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Rheumatoid arthritis and oxidative stress, a review of a decade

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ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune disease that affects approximately 1% of the worldwide population. In recent decades, oxidative stress (OS) has been shown to be involved in the progression of this disease through DNA, lipid, and protein damage, resulting in synovial inflammation. There are many causes of OS; metabolism is involved in the production of reactive oxygen species (ROS), but pollution, diet and microbiota imbalances could lead to the overproduction of these ROS. A decade of research focused on understanding how OS is promoted by known RA risk factors is described herein. The use of antioxidants represents an integrative treatment for patients with rheumatoid arthritis, given the evidence of the damage caused by oxidative stress in this disease. Understanding the different factors that contribute to the development and progression of RA, such as OS, will pave the way not only for better pharmacological treatments but also for recommendations for dietary and health behaviours that will benefit patients with this disease.

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by the infiltration of immune cells into the synovial membrane, resulting in synovial hyperplasia; in the late stages of the disease, RA causes the destruction of articular cartilage and bone. The clinical features are swelling, redness, tenderness, arthralgia, and difficulty of movement in symmetrical joints (1). This disease is mainly associated with genetic and environmental factors, but in recent decades, there has been evidence that diet and microbiota play an important role in this disease. The prevalence of RA ranges from 0.5 to 1% of the world population, with variations in each geographic region (2). RA patients are at high risk of developing several comorbidities, such as ischemic heart disease, osteoporosis, stroke, hypertension, dyslipidemia, diabetes mellitus, and depression (3,4); in addition, RA patients have a mortality rate 1.5% higher than that of the general population (5–7). RA is three to four times more common in females than in males, and this has been related to hormone cell signaling (8). Additionally, RA incidence increases approximately 2% in the elderly population (individuals over 60 years old); some studies suggest that pathologies related to aging affect the immune response, such as alterations in the presentation of antigens, T cell proliferation, increased CD8+ population and decreased CD4+ cells, disruption of cytokine release, apoptosis defects associated with DNA damage of CD4+ T cells, and age-associated epithelial defects in the thymus (9–14).

The early diagnosis and treatment of RA can help prevent irreversible disability, as RA usually causes pain and stiffness in multiple bilateral joints, both large and small, with the most affected small joints being the proximal interphalangeal, proximal metacarpophalangeal, metatarsophalangeal, and wrist joints, whereas the most affected large joints are the knee, ankle, elbow, and shoulder joints. In the fingers, swelling is usually located in the center, in contrast to the swelling in psoriatic arthritis, which affects the whole finger. Morning stiffness is common, and boggy swelling due to synovitis, which is typically soft and distinct from the hard swelling found in osteoarthritis, can be visible or sensed by joint examination. Increased joint destruction can be seen in radiographic studies, ranging

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from minimal abnormalities to severe destructive changes.

The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) developed new classification criteria for RA in 2010. These criteria do not include radiographic erosive changes and rheumatoid nodules, as they are less expected in early RA (1). The target populations for this classification are 1) patients with at least one joint with definitive clinical synovitis and 2) patients with synovitis not better explained by another disease. In addition, a score of 6 to 10 points is needed to classify a patient with RA. The score is divided into four categories (A-D). Category A, joint involvement, awards five points: one large joint = 0 points, 2 to 10 large joints = 1 point, 1-3 small joints =2 points, 4-10 small joints = 3 points, and more than 10 joints (at least 1 small joint) = 5 points. Category B, serology, awards three points: negative for rheumatoid factor (RF) and negative for anti-citrullinated protein antibodies (ACPAs) = 0 points, low-positive RF or low ACPAs = 2 points, and high-positive RF or high-positive ACPAs = 3 points. Category C, acute-phase reactants, awards one point and requires at least one test result for classification: normal C-reactive protein (CRP) and normal erythrocyte sedimentation rate (ESR) = 0 points, and abnormal CRP or abnormal ESR = 1 point. Category D, duration of symptoms, awards one point: less than 6 weeks = 0 points, and 6 weeks or more = 1 point [1]. There are other scales that provide information on disease activity, functional impairment, and damage progression and discriminate between low, moderate, and high disease activity states, such as the disease activity score assessing 28 joints (DAS28), the clinical disease activity index (CDAI), and the simplified disease activity index (SDAI) (15).

