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REVIEW

The Pathophysiological Role of Mitochondrial Oxidative Stress in Rheumatic Diseases

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Abstract: Mitochondria play a crucial role in reactive oxygen species (ROS)-dependent rheumatic diseases, including ankylosing spondylitis, osteoarthritis (OA), systemic lupus erythematosus (SLE) and scleroderma. Mitochondrial DNA (mtDNA), which encodes mitochondrial proteins, is more vulnerable to oxidants compared to nuclear DNA. When mtDNA gets damaged, it leads to mitochondrial dysfunction, such as electron transport chain impairment and loss of mitochondrial membrane potential. Moreover, the damaged mtDNA functions as a damage-associated molecular pattern (DAMP), triggering inflammatory and immune responses. In this review, ROS-related transcription factors and downstream cell signaling pathways are investigated. It also explains the mechanism of mitochondrial dysfunction and the clinical significance of major rheumatic diseases, as well as the clinical transformation status of key antioxidants, the risks/reasons for promoting mitochondrial ROS research in rheumatic diseases, and antioxidant therapy. We conclude that targeting oxidative stress with antioxidant agents,such as polyphenols, garlic, pomegranate, Coenzyme Q10, probiotic, α-lipoic acid, N-acetylcysteine (NAC), selenium, microalgae, fucoidan, resveratrol, quercetin, and curcumin should be considered as promising new strategies for treating rheumatic diseases lacking effective treatments.

Keywords: mtDNA, ROS, antioxidant agents, rheumatic diseases, inflammatory

Introduction

Rheumatic diseases represent a pervasive global health challenge, affecting approximately 1.71 billion people worldwide, with osteoarthritis (OA) and rheumatoid arthritis (RA) contributing to 17.1% and 1.3% of global disability, respectively.[1] Low- and middle-income regions bear >80% of the global rheumatic disease burden yet receive <10% of targeted research funding. The resultant economic strain is profound, with annual direct medical expenditures surpassing $328.6 billion and indirect productivity losses exceeding $181.1 billion.[2] Mechanistically, reactive oxygen species (ROS) induced mitochondrial damage significantly elevates mortality, evidenced by a 2.31-fold increased risk of cardiovascular death in advanced rheumatoid arthritis cohorts.[3] These converging epidemiological, economic, and pathophysiological insights necessitate urgent advancement in redox-focused therapeutic strategies.

Human joints are exposed to high oxygen levels. Due to their large surface area and high blood supply, joint sites are prone to oxidative stress-mediated damage.[4–6] The pathological process of rheumatism is closely associated with the damage inflicted by ROS and mitochondria. Moreover, currently, the popular targets for rheumatism treatment involve the regulation of mitochondrial function, the elimination of ROS, and the alleviation of oxidative stress.[7,8] Furthermore, damage to the antioxidant defense system of cells in other organs affected by rheumatism can also result in increased levels of endogenous ROS in tissues.

Mitochondria perform multiple functions in maintaining cell homeostasis. When these functions are disrupted, it can either cause or contribute to disease. For example, mechanisms including cellular energy generation, homeostatic control

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of mitochondrial volume, programmed cell death pathways, extracellular dissemination of organellar constituents, and their subsequent modulation of inflammatory processes or autoimmune pathologies demonstrate this interconnected relationship.[9] In this review, this analysis highlights ROS-mediated mitochondrial homeostatic imbalance and genomically compromised Mitochondrial DNA (mtDNA) species as pathomechanistic drivers in progressive rheumatological disorders, serving as critical mediators through their capacity to potentiate oxidative cascades and activate innate immune surveillance mechanisms. These findings suggest that antioxidants have the ability to neutralize free radicals and regulate oxygen redox reactions. This, in turn, can boost glutathione(GSH) biosynthesis, improve chromatin remodeling, and reduce rheumatic inflammation. Additionally, we will discuss different dietary and pharmacological methods for elevating antioxidant levels in relation to rheumatism and their beneficial impacts on a wide range of rheumatic diseases.

The established etiological linkage between redox imbalance and rheumatological pathologies has catalyzed scientific prioritization of elucidating molecular circuitry governing ROS biosynthesis and scavenging systems, alongside engineering precision redox modulators targeting dual-axis intervention-suppressing free radical genesis while amplifying endogenous antioxidant clearance capacity-as innovative disease-modifying strategies. Importantly, Accumulating evidence from recent clinical investigations has revealed significant limitations in therapeutic strategies aimed at modulating global ROS activity.[10] Notably, clinical trials employing systemic antioxidant administration, particularly those utilizing vitamin C and vitamin E supplementation, have demonstrated limited efficacy in alleviating pathological manifestations of rheumatic diseases.[11,12] This therapeutic gap may stem from the dual role of ROS in both inflammatory signaling and tissue homeostasis,[13] suggesting the need for more targeted modulation strategies. Mounting experimental validation from transgenic rodent paradigms demonstrates mechanistic convergence between mitochondriogenic reactive species (mtROS) overgeneration and defective redox-buffering systems with rheumatological pathogenesis, wherein pathological redox flux through Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase-coupled pathways synergistically instigates metainflammatory cascades characteristic of progressive arthropathies. In this review, we comprehensively examines endogenous generators of ROS within cellular environments, analyzes the pathophysiological implications of oxidative stress in rheumatologic disorders, evaluates recent findings connecting mitochondrial-derived ROS to disease pathogenesis, assesses the therapeutic potential of redox-modulating interventions in rheumatology, and highlights novel developments in organelle-specific antioxidant strategies with particular relevance to autoimmune connective tissue diseases.

Exogenous and Endogenous ROS

The biologically significant ROS and RNS encompass both free radicals and highly reactive molecules, notably hydrogen peroxide (H_2O_2), superoxide anion (O_2^-), hydroxyl radical (•OH), nitric oxide (NO•), and peroxynitrite ($ONOO^-$).[14] Significantly, these oxidants are endogenously produced during mitochondrial oxidative phosphorylation. In aerobic organisms, molecular oxygen (O_2) functions as the terminal electron acceptor. In particular, the generation of ROS, which encompasses organic peroxides, takes place as an unavoidable by-product of the activity of the electron transport chain during cellular respiration.[15] Crucially, this redox paradox is evolutionarily conserved: while aerobic metabolism enables efficient energy production through O_2 utilization, it simultaneously establishes a persistent oxidative burden. This dual-edged mechanism underlies both physiosteoarthritisological redox signaling and pathological oxidative damage, with mitochondrial respiration accounting for >90% of cellular ROS generation in metabolically active tissues.

ROS plays an important role in development.It may activate the NOD-like receptor thermal protein domain associated protein 3-inflammasone (NLRP3 inflammasome). This molecular pathway initiates pronounced upregulation of pivotal inflammatory mediators (IL-1β and IL-18), driving progressive synovial tissue inflammation and accelerating articular cartilage matrix breakdown via perpetuating activation of NF-κB-mediated transcriptional regulatory circuits.[16] Age-related mitochondrial dysfunction is associated with decreased superoxide dismutase 2(SOD_2) activity and increased mitochondria-produced ROS, partly due to the increase of ROS in chondrocytes with age.[17] Collectively, the disruption of redox homeostasis characterized by overwhelmed antioxidant defenses and persistent oxidant overproduction constitutes a central pathogenic axis in ROS-driven rheumatic disorders, spanning from localized OA to systemic autoimmune conditions.

