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Oxidative Stress as a Driver of Rheumatoid Arthritis: Mechanisms, Clinical Biomarkers, and Therapeutic Targeting

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ABSTRACT

This review focuses on the critical role of reactive oxygen species (ROS) in the pathogenesis of rheumatoid arthritis (RA) and explores potential therapeutic strategies targeting oxidative stress. ROS, including free radicals and non-radical species, are generated as byproducts of normal metabolic processes, but their excessive production leads to oxidative stress, contributing to inflammation and joint destruction in RA. We discuss mechanisms by which ROS drive synovial inflammation, activate immune cells, and modulate key transcription factors like NF-κB and Nrf2, enhancing the inflammatory response. The review highlights the significance of lipid peroxidation and oxidative damage markers, such as malondialdehyde and 8-hydroxy-2-deoxyguanosine, in RA pathology. Additionally, we examine various antioxidant strategies, including the application of natural compounds and mitochondrial-targeted therapies, aimed at mitigating oxidative stress. By addressing the inflammatory cycle perpetuated by ROS, this article underscores the potential of antioxidant therapies to alleviate RA symptoms and slow disease progression, paving the way for novel treatment approaches in clinical practice.

INTRODUCTION

Reactive oxygen species (ROS) are highly reactive molecules derived from the metabolism of oxygen. These species include free radicals such as superoxide anion (O2•-), hydroxyl radical (•OH), and non-radical species like hydrogen peroxide (H2O2) and singlet oxygen (1O2) [1,2]. A free radical is “a molecule containing one or more unpaired electrons and capable of independent existence”. Free radicals are highly reactive species and are involved in several metabolic processes including oxidative reactions in mitochondria, “oxidative burst” of phagocytes, etc [3-5]. In excess, free radicals lead to diseases including autoimmune, cardiovascular, neurodegenerative, cancer, and must be reduced to minimize these pathological conditions. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are two types of free radicals generated in the body and consist of both radical and non-radical molecules. Under normal conditions, living organisms use respiration to survive, they undergo the process of reducing oxygen molecules by attaching four electrons, resulting in the formation of water [6-8]. This process produces molecules such as superoxide anion (O2-), hydrogen peroxide (H2O2) and hydroxyl radical (OH-) as a byproduct. In the process of energy transfer via electron transport of molecular oxygen, O2- is formed intracellularly in mitochondria, potentially leading to the development of various pathophysiological conditions. In the context of rheumatoid arthritis (RA), ROS play a significant role in the pathogenesis and progression of the disease [9-11]. RA is a chronic inflammatory disorder characterized by synovial inflammation and joint destruction. The overproduction of ROS in RA is largely due to the activation of immune cells, such as macrophages, neutrophils, and

T cells, within the inflamed synovial tissue. These cells generate ROS through various enzymatic systems, including NADPH oxidase, myeloperoxidase, and the mitochondrial electron transport chain [12-14].

The excess ROS in RA contributes to oxidative stress, a state where the antioxidant defenses of the body are overwhelmed, leading to damage of cellular components like lipids, proteins, and DNA. One of the critical biochemical pathways involved in ROS generation in RA is the activation of NADPH oxidase, which produces superoxide anion [15-17]. This superoxide anion can further react to form hydrogen peroxide, either spontaneously or catalyzed by superoxide dismutase (SOD). Hydrogen peroxide can then be converted to the highly reactive hydroxyl radical in the presence of transition metals like iron or copper via the Fenton reaction. These ROS can initiate lipid peroxidation, resulting in the formation of malondialdehyde and 4-hydroxynonenal, which are markers of oxidative damage and can alter cell membrane integrity and function [18,19].

In RA, the presence of ROS contributes to the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a transcription factor that regulates the expression of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) [20]. These cytokines further amplify the inflammatory response and ROS production, creating a vicious cycle of inflammation and oxidative stress. Additionally, ROS are involved in the modification of extracellular matrix components in the synovium, leading to the activation of matrix metalloproteinases (MMPs). MMPs degrade collagen and other matrix proteins, contributing to cartilage destruction and joint erosion characteristic of RA [21-23].

