants such as MitoQ and SkQ1 dampen the activation of T cells and the secretion of cytokines, suggesting that the modulation of mitochondrial ROS may re-establish immune homeostasis in degenerative joint diseases (76).

*Cytokines, chemokines and the mitochondrial stress response.* Cytokines, such as IL-1β, TNF-α and IL-6, are not only induced by mitochondrial ROS but also feedback to further disrupt mitochondrial integrity and function. These cytokines impair mitochondrial membrane potential, increase the generation of ROS and inhibit mitophagy, forming a positive feedback loop of oxidative inflammation (77). However, anti-inflammatory cytokines (such as IL-10) may promote mitophagy and mitochondrial quality control by activating pathways such as SIRT3 or AMPK-PGC-1α (78).

Chemokines, such as chemokine (C-C motif) ligand 2 and chemokine (C-X-C motif) ligand 8, recruit immune cells into inflamed joints and are also modulated by mitochondrial oxidative stress (70). Therefore, therapeutic strategies targeting mitochondrial pathways may reduce tissue damage and immune cell infiltration.

## 7. Clinical prospects and challenges

*Limitations of animal models and preclinical studies.* Although mitochondria-targeted antioxidants such as MitoQ, MitoTEMPO and SkQ1 reveal notable protective effects on joints in animal models (including rodents such as mice and rats, mid-sized models such as rabbits, and large animals such as dogs and sheep), the pathological processes in animal models are more acute or controlled compared with clinical populations. Therefore, these animal models do not fully replicate the chronic, long-term degenerative processes observed in humans (79). Additionally, there are notable differences in pharmacokinetics and drug sensitivity in different species (80). Therefore, translating results from animal studies into clinical applications necessitates further validation through extensive clinical trials (8,18,32).

*Administration methods and safety considerations.* The majority of studies on mitochondria-targeted antioxidants rely on intra-articular injections or local administration (79,81). Although several mitochondria-targeted antioxidants, such as MitoQ, SkQ1 (Visomitin) and to an extent MitoTEMPO, can be administered orally, systemic delivery raises concerns regarding bioavailability, mitochondrial targeting efficiency, and systemic safety profiles (2,32). Local injections also have risks of tissue trauma and infection. Advancements in drug delivery systems, such as hydrogels and nanocarriers combined with mitochondria-targeting ligands, may overcome these limitations. However, achieving efficient, sustained and localized drug release at the joint is still challenging at present (3,6,82).

*Potential side effects of long-term medication.* While drugs such as MitoQ and SkQ1 demonstrate good tolerability at low doses [for example, SkQ1 at 0.25-1.25 nmol/kg/day (0.13-0.70 $\mu$g/kg/day) in rat models and MitoQ at ~20 mg/day in human trials] (8), long-term administration (defined as continuous dosing for 3-6 months or longer in preclinical and clinical studies) requires vigilant monitoring to avoid causing redox imbalances in normal tissues. Additionally, moderate levels of ROS serve critical physiological roles in signaling and tissue repair in degenerative joint diseases. Excessive clearance of ROS may disrupt essential cellular signaling pathways (1,15). Therefore, calibrating the dose and duration of mitochondria-targeted antioxidants is crucial for clinical application.

*Combination therapies.* Numerous studies increasingly advocate for combining mitochondria-targeted antioxidants (such as MitoQ, SkQ1 and MitoTEMPO) with autophagy regulators (such as apigenin and rapamycin), inflammasome inhibitors (such as MCC950 and CTSB inhibitors), growth factors (such as TGF-β and IGF-1) or conventional anti-inflammatory medications (such as non-steroidal anti-inflammatory drugs and disease-modifying anti-rheumatic drugs) in order to achieve synergistic therapeutic effects on degenerative joint diseases (7,62). For example, combining MitoTEMPO with autophagy activators, such as salidroside, honokiol or urolithin A, simultaneously reduces excessive ROS and increases the clearance rate of damaged mitochondria, which potentially inhibits apoptosis in cartilage or intervertebral discs (83).

In addition, cellular and organelle-level strategies enhance mitochondrial restoration. One such approach is mitochondrial transplantation, in which healthy exogenous mitochondria are delivered into dysfunctional cells to rescue energy production and reduce oxidative stress (84). Recent studies demonstrate that mitochondrial transplantation improves joint tissue homeostasis and attenuates degeneration in *in vitro* chondrocyte and NP cell models, as well as *in vivo* mice with destabilization of the medial meniscus-induced OA and rat with needle puncture-induced IVDD models (85,86). This strategy may be biologically complementary to chemical antioxidant therapies.