Methotrexate, a folic acid metabolism inhibitor initially developed for treating malignancies, has now emerged as a cornerstone therapy for rheumatoid arthritis.[18] Its immunomodulatory effects are mediated through the induction of ROS,

with ROS accumulation playing a pivotal role in T-cell cytotoxicity.[19] Studies demonstrate that it reduces antioxidant enzyme activities such as superoxide dismutase (SOD) and catalase (CAT), while elevating caspase-3 expression to trigger apoptosis.[20]

Regarding oxidative stress mechanisms, the drug may disrupt redox balance by inhibiting NADPH metabolism. In the pentose phosphate pathway, NADPH serves as a critical cofactor for glutathione reductase to maintain cellular GSH levels a central antioxidant. Methotrexate-induced GSH depletion compromises systemic antioxidant defenses.[21] Additionally, it induces mitochondrial dysfunction characterized by reduced dehydrogenase activity, altered membrane potential, diminished Adenosine Triphosphate (ATP) synthesis, and enhanced lipid peroxidation (LPO).[22]

Notably, while experimental studies confirm its pro-oxidant effects, clinical observations suggest potential antioxidant properties. When combined with glycosides for managing rheumatic diseases, concurrent reductions in inflammatory markers and oxidative stress indicators have been documented.[23] Comparative studies in female rheumatoid arthritis patients revealed characteristic changes in methotrexate-treated groups, including decreased LPO levels and elevated GSH concentrations compared to untreated controls.[24] Furthermore, the drug modulates the expression of multiple inflammation-associated cytokines and alters inflammatory response patterns in immune cells.[25]

Research indicates that melatonin can alleviate methotrexate-induced hepatorenal damage by modulating oxidative stress markers. Animal studies demonstrate its efficacy in counteracting methotrexate-triggered elevation of malondialdehyde (MDA) content, abnormal myeloperoxidase activity, and GSH depletion in hepatic and renal tissues.[26] A-Lipoic acid exhibits notable hepatoprotective effects against methotrexate toxicity. Functioning as a natural coenzyme in the pyruvate dehydrogenase complex, this endogenous mitochondrial compound is frequently utilized as a dietary supplement due to its antioxidant capacity.[27] Murine models reveal that α-lipoic acid significantly reduces methotrexate-induced lipid peroxidation, protein carbonylation, and mitochondrial hydroxyl radical levels while restoring antioxidant defense mechanisms.[28] N-acetylcysteine (NAC) has been shown to reverse methotrexate's inhibitory effects on GSH, SOD, and CAT in hepatic specimens while decreasing MDA concentrations.[29] In rheumatoid arthritis models, the endogenous antioxidant carnosine demonstrates therapeutic potential. This dipeptide, predominantly distributed in skeletal muscle, myocardium, liver, and central nervous system, plays crucial roles in maintaining redox homeostasis and scavenging reactive oxygen species.[30] Compared to methotrexate monotherapy, combination with carnosine significantly reduces plasma lipid peroxides and C-reactive protein levels.[31] Furthermore, combined administration of methotrexate with vitamins A, C, and E exhibits synergistic benefits in ameliorating disease biomarkers.[32]

Mitochondrial Metabolism and functions

Historically viewed as the cell's primary energy-generating hubs and metabolic controllers, mitochondria have increasingly revealed multifaceted biological roles over time. Contemporary research recognizes these sophisticated organelles as dynamic signaling centers that mediate communication within and between cells via release of proteins, mitochondrial DNA, lipid compounds, metabolic intermediates, and reactive oxygen species. Furthermore, certain mitochondrial constituents possess the ability to directly trigger immune responses by interacting with pattern recognition systems.

The dynamic equilibrium of mitochondrial fusion-fission cycles orchestrates ultrastructural architecture and subcellular positioning dynamics of these organelles, serving as critical determinants of multifaceted functional competencies ranging from genomic nucleoid partitioning and bioenergetic output optimization to reactive species homeostasis and programmed cell death initiation. Furthermore, these continuous remodeling processes mediate bidirectional communication with cellular metabolic states through pleiotropic mechanisms, thereby establishing mitochondrial dynamics as a pivotal modulator of interorganellar signaling networks and systemic stress adaptation mechanisms.[33]

While mitochondrial dynamics establish the structural foundation for cellular energy distribution and quality control,[34] perturbations in fission, fusion, and mitophagy directly precipitate functional deficits.[35] This highlights the critical role of mitochondrial remodeling and dysfunction in immune cell activation. Specifically, aberrant dynamics impair oxidative phosphorylation system (OXPHOS) efficiency, disrupt metabolite flux, and trigger pathological ROS production.[35–37] These metabolic disruptions fundamentally reprogram immune cell metabolism,[38] redirecting bioenergetic pathways toward chronic inflammation and autoimmunity.[39] Consequently, mitochondrial dysfunction manifests as profound metabolic reprogramming, a hallmark of pathogenic immune responses in autoimmune diseases.[40] Autoimmune disorders originate from the immune system's misguided assault on healthy tissues, triggering inflammatory

responses and tissue destruction. Distinct disease entities demonstrate characteristic immunometabolic disturbances during pathogenesis: In RA, immune cells exhibit dynamic metabolic profile alterations and mitochondrial/lysosomal dysfunction correlating with disease progression. Systemic lupus erythematosus (SLE) manifests type I interferon-driven metabolic dysregulation in immune cells, establishing a vicious cycle between cellular activation states and metabolic reprogramming. Mitochondrial abnormalities in systemic sclerosis reshape fibroblast metabolism and modulate immune responses. Patients with idiopathic inflammatory myopathies (IIM) commonly present mitochondrial dysfunction and metabolic derangements, while primary Sjögren's syndrome (pSS) features disrupted metabolic networks in immune cells accompanied by mitochondria-mediated cellular damage. Serving as a critical interface between cellular energy demands and immune dysregulation, metabolic reprogramming drives inflammatory progression, tissue injury, and clinical manifestations across these conditions, while simultaneously governing essential immune functions including cellular differentiation, proliferation, and effector molecule secretion. This comprehensive analysis evaluates the therapeutic potential of metabolic pathway modulation in reestablishing immune homeostasis, proposing conceptual frameworks for advancing mechanistic understanding and therapeutic innovation in autoimmune diseases.

Rheumatic diseases are a complex group of disorders involving various abnormal conditions. These include joint pain, stiffness, swelling, and reduced mobility, often accompanied by systemic manifestations such as fatigue, fever, and organ-related symptoms. These symptoms occur simultaneously and increase the risk of joint deformity, functional impairment, and even impact on internal organs like the heart, lungs, and kidneys (Figure 1). Rheumatic diseases have emerged as a major health concern in modern society, imposing a significant social, personal, and economic burden in both developing and developed countries.[1,41–45] Previous research has shown the interaction between genetic factors and environmental triggers that contribute to the increasing prevalence of rheumatic diseases.[46–48] A number of studies suggest the role of oxidative stress and mitochondrial dysfunction in the development of rheumatic diseases, as well as in their progression and associated complications.[49–51] However, the fundamental mechanisms underlying the pathogenesis of rheumatic diseases are still not fully understood.

Beyond serving as cellular powerhouses, mitochondria emerge as pivotal regulators of oxidative stress-mediated inflammatory cascades and programmed cell death,[52] highlighting their growing significance in autoimmune pathology.

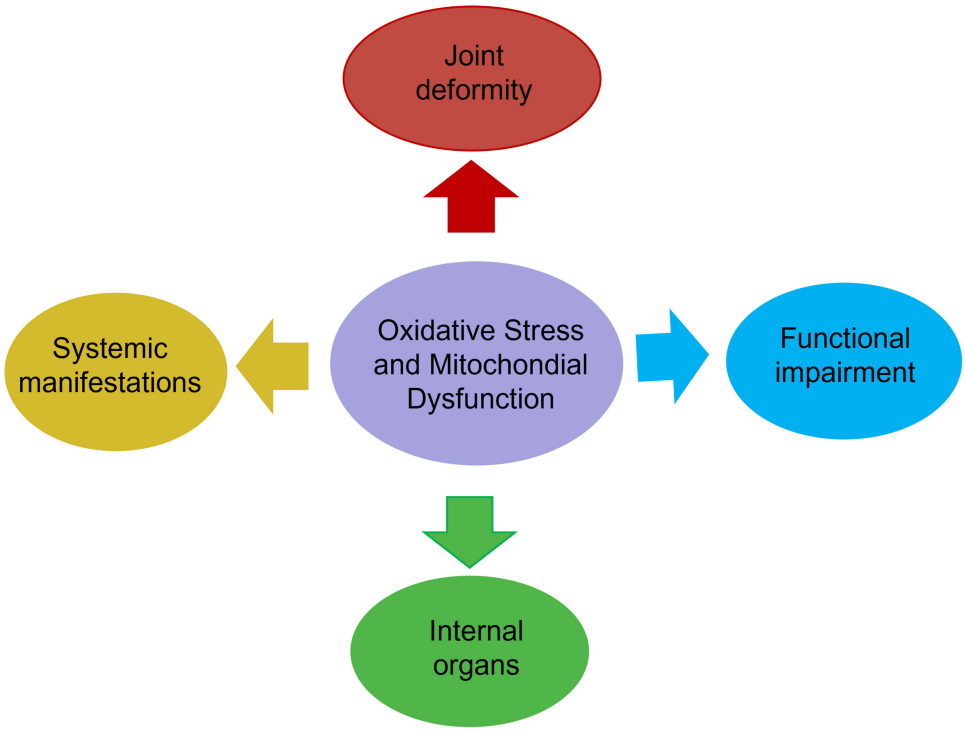

Figure 1 Risk factors associated with rheumatic diseases.