The antioxidant defense mechanisms in RA patients are often compromised, exacerbating the effects of oxidative stress. Enzymatic antioxidants such as superoxide dismutase, catalase, and glutathione peroxidase, as well as non-enzymatic antioxidants like vitamin C, vitamin E, and glutathione, are found at reduced levels in RA synovial fluid and plasma. This imbalance between ROS production and antioxidant defense leads to sustained oxidative damage and inflammation [24,25].

OXIDATIVE STRESS AND MARKERS

Oxidative stress is a biochemical condition characterized by an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify these reactive intermediates or repair the resultant damage [26-28]. ROS are highly reactive molecules that include free radicals like superoxide anion (O2•-), hydroxyl radical (•OH), and non-radical species like hydrogen peroxide (H2O2). Under normal physiological conditions, ROS play essential roles in cell signaling and homeostasis. However, excessive ROS production or insufficient antioxidant defenses can lead to oxidative stress, resulting in damage to lipids, proteins, and nucleic acids [2,29-31].

Lipid peroxidation is a primary outcome of oxidative stress, where ROS attack polyunsaturated fatty acids in cell membranes, initiating a chain reaction that produces lipid peroxides. These lipid peroxides further decompose into reactive aldehydes such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) [32,33]. MDA and 4-HNE are commonly used as biomarkers of oxidative stress, as they can form adducts with proteins and DNA, disrupting their normal function. The measurement of MDA levels, typically through thiobarbituric acid reactive substances (TBARS) assay, provides an indication of the extent of lipid peroxidation [34].

Proteins are another major target of ROS, leading to the formation of carbonyl groups on amino acid side chains, disulfide bonds, and nitrotyrosine through the reaction with reactive nitrogen species. Protein carbonyl content is a widely used marker of oxidative stress, often measured by the reaction with 2,4-dinitrophenylhydrazine (DNPH) to form hydrazones, which can be quantified spectrophotometrically [35-37]. Additionally, advanced oxidation protein products (AOPPs) and the presence of nitrotyrosine residues are indicative of oxidative modifications to proteins and are used as markers of oxidative stress [38].

Nucleic acids, particularly DNA, are susceptible to damage by ROS, resulting in the formation of various modified bases, strand breaks, and cross-linking. One of the most studied oxidative DNA lesions is 8-hydroxy-2'-deoxyguanosine (8-OHdG), which occurs due to the oxidation of guanine. 8-OHdG can be measured in cells, tissues, and bodily fluids, serving as a biomarker for oxidative stress and DNA damage [39,40]. The comet assay, also known as single-cell gel electrophoresis, is another technique used to assess DNA damage and repair, providing information on the extent of strand breaks. In RA patients, 8-OH-dG levels are significantly reduced by methotrexate or TNF inhibitors such as infliximab and etanercept [41,42].

Antioxidant defense systems, including enzymatic antioxidants like superoxide dismutase (SOD), catalase, and glutathione peroxidase, play crucial roles in mitigating oxidative stress. SOD catalyzes the dismutation of superoxide anion into hydrogen peroxide, which is then broken down into water and oxygen by catalase or glutathione peroxidase [43]. Non-enzymatic antioxidants, such as vitamin C, vitamin E, and glutathione, also contribute to neutralizing ROS and preventing cellular damage. The levels and activities of these antioxidants can be measured to assess the antioxidant capacity of an organism [44].

The glutathione system, in particular, is central to cellular redox homeostasis. Glutathione exists in reduced (GSH) and oxidized (GSSG) forms, with the GSH/GSSG ratio serving as an indicator of cellular oxidative stress. Under oxidative conditions, GSH is consumed and converted to GSSG, and the GSH/GSSG ratio decreases. The measurement of this ratio provides insights into the redox state of the cell [45,46].

Biologic drugs are widely used in clinical practice in patients with RA, but side effects are a concern. If other targets, such as antioxidants or agents that inhibit or stimulate ROS, are acted upon, the clinical symptoms of RA-the number of tender joints, arthralgias, joint swelling, and osteoarthritic joint disease-are reduced [47,48]. Physical activity, such as knee flexion, may also improve. Common markers of oxidative stress include 8-hydroxy-2-deoxyguanosine (8-OHdG), thiobarbituric acid reactive substances, malondialdehyde (MDA), isoprostane (IsoPs) and its metabolites, allantoin, and the end product of progressive glycation (AGE) [49].