Furthermore, future therapeutic paradigms may involve mitochondrial genome editing to correct mitochondrial DNA mutations that are associated with joint degeneration. Emerging tools such as mitochondria-targeted zinc finger nucleases and mitochondria-targeted transcription activator-like effector nucleases demonstrate potential in restoring mitochondrial integrity and function in tissues with OA (87,88). Although these technologies are still mostly experimental, they could potentially be used in precision mitochondrial medicine for degenerative joint diseases in the future (87).

## 8. Conclusions

Mitochondrial dysfunction and an excessive generation of ROS are central pathological mechanisms underlying degenerative joint diseases, including OA, IVDD and RA. The present study demonstrated the role of mitochondrial oxidative damage in promoting disease progression, from the degradation of the cartilage ECM in OA and NP cell death in IVDD, to chronic synovitis and immune activation in RA. Mitochondria-targeted antioxidants, such as MitoQ, MitoTEMPO, SkQ1 and SS-31, demonstrate potential in mitigating oxidative stress and slowing disease deterioration. These findings provided theoretical support for a paradigm shift from symptom-based management toward mitochondria-centered interventions.

At present, despite promising preclinical data, the evidence is mostly limited to *in vitro* and small-animal studies, such as mice and rats, with scarce validation in human tissues or large-scale clinical settings. Additionally, the heterogeneity of degenerative joint diseases further complicates the interpretation of therapeutic efficacy. In particular, differences in mitochondrial activity, ROS levels and drug responsiveness among OA, IVDD and RA are yet to be fully characterized. Furthermore, the lack of multicenter randomized clinical trials evaluating dosing, safety profiles and delivery methods for mitochondria-targeted antioxidants is a notable limitation. Additionally, the majority of studies overlook long-term outcomes and potential off-target effects, especially in elderly or comorbid populations.

Future studies should investigate the temporal and spatial regulation of mitochondrial ROS in specific joint tissues and immune cell subpopulations. In particular, the association between mitochondrial dysfunction and epigenetic regulation, cytokine signaling or metabolic reprogramming warrants further investigation. Elucidating how mitochondrial stress interacts with cartilage calcification, subchondral bone

remodeling and synovial hyperplasia may reveal additional therapeutic checkpoints. The use of advanced models such as patient-derived organoids, single-cell mitochondrial profiling and spatial transcriptomics may aid mechanistic investigations. Additionally, mitochondrial-nuclear crosstalk or sex-specific mitochondrial responses should also be investigated in the future.

Clinical translation should prioritize the development of delivery systems, including hydrogels, nanoparticles and scaffold-based platforms that enable a localized, sustained release of mitochondria-targeted antioxidants (such as MitoQ, MitoTEMPO or SkQ1). Additionally, their combination with autophagy enhancers (such as rapamycin, spermidine or resveratrol) or regenerative factors [such as bone morphogenetic proteins (BMP)-2 and -7] or TGF-β) at degenerative sites should be investigated. Furthermore, integrating mitochondria-targeted antioxidants with mitophagy enhancers (such as rapamycin, urolithin A and salidroside), immune modulators (such as IL-17A antibodies, Treg enhancers and fumaric acid derivatives) or regenerative therapies (such as stem cells or exosome-based systems) may also offer a therapeutic effect. Such combination regimens may synergistically halt or reverse disease progression. Furthermore, precision medicine frameworks leveraging genetic, metabolic or imaging biomarkers may allow for personalized dosing and treatment selection, which may also enhance therapeutic outcomes.

Mitochondria-centered therapies involve multi-disciplinary teams from orthopedics, immunology, geriatrics and bioengineering. However, a number of controversies remain unresolved. For example, contradictory findings regarding the role of ROS as only deleterious vs. the role of ROS as signaling mediators in joint homeostasis. Moreover, the possibility that prolonged ROS suppression might impair physiological defense mechanisms or tissue remodeling should be investigated. Interdisciplinary dialogue and standardized methodological approaches will likely be required to address these issues and guide the rational design of future therapies.

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## Authors' contributions

YH designed the study and drafted the manuscript. XY summarized the comments from the reviewers, drafted the responses and contributed to manuscript revision and language editing. TZ contributed to the literature review and assisted in data interpretation. YG revised the manuscript. JS designed the present study, revised the manuscript and supervised the project. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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