One molecular characteristic of RA could be the presence of autoantibodies specific for self IgG-Fc, known as RF, but it is not specific for RA. ACPAs are more specific for RA; in this regard, two main subtypes of RA have been classified according to the presence or absence of ACPAs. Citrullination is mediated by the PAD enzyme, which changes (positively charged) arginine to neutral citrulline as a posttranslational modification. ACPAs can be useful in diagnosing early and undifferentiated arthritis. This ACPA-positive class of RA has been reported to be more aggressive than the ACPA-negative class of RA (16). It is estimated that 50 to 80% of RA patients have one or both antibodies (17,18).

The onset of RA can occur years before the clinical manifestations. There are multiple symptoms that are associated with certain risk factors, which can be divided into genetic and environmental risk factors and will be more thoroughly discussed in the following sections. RA patients can be classified into two main groups: patients who are seropositive for autoantibodies (RF and ACPAs) and patients who are seronegative for them. The seropositive form of RA is the most common, and it is also the most studied. The proteins that can be citrullinated are fibronectin, fibrin, vimentin, α-enolase, histones, Epstein–Barr-1 nuclear antigen (EBNA-1), and type I collagen (19,20). These modified proteins can induce ACPAs production by plasma cells; in turn, these ACPAs are able to activate macrophages to release proinflammatory cytokines, such as TNF-α and IL-6, which induce the production of other proinflammatory cytokines, chemokines, and matrix metalloproteinases (MMP), resulting in cartilage degradation

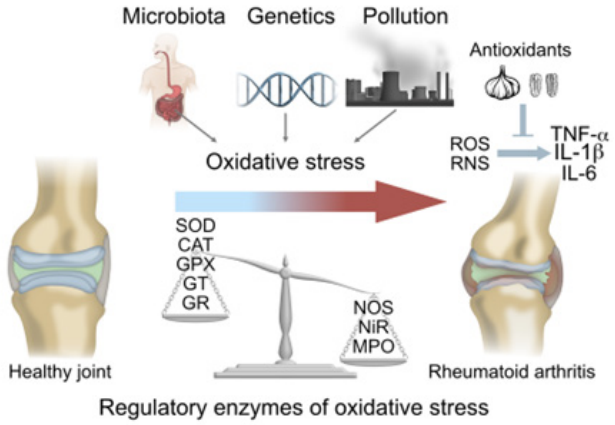

Figure 1. Microbiota, genetics, and pollution could lead to an imbalance of regulatory enzymes of oxidative stress. The production of ROS and RNS increase pro-inflammatory cytokines (such as TNF-a, IL-1b, and IL-6) that promote RA progression. The use of antioxidants as therapy could help give RA patients a comprehensive treatment.

(21,22). ACPAs can also activate osteoclasts to release CXCL8 chemokine, increasing osteoclast activation and maturation and resulting in cartilage and bone degradation (23). CXCL8 also binds CXCR1 and CXCR2 in sensory neurons, and they are responsible for pain sensation (24).

In recent decades, OS has been associated with RA progression. However, there are many unanswered questions regarding the different mechanisms by which OS contributes to the development and progression of RA. Figure 1 shows how different factors, such as pollution, genetics, microbiota and therapies, have been associated with OS and how they impact RA progression.

Materials and Methods

Search criteria and selection process

All relevant literature related to OS in connection with RA published between January 2010 and December 2020 was reviewed. We included original articles about studies on humans and animals. To identify all available studies, a detailed search on the topic of this review was conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (25). A systematic search was performed in the electronic databases PubMed and Embase using the following Medical Subject Headings (MeSH) search terms in all possible combinations: "rheumatoid arthritis," "oxidative stress in rheumatoid arthritis," "microbiota in rheumatoid arthritis," "antioxidants in rheumatoid arthritis," "treatment for rheumatoid arthritis," "environmental pollutants in rheumatoid arthritis," "oxidative stress," "reactive oxygen species," "antioxidants," "environmental pollution," and "smoking". The reference lists of all retrieved articles were also reviewed. In the case of missing data, the corresponding study authors were contacted to try to retrieve the original data. Three authors (YZC, KMF, and GMN) analyzed each article and extracted the data independently. In the case of disagreement, three different researchers were consulted (DCC, JFT, and RSS). Discrepancies were resolved by consensus.