NEUTROPHILS AND AUTOPHAGY IN RA AND ROS

In the context of ROS in RA firstly it is important to describe the role of neutrophils and autophagy in pathogenesis and inflammation process. Neutrophils are white blood cells essential to the innate immune system and play a critical role in the pathophysiology of rheumatoid arthritis (RA) [50-52]. These cells are among the first responders to sites of inflammation, where they execute various functions, including phagocytosis, degranulation, and the release of reactive oxygen species (ROS) to combat pathogens. In RA, neutrophils accumulate in the synovial fluid and tissue, contributing to the chronic inflammatory environment [53-56]. One of the primary biochemical mechanisms through which neutrophils exert their effects in RA is the generation of ROS. Neutrophils produce ROS via the NADPH oxidase complex, which catalyzes the reduction of oxygen to superoxide anion ($O_2^{\bullet-}$). This superoxide anion can dismutate into hydrogen peroxide (H_2O_2) either spontaneously or via the enzyme superoxide dismutase (SOD) [57,58]. Hydrogen peroxide can subsequently produce hydroxyl radicals (•OH) through Fenton reactions involving transition metals like iron, contributing to oxidative stress and tissue damage. Also, In the inflammatory environment of RA, neutrophils can release their granule contents, including myeloperoxidase (MPO), an enzyme that uses hydrogen peroxide to produce hypochlorous acid (HOCl), a potent oxidant that contributes to tissue damage [59]. Neutrophil extracellular traps (NETs), composed of decondensed chromatin and granular proteins, are also released by neutrophils and can exacerbate inflammation and ROS production in RA. The formation of NETs, a process known as NETosis, is influenced by autophagy [60,61].

Autophagy is a cellular process involved in the degradation and recycling of damaged organelles, misfolded proteins, and intracellular pathogens. In neutrophils, autophagy plays a dual role, contributing to both cell survival and the regulation of inflammatory responses. Under conditions of oxidative stress, such as those present in the inflamed synovium of RA patients, autophagy can be upregulated as a protective mechanism [62-64]. The autophagic process involves the formation of autophagosomes, double-membrane vesicles that engulf cytoplasmic components and fuse with lysosomes to form autolysosomes, where the contents are degraded by lysosomal enzymes. Autophagy can facilitate the release of NETs, while ROS are essential for NET formation, creating a feedback loop that perpetuates inflammation [65,66].

Also, there is evidence that neutrophil autophagy can modulate the production of ROS. On one hand, autophagy can help mitigate oxidative damage by removing damaged mitochondria through a specific form of autophagy called mitophagy, thereby reducing the mitochondrial ROS production. On the other hand, excessive or dysregulated autophagy can lead to increased ROS generation [67,68]. For instance, the activation of the autophagy-related gene (Atg) pathway in neutrophils can influence NADPH oxidase activity and thus ROS production. Furthermore, the interplay between ROS and autophagy in neutrophils is complex and involves several signaling pathways. ROS can act as signaling molecules that induce autophagy through the activation of pathways such as the AMP-activated protein kinase (AMPK) pathway and the inhibition of the mammalian target of rapamycin (mTOR) pathway. Conversely, autophagy can regulate ROS levels by degrading ROS-producing organelles and proteins [69,70].

Table 1: Mechanisms of ROS in Rheumatoid Arthritis

Mechanism	Description
ROS Generation	Produced primarily by immune cells (macrophages, neutrophils, T cells) via NADPH oxidase and mitochondrial processes
Lipid Peroxidation	ROS attack polyunsaturated fatty acids, generating products like malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE)
DNA Damage	Formation of 8-hydroxy-2'-deoxyguanosine (8-OHdG) due to ROS, serving as a biomarker for oxidative damage
Transcription Factors	Activation of NF-κB and Nrf2 by ROS, leading to increased expression of pro-inflammatory and antioxidant genes
Cytokine Release	Enhanced production of TNF-α and IL-1β, perpetuating the inflammatory cycle through ROS feedback