Mitochondrial aberrations constitute a hallmark feature in myopathies,[53] with dysfunctional mitochondrial activity being central to IIM pathogenesis.[54] Initial investigations suggested preserved environmental adaptability in mitochondria of human-derived IIM myoblasts without overt functional impairment,[55] yet these cells demonstrated heightened vulnerability to oxidative insults, correlating with elevated mortality rates. This observation implies mitochondrial dysregulation may directly contribute to muscular weakness and atrophy in IIM patients.[56] Experimental evidence reveals that abnormal mitochondrial genome copy number expansion precipitates functional deficits, potentially initiating polymyositis/dermatomyositis (PD/DM), while disease-specific accumulation of single nucleotide polymorphisms (SNPs) strengthens this association. Comprehensive analyses of muscle tissues from dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM) patients demonstrate profound alterations in mitochondrial architecture, genetic material, proteomic profiles, and functional networks, underscoring the centrality of mitochondrial energy metabolism in disease progression. These pathological changes correlate with disrupted tricarboxylic acid cycle activity, suppressed oxidative phosphorylation, and excessive ROS generation, collectively driving oxidative damage, myofiber inflammation, and strength deterioration.[57] Functioning as metabolic hubs, mitochondria orchestrate cellular homeostasis through metabolic reprogramming and immune signaling modulation.[57] During respiratory metabolism, mitochondrial-derived metabolites potentiate proinflammatory cell activation and autoimmune cytokine production, thereby perpetuating inflammatory milieus within affected muscle tissues.[52]

PSS is characterized by prominent mitochondrial anomalies and oxidative injury. Oxidative stress persists throughout the disease continuum, with subclinical oxidative damage escalation and glandular disintegration potentially initiating during early pathogenesis.[58] Investigations on salivary gland epithelial cells demonstrate abnormal mitochondrial morphometrics and functional impairment, constituting critical pathogenic determinants.[59] Compromised mitochondrial integrity facilitates cytoplasmic release of mtDNA as damage-associated molecular patterns (DAMPs), instigating inflammatory cascades via cGAS-STING signaling activation and type I interferon pathway dominance.[60,61] At the immunometabolic interface, mitochondrial dysregulation and redox imbalance profoundly modulate cellular metabolism: aberrant lipid metabolism in T lymphocytes compromises chemotactic and tissue-retention capacities,[62] while proinflammatory macrophage polarization towards glycolytic metabolism starkly contrasts with anti-inflammatory phenotypes, collectively forming intricate pathophysiological networks.[63,64] Proteomic profiling of salivary epithelium reveals energy metabolism pathway remodeling, indicating intrinsic connections between metabolic disturbances and clinical manifestations.[65] Mitochondrial damage further induces immune cell metabolic reprogramming, with mitochondrial-derived DAMPs activating B/T lymphocytes to generate effector molecules that mediate programmed cell death and senescence in salivary gland epithelial cells.

The PINK1/Parkin pathway represents the primary mechanism for selective mitophagy. Activated by mitochondrial depolarization, typically from oxidative stress.[66] Stabilized PINK1 kinase on the outer mitochondrial membrane (OMM) phosphorylates ubiquitin and the E3 ligase Parkin, triggering Parkin's translocation.[67] Parkin subsequently decorates OMM proteins with ubiquitin chains.[68] Phospho-ubiquitin chains then recruit autophagy adaptors (eg, OPTN, NDP52), which tether damaged mitochondria to LC3-II-labeled phagophores for lysosomal degradation.[69] This cascade is essential for eliminating dysfunctional mitochondria.[70]

A critical reciprocal relationship exists between PINK1/Parkin mitophagy and oxidative stress. While ROS are a major instigator of mitochondrial damage that initiates the pathway,[15] failure of mitophagy conversely exacerbates redox imbalance.[71] Impaired clearance leads to accrual of ROS-generating, defective mitochondria.[68] This establishes a self-reinforcing cycle: accumulated ROS inflict further mitochondrial injury, and damaged organelles leak more ROS.[72] This environment promotes NLRP3 inflammasome activation via mitochondrial ROS and releases mtDNA that function as DAMPs, amplifying inflammation through cGAS-STING signaling.[73] Consequently, PINK1/Parkin dysfunction and its oxidative stress-inflammation axis are increasingly implicated in chronic inflammatory disorders including rheumatic diseases.[74]

ROS-Induced mtDNA Damage

The pathogenesis of rheumatic diseases, such as RA and SLE, is closely associated with mitochondrial dysfunction. The human mitochondrial DNA constitutes a closed-loop double-stranded DNA structure spanning 16.6 kilobase pairs (kbp), harboring a conserved genetic complement of 37 evolutionarily conserved loci. These include: thirteen protein-coding

sequences specifying core catalytic components of the OXPHOS (Complexes I, III–IV, and V); a complete mitochondrial translation machinery comprising 22 transfer RNA genes facilitating codon recognition, alongside 2 ribosomal RNA constituents forming the structural scaffold of mitochondrial ribosomes. A single mitochondrion contains 2–10 copies of mtDNA, and each cell harbors approximately 100 mtDNA copies. Proteins encoded by mtDNA account for 3% of total mitochondrial proteins.[75] These proteins regulate key molecules such as 8-oxoguanine glycosylase (OGG_1), aconitase 2 (ACO_2), and mitochondrial transcription factor A (Tfam), thereby participating in oxidative stress responses and inflammatory signaling pathways.[76]

The structural vulnerability profile of mtDNA arises from three cardinal determinants: anatomic colocalization with ETC bioenergetic microdomains generating ROS flux saturation, absence of nucleosome-based chromatin architecture providing epigenetic shielding, and deficient enzymatic repair machinery repertoire. Collectively, these molecular liabilities render mtDNA demonstrates an 50-fold increased vulnerability coefficient to oxidative lesion accumulation when benchmarked against its nuclear genomic counterpart.[77,78] In rheumatic diseases, chronic inflammation drives persistent generation of ROS, leading to mtDNA fragmentation and mutations, which further exacerbate mitochondrial energy metabolism dysfunction. Damaged mtDNA can be released into the cytoplasm, where it activates the cGAS-STING pathway and NLRP3 inflammasome, promoting the secretion of proinflammatory cytokines (eg, IL-1β, IL-18) and forming a "mitochondria-inflammation cycle".[73,79] Clinical studies have revealed significantly reduced mtDNA copy numbers in synovial cells of rheumatoid arthritis patients, with elevated levels of the oxidative damage marker 8-hydroxy-2′-deoxyguanosine (8-OHdG) positively correlating with disease activity (Figure 2).[80]

Damaged mtDNA Acts as a DAMP

Distinct from nuclear genomic transmission patterns, mtDNA strictly adheres to maternal inheritance. Of clinical significance, pathogenic variants in oxidative phosphorylation-related mitochondrial genes underpin the multifaceted clinicopathological manifestations observed in numerous degenerative disorders and metabolic syndromes. Following cellular damage, while autolysosomal DNase II typically processes mtDNA fragments into metabolically inert