Inclusion and exclusion criteria

The following types of publications were excluded:

articles not published in English, case reports, and letters to the editor. The search results were filtered to avoid duplicates. Titles, abstracts, and full reports of the identified articles were systematically filtered using inclusion and exclusion criteria. Given the properties of the studies involved, the methodological quality of each study was evaluated with the Newcastle–Ottawa Scale, which was specifically developed to assess the quality of nonrandomized observational studies (26).

Results

Approximately 7211 publications published between January 2010 and December 2020 were identified in the PubMed and Embase databases, but only 85 full-text articles were assessed to be eligible for the study. The results of the search strategy are illustrated in Figure 2.

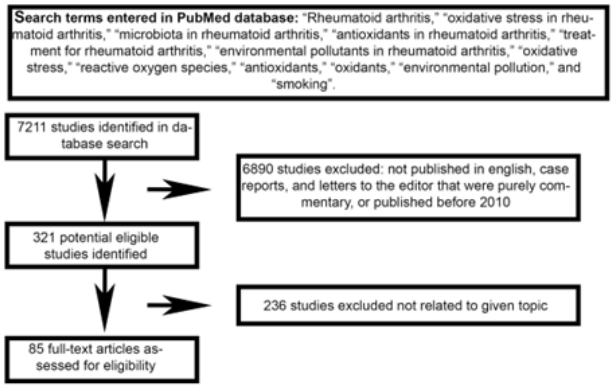

Figure 2. Method to integrate the review.

Mechanisms of oxidative stress in rheumatoid arthritis

In RA, the interaction between the immune response and endogenous and/or exogenous antigens induces the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) (27,28). Reactive species are formed during physiological processes and are normally formed at relatively low levels in all cells and tissues (29), and their main endogenous source is the electron transport chain in mitochondria.

The aerobic production of energy for the different cellular processes occurs through oxidative phosphorylation, in which oxidation-reduction reactions (redox) lead to ATP synthesis. During this process, the oxygen is the final electron acceptor, producing H_2O as the final product. Some intermediate products of these redox reactions are highly reactive oxygen metabolites or ROS. Approximately 2% of partially reduced oxygen is capable of damaging cellular molecules and structures, particularly proteins, carbohydrates, cell membrane lipids, and DNA (30).

The main ROS radicals are superoxide anion (O^-), superoxide ion (O_2^-), peroxyl (ROO), hydroperoxyl radical (HO_2^-), hydroxyl (OH^-), and the nonradicals hydrogen peroxide (H_2O_2) and molecular oxygen (O_2). The RNS include nitric oxide (NO^-), nitrogen dioxide (NO_2^-), and peroxynitrite ($OONO^-$). Hypochlorous acid (HClO) (31,32), sulfur and hydrogen sulfide (H_2S) has been found in the patellar joint and synovial fluids (SF) of patients with RA, either in the acute or chronic phases of the disease (33).

The overproduction or inappropriate elimination of reactive species leads to an imbalance between ROS and RNS production and endogenous and/or exogenous antioxidant systems; this is known as OS (Figure 1). OS is one of the key factors involved in the pathogenesis and pathophysiology of RA because it can activate different signal transduction pathways involved in the expression of proinflammatory cytokines and chemokines, such as the nuclear factor kappa-β (NF-κB) signaling pathway (27,34,35), which has been positively correlated with RA severity (36).