MAIN TRANSCRIPTIONAL FACTORS ASSOCIATED WITH ROS

Main transcriptional factors associated with reactive oxygen species (ROS) and redox signaling play critical roles in cellular responses to oxidative stress and the maintenance of redox homeostasis. One of the primary transcription factors modulated by ROS is nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [71,72]. NF-κB is a key regulator of inflammatory responses and is activated by oxidative stress. In its inactive state, NF-κB is bound to inhibitory IκB proteins in the cytoplasm. Upon stimulation by ROS or other signals, IκB is phosphorylated by the IκB kinase (IKK) complex, leading to its ubiquitination and proteasomal degradation. This releases NF-κB, allowing it to translocate to the nucleus, where it binds to specific DNA sequences and promotes the transcription of genes involved in inflammation, immune responses, and cell survival [73,74].

Another crucial transcription factor influenced by ROS is nuclear factor erythroid 2-related factor 2 (Nrf2). Nrf2 is a master regulator of the cellular antioxidant response. Under normal conditions, Nrf2 is bound to its inhibitor, Kelch-like ECH-associated protein 1 (Keap1), in the cytoplasm, which facilitates its ubiquitination and degradation. Oxidative stress leads to the modification of cysteine residues on Keap1, causing a conformational change that releases Nrf2 [75,76]. Free Nrf2 translocates to the nucleus, where it binds to antioxidant response elements (ARE) in the promoter regions of target genes. These genes encode various antioxidant proteins and enzymes, such as heme oxygenase-1 (HO-1), glutathione S-transferases (GSTs), and NAD(P)H oxidoreductase 1 (NQO1), which help mitigate oxidative stress and restore redox homeostasis [77].

In this context it is important also to consider the process of redox signaling. In redox signaling, the controlled generation of ROS typically originates from specific cellular sources such as mitochondria, NADPH oxidases (NOX), and other enzymatic systems. Mitochondria are major sites for ROS production during the process of oxidative phosphorylation, where the electron transport chain can leak electrons that react with molecular oxygen to form superoxide anion [78-80]. Superoxide is then rapidly dismutated to hydrogen peroxide by the action of superoxide dismutases (SODs). Hydrogen peroxide, unlike other ROS, is relatively stable and can diffuse across membranes, making it a critical redox signaling molecule. NADPH oxidases are another significant source of ROS, particularly in the context of immune cell activation and inflammatory responses [81,82].

Hydrogen peroxide serves as a signaling molecule primarily through its ability to reversibly oxidize specific cysteine residues in target proteins. These cysteine residues, often found in the active sites of enzymes or in regulatory domains, can form disulfide bonds or sulfenic acid intermediates upon oxidation [83,84]. This reversible modification can alter protein function, activity, localization, or interactions, thereby modulating cellular signaling pathways. For instance, the oxidation of cysteine residues in protein tyrosine phosphatases (PTPs) can inhibit their activity, leading to sustained phosphorylation and activation of signaling cascades such as those mediated by receptor tyrosine kinases [85,86].

Redox-sensitive transcription factors play crucial roles in redox signaling. Nuclear factor erythroid 2-related factor 2 (Nrf2) is a master regulator of the antioxidant response. Under basal conditions, Nrf2 is sequestered in the cytoplasm by Kelch-like ECH-associated protein 1 (Keap1) and targeted for degradation [87,88]. In response to oxidative stress, cysteine

residues on Keap1 are modified, leading to the release and stabilization of Nrf2. Nrf2 then translocates to the nucleus, where it binds to antioxidant response elements (AREs) in the promoters of genes encoding detoxifying and antioxidant enzymes, such as heme oxygenase-1 (HO-1), glutathione S-transferases (GSTs), and NAD(P)H quinone dehydrogenase 1 (NQO1) [89,90].

Another important redox-sensitive transcription factor is nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). In its inactive state, NF-κB is bound to inhibitory proteins called IκBs. Upon exposure to ROS or other stimuli, IκB is phosphorylated by the IκB kinase (IKK) complex, leading to its ubiquitination and degradation. This allows NF-κB to translocate to the nucleus and activate the transcription of genes involved in inflammation, immune response, and cell survival [91].