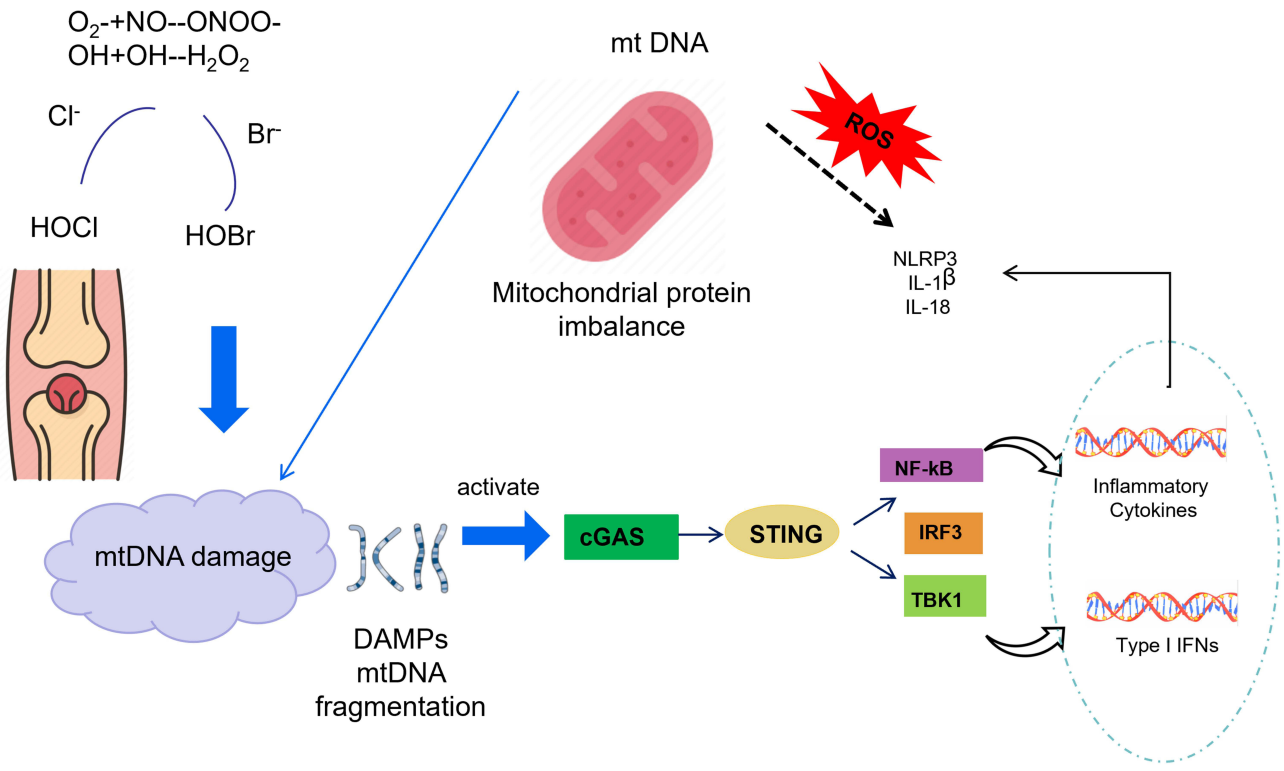

Figure 2 Proposed model for mitochondria-centered pathogenesis in ROS-induced rheumatic diseases.

nucleotides, emerging evidence implicates these degradation products in rheumatic pathogenesis. Specifically, oxidatively modified mtDNA escaping lysosomal clearance demonstrates dual functionality: extracellularly, these fragments act as DAMPs that engage Toll-like receptor 9 (TLR9) and NALP3 inflammasomes to propagate pro-inflammatory cascades via caspase-1 activation; intracellularly, they stimulate mitophagy through retrograde signaling upon mitochondrial extrusion.[76,81] Under conditions of trauma-induced critical illness, circulating mtDNA exhibits significant plasma accumulation, functioning as a canonical DAMP molecule. This pathogen-agnostic immune activator concomitantly triggers two distinct but synergistic pathways: TLR9-mediated myeloid cell priming and NACHT, LRR and NALP3 inflammasome axis activation culminating in proteolytic maturation of caspase-1. The cross-talk between these two pattern recognition systems orchestrates multiplexed inflammatory cascades through coordinated amplification of interleukin processing and NF-κB nuclear translocation events.[81,82]

Endogenous reactive oxygen species and reactive nitrogen clusters produced by chronic inflammatory responses can lead to DNA damage and genetic changes. Studies have shown that DNA damage in RA patients is increased and correlated with total oxidation status, and extracellular mtDNA is increased in synovial fluid and blood of RA patients,[83] and it is confirmed that mtDNA contains 8-oxodG residues.[84] It was found that the DNA of RA synovial genome showed microsatellite instability,[85] and there were p53 mutations mainly based on base replacement in the lining of RA synovial tissue and in cultured RA fibroblast-like synovial cells.[86] In addition, the mitochondrial membrane of RA patients was depolarized due to oxidative stress, and the transmembrane potential increased, which was conducive to the entry of mitochondrial contents into the cytoplasm and further participate in the production of autoantibodies.

Transcription Factor and Cell Signaling Pathway Changes After mtDNA Damage

NF-Kappa B (NF-κB)

The NF-κB signaling complex holds the distinction of being the chronologically identified pioneer redox-sensitive transcription factor in eukaryotic systems to demonstrate stimulus-responsive activation kinetics to pro-oxidant microenvironments, serving as a molecular rheostat for inflammatory gene induction.[87] It is critical in modulating multiple genes associated with immune and inflammatory responses.[88] Notably, diverse proinflammatory stimuli including tumor necrosis factor (TNF), interleukin-1 (IL-1), phorbol esters,bacterial lipopolysaccharides, and ultraviolet radiation serve as canonical activators of NF-κB signaling in cellular systems.

Through redox-sensitive signaling mechanisms, hydrogen peroxide (H_2O_2) exposure triggers rapid nuclear translocation of NF-κB across diverse cellular systems, thereby establishing this reactive oxygen species as a pivotal secondary messenger in prooxidant-driven NF-κB signaling cascades.

Activator Protein-1 (AP-1)

AP-1 functions as a transcriptional regulator that modulates the expression of collagen-related genes, pro-inflammatory cytokines (including TNF, IL-3, IL-8, IL-9, and IFN), cell adhesion proteins associated with atherosclerotic plaque development, and genetic components governing cell cycle progression and mitotic activities.[89] The activation dynamics of AP-1 are triggered through combinatorial exposure to redox-active metal ions in synergy with hydrogen peroxide (H_2O_2), coupled with proinflammatory cytokine signaling and diverse environmental stressors spanning biomechanical forces to xenobiotic compounds.

ROS as a Therapeutic Target for Rheumatic Diseases

The pathogenic links among excessive ROS production, oxidative damage, and autoimmune disorders (eg, rheumatoid arthritis and lupus erythematosus) have positioned ROS-scavenging interventions as a strategic focus in rheumatology. Current pharmacological innovations prioritize the amplification of endogenous antioxidant defense systems while improving ROS-neutralizing pathways (Table 1). This review synthesizes evidence from pivotal human trials investigating pan-antioxidant therapies for immune-mediated joint disorders. Preliminary clinical observations indicate that systemic antioxidant agents—such as ascorbic acid, α-tocopherol, and NAC—may demonstrate disease-modifying

Table 1 Summary of Animal Models of Mitochondrial ROS and Rheumatic Diseases Pathogenesis

Genes/Interventions	Animal Model	Phenotype/Effects	References
TNF-α overexpression	HLA-B27 transgenic rat	Spontaneous inflammatory arthritis, colitis	Taurog et al[90]
IL-23/IL-17 axis inhibition	Mouse CIA	Reduced synovitis and bone erosion	Sherlock et al[91]
MRL/lpr mouse model	MRL/lpr mouse	SLE: autoantibodies, glomerulonephritis	Theofilopoulos et al[92]
BAFF blockade	NZB/W F1 mouse (SLE)	Delayed autoantibody production, improved survival	Stohl et al[93]
HLA-DR4 transgenic	DR4-Tg mouse	Autoimmune arthritis with citrullinated peptide reactivity	Lundberg et al[94]
Anti-dsDNA antibody induction	BALB/c mouse (SLE)	Glomerular immune complex deposition	Kaliyaperumal et al[95]
NOD mouse model	NOD mouse	Sjögren's syndrome: salivary gland inflammation	Gao et al[96]
STAT4 knockout	Mouse CIA	Reduced Th1/Th17 differentiation, milder arthritis	Thieu et al[97]
IL-6 receptor antagonist	Rat adjuvant-induced arthritis (AIA)	Suppressed synovial hyperplasia	Mihara et al[98]
TGF-β1 overexpression	Transgenic mouse	Fibrosis in scleroderma-like skin disease	Krzistetzko et al[99]
CD4+ T cell depletion	Mouse K/BxN serum transfer	Attenuated joint inflammation	Kouskoff et al[100]
Rituximab (anti-CD20)	Pristane-induced lupus mouse	Reduced autoantibodies and kidney damage	Satoh et al[101]
ANKH gene mutation	Progressive ankylosis mouse (ank/ank)	Spontaneous joint calcification (ankylosis)	Ho et al[102]

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effects through reduction of synovial inflammatory responses and modulation of clinical severity indices. However, expanded studies with larger patient cohorts failed to demonstrate significant clinical benefits from long-term supplementation with vitamin C or vitamin E, while the efficacy of NAC in larger rheumatic disease populations remains to be confirmed (Table 2). Notably, the oxidative stress mechanisms in rheumatic diseases involve complex immune-inflammatory network regulation, which may partially explain the limitations of antioxidant monotherapy. Current research is shifting focus toward precision interventions targeting specific ROS signaling pathways or combining antioxidants with immunomodulatory therapies.