Reactive species can be formed in the inflamed joints of RA patients by chondrocytes, macrophages, and polymorphonuclear cells from the synovial membrane and inflamed SF. When activated, these cells promote the formation of O^-, H_2O_2, OH^-, and proinflammatory cytokines, such as tumor necrosis alpha (TNF-α), interleukin-1 beta (IL-1β), and interferon-gamma (IFN-γ), which activate the NADPH oxidase (NOX) complex that catalyzes the conversion of O_2 into the O^- radical involved in the progression of RA (29,36,37).

In RA, ROS can also be produced by enzymatic sources, such as those generated by nitric oxide synthases (NOS), nitrite reductases (NiR), H_2S-producing enzymes, and myeloperoxidase (MPO) of phagocytic cells, which produces HClO (33). The high pressure in the synovial membrane and the decrease in the joint wall due to inflammation produce hypoxic reperfusion and fibrosis of the joint, resulting in a reduction in capillary density and an increase in its metabolic rate. This elevated intra-articular pressure induces ischaemia–reperfusion injury in the joint (12).

Oxidative damage from hypoxia and inflammation promotes genomic instability that leads to respiratory disturbances in synoviocytes. Hypoxia overproduces ROS that oxidize polyunsaturated fatty acids in plasma and mitochondrial membranes, generating lipid peroxidation products, such as 4-hydroxy-2-nonenal (4-HNE), which form covalent adducts with DNA, phospholipids, and amino acids (12). OS is related to inflammation and accelerated destruction of the joints, as ROS are mediators of tissue damage in RA (28).

In addition to the increase in ROS/RNS, the endogenous antioxidant system in RA patients is disturbed (35). This system is made up of enzymes that prevent oxidative damage, such as superoxide dismutase (SOD), which removes O_2- by converting it into H_2O_2, which in turn is transformed into H_2O by catalase (CAT) and glutathione peroxidase (GPX), glutathione transferase (GT), and glutathione reductase (GR) (36,38). Therefore, low levels of these antioxidants or their enzymatic activities can be a risk factor for RA onset and development.

The exact mechanisms through which OS may contribute to the initiation and spread of local inflammation in the joint and systemic milieu in RA, particularly in the early stages, have yet to be determined (38). Some OS biomarkers found in RA patients are malondialdehyde (MDA) and nitrotyrosine, which are associated with increased myocardial tension. RA patients have increased serum levels of MPO and advanced glycosylation end products, which have been associated with endothelial dysfunction (39).

In the case of MDA, its concentration is elevated not only in the serum but also in the SF of RA patients. SF lacks antioxidant components such as GR, GPX, and SOD. Therefore, ROS triggered by phagocytosis in the inflamed

rheumatoid joint are not removed efficiently, resulting in increased levels of lipid peroxidation products (29). SF and tissue analyses in RA patients have shown OS-related damage by hyaluronic acid depolymerization, which leads to a loss of viscosity in the SF and an increase in lipoperoxidation products, oxidation of low-density lipoproteins (LDL) and carbonyl groups in proteins, DNA oxidation, and increased CAT activity (29).

OS in patients with RA is identified by an increase in serum lipids oxidation markers, such as thiobarbituric acid reactive products, lipid hydroperoxide, conjugated dienes, carbonyls, 8-oxohydrodeoxyguanosine (OhdG), and thioredoxin, which participate in the redox regulation of cellular proteins, coupled with a decrease in the thiol group in proteins and deterioration of the enzymatic activities of GR, GPX, and SOD (29). OS biomarkers and RA activity have been correlated with high levels of lipid peroxidation not only in serum and SF but also in urine. The presence of lipid peroxidation products is indirect evidence of the effect of free radicals as mediators of tissue damage and inflammatory arthropathy in the pathogenesis of RA (29).

Patients with the active chronic inflammatory joint disease suffer intense OS characterized by the elevation of inflammatory mediators, such as TNF-α, posttranslational modifications of proteins, and a decrease in antioxidant systems since RA patients have lower serum levels of vitamin E, vitamin C, β-carotene, selenium, and zinc. Thus, these biomarkers could be used as indicators of the RA activity-inactivity status (40,41). The role of ROS in ligament degradation is associated with cartilage-derived peroxidation products, LDL modified with a nitrous collagen II peptide and oxidized IgG (35).