The redox state of the cell is also tightly regulated by the glutathione (GSH) system. Glutathione exists in a reduced (GSH) and oxidized (GSSG) form. The ratio of GSH to GSSG is a key indicator of cellular redox status. GSH can directly scavenge ROS or serve as a substrate for glutathione peroxidases (GPx) and glutaredoxins, enzymes that reduce peroxides and disulfides, respectively. The regeneration of GSH from GSSG is catalyzed by glutathione reductase (GR), using NADPH as a reducing agent [92].

Peroxiredoxins (Prxs) and thioredoxins (Trxs) are other critical components of the cellular redox regulatory network. Peroxiredoxins reduce hydrogen peroxide to water and are regenerated by thioredoxins, which in turn are reduced by thioredoxin reductase using NADPH. This system not only detoxifies ROS but also participates in redox signaling by modulating the redox state of cysteine residues in target proteins [93].

Nitric oxide (NO), another significant redox-active molecule, modulates signaling pathways through S-nitrosylation, the addition of a nitric oxide group to the thiol side chain of cysteine residues in proteins. This modification can influence protein function and interactions, impacting processes such as vasodilation, neurotransmission, and immune responses [94].

TARGETING ROS OR MITOCHONDRIA IN RA THERAPY DRUGS

RA is characterized by the persistent infiltration of immune cells into the synovial joints, leading to excessive ROS production. These ROS contribute to the pathogenesis of RA by promoting inflammatory cytokine release, synovial hyperplasia, and joint destruction. Consequently, therapeutic strategies aimed at reducing ROS levels or improving mitochondrial function hold promise for alleviating RA symptoms and slowing disease progression [95,96].

One key therapeutic strategy involves the use of antioxidants to neutralize ROS. Antioxidants such as N-acetylcysteine (NAC) and vitamin E have been investigated for their potential to reduce oxidative stress in RA patients [97,98]. NAC, a precursor to glutathione, replenishes intracellular glutathione stores, thereby enhancing the cell's antioxidant capacity. This reduces the damaging effects of ROS on synovial cells and may decrease inflammation. Similarly, vitamin E, a lipid-soluble antioxidant, can scavenge free radicals within cell membranes, protecting lipids from peroxidation and preserving cell integrity [99,100].

Targeting the mitochondrial sources of ROS production is another promising approach in RA therapy. Mitochondria are major producers of ROS during oxidative phosphorylation, and mitochondrial dysfunction in RA synoviocytes and immune cells contributes significantly to oxidative stress [101]. Mitochondria-targeted antioxidants such as mitoquinone (MitoQ) have been developed to specifically accumulate within mitochondria. MitoQ comprises a ubiquinone moiety linked to a lipophilic cation, which drives its selective uptake into mitochondria. By localizing within mitochondria, MitoQ can effectively neutralize ROS at their source, reducing mitochondrial oxidative damage and improving mitochondrial function [102,103].

Mitochondrial uncouplers like 2,4-dinitrophenol (DNP) have also been explored as a means to modulate mitochondrial ROS production. Uncouplers dissipate the proton gradient across the mitochondrial inner membrane, reducing the production of superoxide by the electron transport chain [104]. Although classical uncouplers like DNP are not suitable for clinical use due to toxicity, newer, safer uncouplers are under investigation for their potential to reduce mitochondrial ROS and ameliorate inflammation in RA [105,106].

Another aspect of targeting mitochondria in RA therapy involves enhancing mitochondrial biogenesis and function. Agents such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) activators can promote the generation of new mitochondria and improve mitochondrial efficiency [107,108]. By boosting mitochondrial biogenesis,

cells can better manage energy production and reduce the overproduction of ROS, which is often a consequence of mitochondrial dysfunction [109].

Inhibition of specific enzymes involved in ROS production has also been considered. NADPH oxidase (NOX) enzymes are major sources of ROS in immune cells. Inhibitors of NOX enzymes, such as apocynin, have shown potential in reducing ROS levels and inflammatory responses in RA. Apocynin inhibits the assembly of the NOX complex, thereby preventing the formation of superoxide and subsequent ROS. This inhibition can reduce the oxidative stress and inflammatory damage in RA joints [110,111].