ROS and Ankylosing Spondylitis

Several analytical investigations have delved into mitochondrial function in ankylosing spondylitis (AS). Especially, these studies identified that the AS serum environment triggers mitochondrial dysfunction in mesenchymal stem cells (MSCs), leading to elevated ROS levels and ultimately driving MSC senescence. These findings suggest that mitochondrial dysfunction is intricately involved in AS pathogenesis and could represent a novel therapeutic target.Significantly, recent research has demonstrated the efficacy of JAK/STAT inhibitors (eg, tofacitinib and filgotinib) in AS treatment,[114,115] with evidence showing their capacity to restore mitochondrial function. This provides compelling support for the centrality of mitochondrial dysregulation in AS progression.

ROS and OA

In OA chondrocytes, mitochondrial functions,particularly MRC activity and ATP production, are markedly impaired. Critically, such mitochondrial dysregulation may drive key pathological cascades in OA, ranging

Table 2 Summary of Selected Antioxidant Threapies for Rheumatic Diseases

Therapy	Disease	Model	Summary	References
Global Antioxidants				
Curcumin	RA	Human (Clinical Trial)	Reduced joint swelling and CRP levels; inhibited NF-κB signaling	Chandran et al[103]
	SLE	MRL/lpr mouse	Decreased autoantibodies and renal inflammation	Bruschi et al[104]
Resveratrol	RA	CIA mouse	Suppressed synovial inflammation and Th17 differentiation	Elmali et al[105]
Coenzyme Q10	Fibromyalgia	Human (Clinical Trial)	Improved pain and fatigue scores	Cordero et al[106]
Mitochondria-Targeted Therapies				
Therapy	Disease	Model	Summary	References
MitoTEMPO	SLE	NZB/W F1 mouse	Reduced mitochondrial ROS, improved glomerular function	Hawtin et al[107]
MitoQ	OA	Human chondrocytes	Preserved mitochondrial membrane potential; inhibited IL-1β-induced apoptosis and MMP-13 expression	Collins et al[108]
Elamipretide	Sjögren's Syndrome	NOD mouse	Restored mitochondrial function in salivary glands; reduced lymphocytic infiltration and TNF-α levels	Mao et al[109]
NAC	SLE	Human (Clinical Trial)	Reduced oxidative stress and disease activity	Perl et al[110]
Tocilizumab (Anti-IL-6R)	RA	Human (Clinical Trial)	Suppressed synovitis and radiographic progression	Gudmann et al[111]
Baricitinib (JAK inhibitor)	RA	Human (Clinical Trial)	Reduced joint damage and inflammation	Lopez-Romero et al[112]
	Psoriatic Arthritis (PsA)	IMQ-induced mouse model	Attenuated skin and joint inflammation; decreased oxidative DNA damage	Choi et al[113]

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from oxidative stress and aberrant chondrocyte metabolism to apoptosis, inflammatory matrix breakdown, and cartilage mineralization. The underlying causes of this dysfunction span somatic mtDNA mutations and extrinsic factors like pro-inflammatory mediators (cytokines, prostaglandins) and reactive molecules (ROS, NO), both of which disrupt mitochondrial energy metabolism. Notably, mtDNA haplogroups emerge as promising biomarkers for OA stratification. Supporting this, their correlation with serum biomarker dynamics reinforces their role in OA heterogeneity and highlights their capacity to define phenotype-specific disease mechanisms.

The evidence synthesized in this review provides compelling support for the hypothesis that mitochondrial dysfunction in chondrocytes acts as a central driver of cartilage degradation initiation and progression in OA. Emerging therapeutic strategies targeting fundamental mitochondrial processes notably energy metabolism dysregulation and excessive free radical production show significant promise in OA management. To validate the mitochondrial hypothesis in OA pathogenesis, however, it is imperative to corroborate these findings through rigorous validation in clinically relevant animal models and large-scale human cohorts, such as the Osteoarthritis Initiative (OAI), Multicenter Osteoarthritis Study, or Framingham OA Cohort.[116]

ROS and SLE

Substantial evidence suggests that excessive ROS generation in SLE pathogenesis stems from dysregulated innate immune responses.Both cross-sectional and longitudinal studies have found that oxidative stress biomarkers exhibit correlations with clinical disease severity.[117,118] Furthermore, iNOS inhibitors have been shown to decrease tissue injury markers and oxidative stress parameters in experimental lupus nephritis models.[119] Notably, elevated NO levels have been linked to progressive renal impairment and diminished therapeutic responsiveness in these patients.[120]

ROS and Scleroderma

In 1993,initial investigations by Murrellproposed the therapeutic potential of free radical scavengers in scleroderma.[121] Accumulating experimental findings have delineated the mechanistic contributions of sustained oxidative stress responses as underlying drivers of pathological fibroblast differentiation and compromised microcirculatory homeostasis. Importantly, experimental studies using scleroderma animal models have revealed three key pathological mechanisms: disrupted NO homeostasis, impaired cytoprotective antioxidant systems and measurable DNA damage,[122] these biochemical alterations demonstrate significant correlations with clinical disease manifestations, particularly pulmonary fibrosis progression and elevated modified Rodnan skin scores (Figure 3).[123,124]

Therapeutic Intervention with Antioxidants

Oxidative stress triggers the activation of various transcription factors, leading to the aberrant expression of pro-inflammatory genes. This pathological cascade represents a core mechanism driving numerous chronic inflammatory disorders (Table 3). Polyphenols have emerged as promising candidates for adjuvant therapy due to their dual anti-inflammatory and antioxidant properties, which include inhibiting enzymes involved in eicosanoid production.[125,126]

Emerging clinical evidence demonstrates that garlic supplementation exerts dual antioxidant effects, with tablet formulations not only elevating serum total antioxidant capacity (TAC) but also reducing MDA concentrations. Complementing these findings, randomized controlled trials reveal that pomegranate extract administration significantly enhances glutathione peroxidase (GPx) activity relative to placebo controls.[142] Coenzyme Q10 significantly reduced malondialdehyde concentration compared to the placebo.[143] In two randomized controlled trials, the administration of melatonin led to a decrease in plasma kynurenine levels among participants in the melatonin-treated group. Concurrently, there was a notable increase in high-density lipoprotein cholesterol (HDL-C) levels.[144,145] Probiotic administration not only significantly reduced nitric oxide metabolite levels but also demonstrated elevated sulfhydryl group concentrations and enhanced total radical-trapping antioxidant capacity relative to the placebo **α**-lipoic group;[146] Another randomized controlled trial demonstrated that the active treatment substantially boosted plasma glutathione levels, with the magnitude of increase far exceeding that observed in the placebo-administered group.[147] Additionally, the intervention group receiving acid treatment exhibited a remarkable enhancement in serum total antioxidant capacity and arylesterase activity, while concurrently experiencing a substantial decrease in malondialdehyde levels.[148] NAC, as a sulfur-