O_2^- has a role in cartilage and bone degradation through the induction of bone resorption since it is produced by osteoclasts and can lead to accelerated damage to the articular cartilage. OS in RA induces T cell hypo-reactivity through proteasomal degradation with a decrease in intracellular GR levels (40). Damage to cartilage, extracellular collagen, and chondrocyte DNA have also been identified. Peripheral blood lymphocytes from RA patients contain elevated levels of 8-OhdG, thioredoxin, and NO in their DNA, which is regulated by an increase in RA synovial tissue and higher levels of nitrite in SF (40).

ROS induce genotoxic events related to mutations of the tumour suppressor gene p53 in fibroblast-like synoviocytes, which could explain the transformed phenotype of these cells and their apoptosis (40). The role of OS in joint inflammation and destruction has also been studied in animal models of RA, in which markers of protein and lipid oxidation have been found to be increased. It has been shown that the use of exogenous antioxidants and antioxidant enzymes reduces cartilage damage (34,37). Currently, OS and NO markers may be useful to assess the response to disease-modifying drugs in RA patients. Studies with infliximab, tocilizumab, methotrexate, and leflunomide have been focused on reducing NO in RA. Tocilizumab showed a significant decrease in ROS/RNS, whereas infliximab caused a reduction in protein oxidation, and etanercept decreased the oxidative damage in DNA (42).

Likewise, there are antioxidant therapies aimed at contributing to the management of OS in RA, such as the use of polyphenols and molecules with anti-inflammatory and antioxidant activity that inhibit NF-kβ translocation from the cytoplasm to the nucleus (43,44); the use of polyphenols to potentially inhibit the activation of signal transduction pathways, which involve kinases and transcription factors; and the production of autoantibodies and autoantigens that lead to RA development (45).

Environmental pollutants and rheumatoid arthritis

Environmental factors have been considered to play an important role in the development or exacerbation of RA (46,47). The environmental pollutants that have been associated with RA development and increased oxidative stress include tobacco smoke, silica particles, fine particulate matter (FPMs) and ultrafine particles (UFPs) (47). Exposure to tobacco smoke may favour the clinical manifestations of asymptomatic individuals with a genetic predisposition to developing RA (40,48).

Several investigations have indicated that tobacco smoke increases the generation of ROS, RNS and sulfur reactive species (SRS), which are strong stimuli for citrullination; therefore, posttranslational changes in proteins and the generation of ACPAs are promoted, resulting in a loss of tolerance of the immune system (42).

It has been reported that tobacco smoke is made up of several toxic substances, such as carbon monoxide, nicotine, tar, formaldehyde, and quinones, that are a source of the semiquinone radical, which can generate O_2^- and H_2O_2. These toxic substances induce proinflammatory cytokines that contribute to RA development (40,49).

O_2^- degrades the articular cartilage and induces depolymerization of hyaluronic acid in the SF, decreasing its viscosity within the joint. This leads to the inactivation of anti-proteinases and the induction of bone resorption, activating osteoclasts. On the other hand, oxidative damage from hyaluronic acid also induces hypo-reactivity of T lymphocytes through effects on proteins and proteasomal degradation that impact the reduction of antioxidant molecules, such as reduced glutathione (GSH).

According to Afridi et al. (50), smoking is a risk factor for RA because it has been involved in 35% of seropositive RA cases. In addition, the authors reported that the heavy metal cadmium (Cd) is responsible for the development of RA because it can remain in the body for more than 10 years. According to Reyes-Hinojosa et al. (46) and Hussain & Tripathi et al. (51), tobacco smoke generates OS because Cd can substitute essential elements (mainly zinc (Zn), copper (Cu), and calcium (Ca) in metalloenzymes and biological structures with sulfhydryl groups, such as antioxidant enzymes SOD, CAT and GSH. This favours protein citrullination and the production of ACPAs that affect the joints.