Furthermore, the role of mitochondrial dynamics, including fission and fusion processes, has gained attention in RA therapy. Mitochondrial fission, mediated by dynamin-related protein 1 (Drp1), is often upregulated in RA, leading to fragmented and dysfunctional mitochondria that produce more ROS. Inhibitors of Drp1, such as mdivi-1, can reduce mitochondrial fragmentation, thereby improving mitochondrial function and reducing ROS production. By modulating mitochondrial dynamics, these inhibitors can potentially restore normal mitochondrial function and reduce the pathological effects of oxidative stress in RA [112,113].

Modulating the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway is an additional therapeutic strategy for targeting ROS in RA. Nrf2 is a transcription factor that regulates the expression of various antioxidant and cytoprotective genes. Under normal conditions, Nrf2 is bound to Kelch-like ECH-associated protein 1 (Keap1) and targeted for degradation [114,115]. However, oxidative stress or pharmacological activators can disrupt the Nrf2-Keap1 interaction, leading to the stabilization and nuclear translocation of Nrf2. Once in the nucleus, Nrf2 binds to antioxidant response elements (AREs) in the promoters of target genes, enhancing the expression of antioxidant enzymes such as heme oxygenase-1 (HO-1), glutathione S-transferases (GSTs), and NAD(P)H quinone dehydrogenase 1 (NQO1). Compounds like bardoxolone methyl activate the Nrf2 pathway, promoting antioxidant defenses and reducing oxidative damage in RA [116,117].

Peroxisome proliferator-activated receptor gamma (PPARγ) agonists also play a role in targeting ROS in RA therapy. PPARγ is a nuclear receptor that regulates lipid metabolism, glucose homeostasis, and inflammation. PPARγ agonists, such as pioglitazone and rosiglitazone, have anti-inflammatory and antioxidant effects. These drugs can modulate the expression of antioxidant enzymes and reduce ROS production, thereby alleviating oxidative stress and inflammation in RA [118,119].

Another approach involves the use of natural compounds with antioxidant properties. Polyphenols, such as resveratrol, curcumin, and quercetin, possess strong antioxidant and anti-inflammatory activities. These compounds can scavenge ROS directly, modulate signaling pathways involved in oxidative stress, and enhance the expression of endogenous antioxidant enzymes. For example, resveratrol activates the SIRT1 pathway, which in turn activates Nrf2, leading to increased antioxidant defenses [120,121].

Therapies that modulate mitochondrial dynamics and function are also being explored. Mitochondrial dysfunction is a hallmark of RA, contributing to increased ROS production and cellular damage. Agents that promote mitochondrial biogenesis, such as peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) activators, can enhance the generation of new mitochondria and improve mitochondrial efficiency. By boosting mitochondrial biogenesis, cells can better manage energy production and reduce ROS overproduction [122,123].

Table 2: Therapeutic Strategies Targeting ROS in RA

Strategy	Description
Antioxidants	Use of compounds like N-acetylcysteine (NAC) and vitamin E to neutralize ROS and enhance antioxidant defenses.
Mitochondria-Targeted Therapies	Application of agents like mitoquinone (MitoQ) to reduce mitochondrial ROS production directly.
NADPH Oxidase Inhibition	Use of inhibitors such as apocynin to decrease ROS generated by immune cells.
Nrf2 Activation	Compounds like bardoxolone methyl that stabilize Nrf2, enhancing expression of antioxidant enzymes.
Natural Compounds	Polyphenols (e.g., resveratrol, curcumin) with antioxidant properties that improve oxidative stress responses.

CONCLUSION

In conclusion, this review underscores the pivotal role of reactive oxygen species (ROS) in the pathophysiology of rheumatoid arthritis (RA). The accumulation of oxidative stress not only exacerbates inflammation but also contributes to joint damage and disease progression. By elucidating the mechanisms through which ROS influence immune responses and synovial inflammation, we highlight the urgent need for targeted therapeutic strategies. Antioxidant therapies, whether through natural compounds or novel pharmaceutical agents, show promise in mitigating oxidative damage and improving clinical outcomes in RA patients. Future research should prioritize clinical trials focusing on these interventions to establish their efficacy and safety. Ultimately, a deeper understanding of ROS in RA can lead to innovative treatments that enhance the quality of life for those affected by this debilitating condition.

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