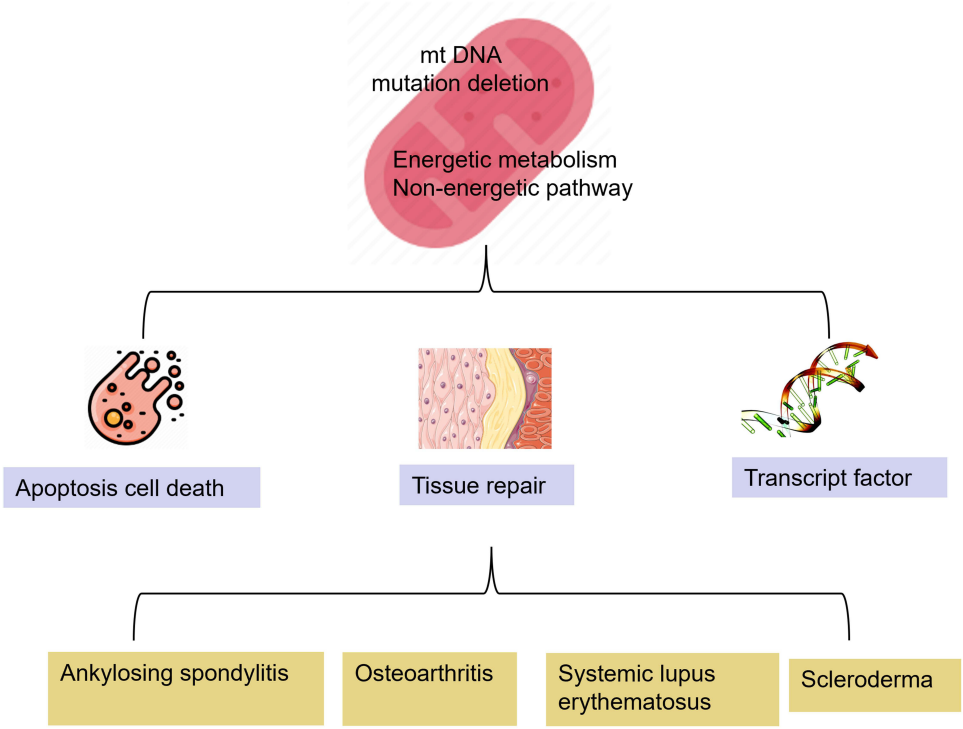

Figure 3 Mitochondrial dysfunction and diverse rheumatic diseases.

containing compound, is connected to the significant reduction in malondialdehyde, NO, IL-6, TNF, erythrocyte sedimentation rate, and C-reactive protein, plus a significant increase in total antioxidant capacity and Total Thiol Groups.[110,149] Similarly, selenium, recognized as an antioxidant, notably augmented the plasma selenium and glutathione peroxidase activity in contrast to the placebo group. Moreover, pain and joint involvement were lessened in the majority of patients treated with selenium.[150] Moreover, 12 weeks of α-tocopherol administration resulted in the oxidative alteration of lipids and proteins. When juxtaposed with the placebo, the overall inflammatory activity remained stable, except for the concentration of apolipoprotein-I, which exhibited a distinct change.[151] Aside from these influences, the compounds described earlier can all initiate other safeguarding effects in RA patients. Such effects include the suppression of joint and systemic inflammatory processes, the elevation of disease activity assessment scores and

Table 3 Comparative Antioxidant Therapeutics in Rheumatic Diseases

Disease	Promising Antioxidant(s)	Key Mechanism(s) Targeted	Evidence and Clinical Notes	References
RA	**Curcumin** (enhanced)	NF-κB inhibition, Nrf2 activation	RCT (n=45): Meriva® 1g/day = diclofenac 100mg in reducing DAS28 & CRP. Bioavailability-critical: Phospholipid formulations ↑ absorption 29-fold vs native. Synergy with DMARDs plausible.	Chandran et al[103] Cuomo et al[127]
	EGCG	MMP inhibition, JAK/STAT suppression	RCT (n=60): 500mg/day ↓ DAS28, RF, anti-CCP ($p<0.01$). Caution: Doses >800mg/day ↑ hepatotoxicity risk (ALT elevation). Limited structural benefit.	Giordano et al[128]
	Vitamin D	Th17/Treg balance, ↓ macrophage ROS	Meta-analysis: Supplementation ↓ DAS28 only in deficient patients (serum <20 ng/mL). Target: 40–60 ng/mL (2000–5000 IU/day).	Heidari et al[129] Aranow.[130]

(*Continued*)

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Table 3 (Continued).

Disease	Promising Antioxidant(s)	Key Mechanism(s) Targeted	Evidence and Clinical Notes	References
OA	**Curcumin** (enhanced)	COX-2/LOX inhibition, ↓ MMP-13	Meta-analysis (8 RCTs): ↓ pain (SMD=−0.99) and ↑ function (SMD=−1.3) vs placebo. Nano-curcumin ↑ synovial bioavailability. Better GI tolerance than NSAIDs.	Dai et al[131] Henrotin et al[132]
	EGCG	↓ ADAMTS-5, ↑ aggrecan synthesis	RCT (n=107): 540mg/day ↓ cartilage degradation biomarkers (MMP-13, CTX-II) but no significant pain relief. Bioavailability limited by poor joint penetration.	Zhong et al[133]
	Resveratrol	SIRT1 activation ↓ NF-κB, ↓ senescence	Preclinical: Protects chondrocytes from IL-1β (in vitro). Human data lacking: Bioavailability <1% limits translation. Micelle formulations show promise.	Elmali et al[134]
SLE	**Vitamin D**	↓ neutrophil ROS, ↑ Treg function	Meta-analysis: Every 10 ng/mL ↑ serum 25(OH)D ↓ SLEDAI by 0.94 (p<0.001). Deficiency doubles flare risk. Supplementation essential (2000–5000 IU/day).	Islam et al[135]
	NAC	Glutathione replenishment, ↓ NETosis	RCT (n=36): 2400mg/day ↓ SLEDAI by 3.6 vs 0.9 with placebo (p=0.002). ↓ renal flares by 50%. Dose-dependent nausea.	Lai et al[136]
	EGCG	↓ anti-dsDNA via T-cell apoptosis	Preclinical: ↓ autoantibodies and glomerulonephritis in MRL/lpr mice. No human SLE trials. Theoretical risk of hepatotoxicity at effective doses.	Wu et al[137]
Gout	**NAC**	NLRP3 inflammasome inhibition	In vitro: Blocks Monosodium Urate crystal-induced IL-1β release. No clinical RCTs. Anecdotal use in acute flares (1200–2400mg/day).	Martinon et al[138]
	Vitamin C	URAT1 inhibition mild urate-lowering	RCT (n=184): 500mg/day ↓ serum urate by 0.5 mg/dL vs placebo (p<0.01). Clinical impact minimal: No reduced flare frequency. High doses (≥2000mg) ↑ kidney stone risk.	Juraschek et al[139]
Scleroderma	**NAC** (IV/high-dose)	Glutathione ↓ vascular ROS	Open-label trial (n=40): IV NAC (5g/day) ↓ Raynaud's attacks and ulcer healing. Fibrosis data inconclusive. Oral high-dose (1800–2400mg/day) commonly used.	Salsano et al[140]
	Antioxidant Cocktails	General ROS scavenging	Trial (n=34): Alpha-Lipoic Acid (300mg) + vitamin C/E ↓ endothelial dysfunction (p=0.03). Modest symptomatic benefit; no disease modification.	Piera-Velazquez et al[141]

Notes: The upward arrows (↑) and downward arrows (↓) are used to concisely indicate changes in levels or effects within the "Evidence & Clinical Notes" column. ↑ Indicates: An increase, enhancement, or elevation. ↓ Indicates: A decrease, reduction, lowering, or inhibition.

other key functional indicators, the mitigation of edema, the reduction in the number of swollen joints, and ultimately, the promotion of improved long term outcomes and functional states in those suffering from RA.To sum up, numerous of the tested antioxidants mainly decrease malondialdehyde levels and boost glutathione activity or total antioxidant capacity levels. For all patients, these alterations can surely be associated with the alleviation of pain and an overall improvement in quality of life and condition.

Microalgae, encompassing both photosynthetic prokaryotic and eukaryotic organisms, have evolved to thrive in a wide range of environments, including those characterized as extreme habitats,[152,153] which are consumed in human nutrition as sources of proteins and other bioactive compounds.[154–158] Several microalgal species produce non-hazardous essential vitamins, lipids, and pigments with therapeutic significance.[159–162] They can be used as adjunctive agents in the management of chronic inflammatory diseases. In addition, the short life cycle and light-dependent autotrophic nature of microalgae allow for extensive cultivation with reduced inputs, unlike heterotrophic microorganisms.

A certain study focused on creating a ROS sensitive polymeric microneedle patch made from fucoidan for the purpose of delivering Sinomenine. Both laboratory (in vitro) and animal (in vivo) experiments illustrated that the microneedle underwent dissolution promptly following skin insertion. The embedded nanoparticles were programmed to sense the high ROS concentrations present in inflamed areas, leading to the release of Sinomenine through structural cleavage. This innovative

ROS responsive drug release system, utilizing insoluble Sinomenine nanoparticles as carriers, substantially increased the drug's transdermal permeability.Furthermore, by combining it with soluble microneedles with high molecular weight fucoidan as the key material, the transdermal delivery of Sinomenine was boosted even more. As a result, transdermally administered Sinomenine was able to more effectively exert its therapeutic effects in the treatment of RA.[163]

Esveratrol, quercetin, and curcumin exert targeted effects in rheumatic diseases through distinct mechanisms: Resveratrol activates SIRT1 to inhibit NF-κB inflammasomes and synovial fibroblasts while directly scavenging ROS and activating Nrf2.[164–166] Curcumin suppresses TLR4/NF-κB signaling and RANKL-mediated osteoclastogenesis.[167,168] Clinically, these polyphenols show significant benefits: resveratrol (100 mg/day) reduces RA disease activity, quercetin (500 mg/day) improves OA joint function,[169,170] and curcumin (1g/day) matches diclofenac's efficacy in RA.[103] This evidence collectively validates their potential for managing oxidative stress-driven rheumatic pathology.

Limitations or Conflicting Findings

While the evidence implicating mitochondrial dysfunction and ROS in rheumatic diseases is compelling, several key limitations of the current research landscape must be acknowledged:

A substantial portion of mechanistic evidence is derived from in vitro cell culture investigations and in vivo animal models (eg, murine arthritis). While these models are indispensable for elucidating causal relationships and dissecting molecular pathways, they frequently fall short in recapitulating the intricate complexity inherent to human rheumatic pathologies. This complexity encompasses disease chronicity, marked heterogeneity, and the multifaceted interplay between numerous cell types and organ systems. The direct translation of insights gained from these models to human therapeutic applications thus represents a considerable challenge, as documented.[171–174]

Human clinical and biomarker studies frequently identify links between indicators of mitochondrial damage (such as elevated serum mtDNA) or oxidative stress (eg, lipid peroxidation products) and disease activity/severity. Nevertheless, these observations are primarily correlative; they cannot confirm whether mitochondrial dysfunction or ROS are primary disease drivers or merely secondary effects of inflammation and tissue damage.[9,72] This inherent difficulty in establishing causality is a core challenge in human pathophysiology research.

Preliminary evidence hints that garlic supplements might influence some antioxidant markers, but robust support for consistent "dual effects" is lacking.[175] The impact of pomegranate extract on GPx activity is variable across randomized controlled trials and meta-analyses, with null outcomes especially common in diseased populations, at lower doses, or when baseline selenium status confounds results, indicating substantial response heterogeneity.[176] Meta-analysis of 17 RCTs found Coenzyme Q10 supplementation did not significantly lower MDA levels compared to placebo.[177] Similarly, evidence for probiotics enhancing systemic antioxidant capacity in patients is unconvincing, showing either negligible, strain-specific, or potentially adverse effects on thiol and total antioxidant capacity—contradicting common claims.[178] Furthermore, current research reveals that oral **α**-lipoic acid neither boosts serum total antioxidant capacity or arylesterase activity nor significantly reduces MDA; paradoxically, it may increase oxidative stress in chronic conditions, potentially via copper chelation-mediated suppression of arylesterase.[179]

Clinical Translation

In SLE, impaired mitochondrial function critically exacerbates core disease mechanisms, including autoimmunity, NETosis, and interferonopathy. Specifically, damaged organelles release mtDNA into the cytosol and circulation. This mtDNA acts as a DAMP, hyperstimulating endosomal TLR9 and cytosolic cGAS-STING pathways, which triggers pathogenic type I interferon storms.[73] Metabolically, CD_4^+T-cells exhibit reprogramming, abandoning OXPHOS for glycolysis while exhibiting defective mitochondrial respiration. This shift favors pro-inflammatory Th17 cell differentiation and compromises regulatory T-cell function.[180] Moreover, defective mitophagy—attributable to PINK1/Parkin pathway impairments, enables the buildup of ROS-generating mitochondria. This contributes to the prolonged survival of autoreactive B-cells, further entrenching the autoimmune state.[181] Moreover, defective mitophagy—attributable to PINK1/Parkin pathway impairments, enables the buildup of ROS-generating mitochondria. This contributes to the prolonged survival of autoreactive B-cells, further entrenching the autoimmune state.

In OA, dysfunctional mitochondria are central to chondrocyte breakdown, acting via hypoxia adaptation, genetic, and senescence mechanisms. Pathologically, OA disrupts the normal hypoxic response: it downregulates PGC-1αand excessively activates Drp1-mediated fission, generating ROS from fragmented organelles.[182] Additional insults come from cartilage-specific mtDNA mutations, which compromise Complex I, further increasing ROS and activating collagenases like Matrix Metalloproteinase-13 (MMP-13).[183] Consequently, oxidative stress induces telomere damage and senescence in chondrocytes, hindering ECM production. Promising therapeutic strategies include mitochondrial-targeted antioxidants, shown to reduce oxidative damage in models and early trials, and fission inhibitors, which improve mitochondrial integrity and chondrocyte activity in vitro.[184]

In SSc, impaired mitochondrial function propels the vasculopathy-to-fibrosis transition through metabolic reprogramming and oxidative stress. Pathological "glycolytic addiction" in fibroblasts suppresses OXPHOS via PGC-1α downregulation, elevating lactate levels that activate TGF-β and drive pathological collagen synthesis.[185] Simultaneously, disease-specific autoantibodies compromise Complex I activity in the electron transport chain, generating excessive ROS. This ROS surge amplifies myofibroblast differentiation and fibrotic progression.[186] Within the vasculature, mitochondrial-derived ROS upregulates NOX4, triggering endothelial apoptosis and microvascular rarefaction, clinically manifesting as Raynaud's phenomenon and digital ulcers.[187] Therapeutically, PGC-1α agonists restore mitochondrial respiration to curb fibrogenesis in preclinical studies, while ROS scavengers such as NAC improve vascular outcomes in clinical trials.[172,173]

In RA, organellar dysregulation in synovial fibroblasts and T-cells propels synovial hyperplasia and bone erosion through divergent mechanisms. Pathogenic fibroblast-like synoviocytes (FLS) develop hyperfused mitochondrial networks driven by Optic Atrophy 1 (OPA1) upregulation, which augments organelle mass and elevates ATP synthesis to fuel actin polymerization. This bioenergetic adaptation enables aggressive FLS migration, tissue invasion, and joint degradation.[188] Conversely, CD_8^+ T-cells exhibit impaired clearance of damaged mitochondria due to mitophagy defects. Resultant organelle accumulation compromises metabolic plasticity and confers apoptosis resistance, sustaining chronic inflammatory T-cell infiltration within the synovium.[189] Therapeutically, inhibiting mitochondrial hyperfusion via OPA1 antagonists suppresses FLS invasiveness and attenuates arthritis in preclinical models, providing a targeted approach to mitigate synovial inflammation.[190]

Clinical Translation Status of Key Antioxidants

Polyphenols (eg, curcumin, resveratrol, quercetin) exhibit modessystemic lupus erythematosust therapeutic effects in rheumatic diseases but confront significant pharmacokinetic challenges. In randomized controlled trials, curcumin (500 mg twice daily) reduced RA disease activity (DAS28) with efficacy comparable to methotrexate.[103] However, its clinical application is limited by <1% oral bioavailability and dose-dependent hepatotoxicity at high doses (>8 g/day).[191] Resveratrol improved endothelial function in patients, yet Phase II trials demonstrated no reduction in disease flares.[192] Quercetin, despite potent in vitro anti-inflammatory activity, lacks robust clinical evidence for human rheumatic disease efficacy.[193]

Garlic (allicin-derived compounds) and pomegranate (ellagitannin metabolites) demonstrate epidemiologically correlated anti-inflammatory properties. Clinical studies report that garlic supplementation significantly reduced CRP levels in rheumatoid arthritis patients,[194] while pomegranate extract improved Western Ontario and McMaster Universities Osteoarthritis Index scores in knee OA cohorts.[195] However, neither intervention has undergone large-scale randomized controlled validation. Crucially, garlic's potent antiplatelet effects necessitate caution regarding perioperative bleeding and warfarin interactions.[196]

Coenzyme Q10 (200 mg/day) demonstrated significant fatigue reduction in SLE patients,[197] though failed to attenuate radiographic joint damage progression in rheumatoid arthritis.[143] Probiotic interventions (eg, Lactobacillus casei 01) yielded modest improvements in DAS28,[198] yet benefits remain strain-dependent and clinically transient. Alpha-lipoic acid (600 mg/day) showed efficacy against neuropathic pain in fibromyalgia,[199] but lacks randomized controlled evidence for autoimmune disease applications.[200]

NAC significantly attenuated ROS in RA synovial fluid.[136] However, a 2.4 g/day clinical regimen in SLE patients yielded only fatigue improvement, without modulating anti-dsDNA titers or renal endpoints.[201] Separately, 200 μg/day

selenium supplementation reduced CRP in mild RA,[202] yet demonstrated no efficacy in advanced RA and poses toxicity concerns at elevated doses.

Trehalose, a naturally occurring disaccharide, demonstrates significant autophagy-enhancing properties that support cellular homeostasis. Research indicates it facilitates the selective clearance of manganese-damaged mitochondria in murine striatal neurons via activation of the PINK1/Parkin mitophagy pathway. Supplementation studies further reveal trehalose's ability to normalize Parkin and SIRT3 expression while increasing levels of the mitophagy-associated protein BNIP3.[203,204] Mechanistically, trehalose activates AMPK-ULK1 signaling to drive mitophagic processes, effectively reducing oxidative stress-induced chondrocyte apoptosis in osteoarthritis models. These findings highlight its translational potential for OA prevention and treatment strategies.[204]

Rapamycin, a recognized autophagy inducer, alleviates senescence-associated phenotypes across preclinical models. Studies further establish its capacity to stimulate mitophagy. Through modulation of autophagy and mitophagy pathways alongside restoration of cellular homeostasis, rapamycin exhibits therapeutic potential in mitigating oxidative stress-induced senescence and associated pathological consequences.[205]

Vitamin E, a potent lipid-soluble antioxidant, shows therapeutic promise for OA management. Its efficacy arises from multimodal protection against mitochondrial impairment: directly neutralizing ROS while stabilizing membrane lipid integrity to reduce oxidative damage. Crucially, vitamin E modulates mitochondrial calcium balance, maintains fission-fusion dynamics, and regulates apoptotic signaling cascades.[206] Furthermore, it potentiates endogenous antioxidant systems by enhancing SOD and GPx activity, thereby strengthening cellular defense against cartilage-degrading oxidative stress.[207]

Advancing Mitochondrial ROS Research in Rheumatology

This review could be strengthened through coverage of emerging mtROS detection technologies that transcend classical methodological constraints, thereby unlocking novel pathogenic insights in rheumatic diseases.

Targeted ROS Probes

Cell-type-resolved mtROS monitoring via mitochondrial probes (MitoSOX, mito-roGFP) captures compartmentalized oxidative responses during inflammation.[208,209] This methodology exposes disease-relevant heterogeneity in synovial fibroblasts and immune cells.

Precision Genome Editing

Targeted mitochondrial genome editors (eg, mito-TALENs) enable precise correction of pathogenic mtDNA variants.[210] When integrated with nuclear gene modulation (eg,SOD_2/PGC-1αediting), this dual-pathway strategy establishes causative relationships between mtROS dysregulation and autoimmune activation.[211]

Integrated Multi-Omics

Combining mitochondrial proteomics, metabolomics, and single-cell transcriptomics identifies disease-specific signatures in rheumatic conditions.[38,212] This uncovers mtROS-related metabolic rewiring (eg, TCA cycle alterations) and biomarker candidates in patient-derived samples.

Incorporating these techniques shifts the focus from correlation to causation, revealing novel therapeutic targets and advancing personalized strategies in rheumatology. Despite antioxidant therapy's potential against mtROS-driven rheumatic pathology, clinical implementation faces significant translational barriers.

Risks and Rationale for Antioxidant Therapy in Rheumatic Diseases

The clinical deployment of antioxidants necessitates careful risk-benefit assessment due to their potential to disrupt physiological redox signaling. ROS serve as essential secondary messengers regulating immune cell differentiation, autophagic processes, and inflammatory responses.[213,214] Non-selective antioxidants may compromise antimicrobial defense by inhibiting neutrophil extracellular trap formation (NET), dysregulate T-cell homeostasis through altered Treg/Th17 balance, and impair hypoxia-inducible factor (HIF)-mediated tissue repair. This therapeutic paradox is

exemplified in rheumatoid arthritis models where chronic vitamin E supplementation exacerbated joint destruction by 47%, highlighting the dualistic nature of ROS in pathophysiological processes.[215,216]

Beyond therapeutic potential, high-dose antioxidants demonstrate context-dependent paradoxes: supratherapeutic concentrations may trigger pro-oxidant conversion in oxygen-rich microenvironments, as evidenced by β-carotene elevating lung cancer incidence by 28% in smokers via quinone genotoxicity,[217] while concurrently impeding conventional therapies, exemplified by vitamin C reducing progression-free survival by 37% during platinum chemotherapy through ROS neutralization;[218] These risks are further amplified by organ-specific toxicities, where excessive flavonoids (eg, >1g/kg quercetin) provoke renal tubular damage via mitochondrial permeability transition pore activation.[219]

Future translational initiatives must prioritize mitochondrially-targeted antioxidants, which achieve >100-fold organellar accumulation to maximize therapeutic efficacy while minimizing systemic toxicity.[220,221] Dosing precision should be guided by quantifiable oxidative stress biomarkers—particularly plasma 8-OHdG and mitochondrial DNA common deletion levels—enabling dynamic therapeutic modulation.[14] Concurrently, development of pathway-discriminating modulators that selectively inhibit pathological ROS sources (eg, NOX_2) while preserving physiological redox signaling represents a critical frontier.[222]

Conclusions

This review's findings underscore the significance of ROS and propose a probable mechanism for how ROS instigates mitochondrial dysfunction and mtDNA damage. Nevertheless, many of the targets identified through animal studies demand further exploration in human subjects to validate their relevance.[223–225] A thorough understanding of how ROS mediated mitochondrial dysfunction affects core cellular functions, namely inflammation, immune responses, and repair processes, will not only yield significant knowledge regarding basic pathological events but also facilitate the identification of more potential therapeutic targets for combating diseases.[226,227] Despite being regarded as having limited protective effects, the reduction of ROS remains a key research target in recent years. Antioxidants can successfully reduce oxidative stress both systemically and at the local tissue level. Serving as the principal means of intervention, they can diminish the damage inflicted by autoimmune diseases like rheumatoid arthritis. Moreover, the development of innovative pharmacological treatments, dietary regimens, and genetic approaches designed to elevate antioxidant levels in rheumatic disorders could provide much needed therapeutic options for rheumatic diseases that are currently difficult to treat effectively.

This review positions ROS as a central driver of mitochondrial impairment and mtDNA damage, while highlighting the inadequacy of empirical antioxidant approaches. Despite their therapeutic utility in conditions like rheumatoid arthritis, antioxidants exhibit dose-dependent paradoxes—high concentrations may provoke mitochondrial toxicity via pore activation—necessitating human validation of preclinical targets to resolve contradictory evidence. Clinical translation faces additional hurdles: tissue-specific redox pathway variations, unquantified epigenetic consequences, and potential suppression of physiological oxidant defenses. These constraints mandate precision frameworks to prevent therapeutic overgeneralization. Emerging technologies now enable spatiotemporally controlled interventions, with AI-guided dosing mitigating risks of pro-oxidant conversion or immune impairment. Ultimately, optimizing redox therapeutics requires integrated calibration of dose-organelle-pathway dynamics to reconcile organ protection with metabolic safety, transforming mechanistic insights into actionable strategies for refractory inflammatory disease.

While the established pathogenic triad of oxidative stress, mitochondrial dysfunction, and inflammation underpins rheumatic diseases,[49,228] critical translational barriers and therapeutic innovation deficits remain unresolved.[229,230] Future research must prioritize developing human-relevant models to address interspecies redox discrepancies,[231] alongside designing spatially-precise antioxidants and dual-pathway modulators (eg, Nrf2/PINK1 co-activators) that circumvent systemic limitations of conventional scavengers.[232,233] Addressing these imperatives will transform mechanistic insights into targeted clinical interventions.

Data Sharing Statement

No datasets were created or examined during the course of this study, the concept of data sharing does not apply to this article.

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Disclosure

The authors declare that they have no competing interests.

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