In 2015, Ansari's group described in a rat model with collagen-induced arthritis type II that cadmium chloride at a dose of 50 ppm induced severe inflammation associated with polymorphonuclear cell flow, cartilage degradation, and a restriction of movement in the legs. They also noted a decrease in the activity of antioxidant enzymes (SOD and CAT), as well as an increase in lipoperoxidation, NO levels, and NF-κB expression (52).

Epidemiological studies have linked the exposure to silica particles found in the environment in rocks, sand, and soil and in the atmosphere as small particles to the development of RA (49,53). It has been suggested that silica particles can activate the immune system by releasing ROS, and they are also capable of activating macro-

phages by stimulating the production of proinflammatory cytokines (49).

Furthermore, a high concentration of particulate matter (PM) of 2.5 micrometers in diameter in the air increases the risk of idiopathic juvenile arthritis in children by 60%; it is also associated with the prevalence of systemic RA (47). Essouma and Noubiap mentioned that the mechanism between polluted air and RA development begins in the lung, generating systemic OS and subsequent inflammation (54). ROS released by MFPs and UFPs or inhaled gaseous pollutants in the respiratory tract activates the factor NFκ-B, an important mediator in the activation of proinflammatory cytokines in RA patients, which increases the number of T-helper lymphocyte type 1 (Th1) cells and consequently activates the production of TNF-α and IL-6. These cytokines activate monocytes that favour the maturation of dendritic cells, which present autoantigens that costimulate autoreactive T lymphocytes that reach the synovial membrane, initiating the process of the destruction of cells expressing autoantigens. Therefore, the generation of OS and chronic inflammation also increase the protein citrullination mechanism for the subsequent production of ACPA antibodies that induce the clinical signs of RA in genetically susceptible people (54). Valessini et al. (2015) found that ROS can aggravate the mechanism of RA by inducing periarticular bone erosion (55). Sigaux et al. (2018) reported that UFPs could induce ROS, as they are responsible for activating and releasing extracellular neutrophil traps (NETs). This process is defined as NETosis, in which senescent neutrophils release a network of protein-coated chromatin strands. In addition, this process induces the elevation of IL-23 and IL-17, which participate in the formation of inducible bronchial tissue-associated lymphoid tissue (iBALT). NETs allow the exposure of citrullinated peptides, and they can promote the transition from an innate immune response to an antigen-specific adaptive immune response (56).

Tsai et al. (2020) studied an *in vitro* model with fibroblast-like synoviocytes from RA patients exposed to 50 µg/cm2 PM for 24 h. They demonstrated that the generation of ROS increases the mRNA and protein expression of IL-6 and COX-2, which come from NOX. ROS led to the phosphorylation of ERK1/2, p38, and JNK. These MAPKs inhibit the expression of hsa-miRNA-137, resulting in the exacerbation of inflammation and, therefore, the development of RA (57). Knowledge of the regulatory mechanisms of OS in the cell can help researchers to develop therapeutic strategies for preventing inflammation (Figure 3).

There are few studies that involve the genetic metabolism of ROS and RA. However, the work of Olofsson et al. showed in an animal model that polymorphisms of the neutrophil cytosolic Factor 1 (Ncf1 or p47phox) gene, a component of the NOX complex, could induce RA. These polymorphisms activate T cells due to a reduced oxidative burst response (58).

The microbiota and rheumatoid arthritis

The study of the microbiota, the set of microorganisms that inhabit a given anatomical niche, has attracted great attention in recent years. An imbalance in the composition of the microbiota, a term known as dysbiosis, has been shown to be associated not only with metabolic diseases but also with autoimmune diseases, such as RA (59).

The role of the gut microbiota in OS processes is associated with different molecules that in turn have been found to be independently associated with RA. First, there are short-chain fatty acids, which are produced by certain bacteria of the intestinal microbiota that colonize the gut when individuals have diets high in fiber content. Short-chain fatty acids are essential for balancing redox equivalent production in the intestine (60). Within this group of molecules, one of great interest in the intestinal microbiota, because it is the most abundant metabolite, is butyrate, or butyric acid. Wang Q et al. reported that butyrate production is strongly related to RA at the functional, genetic, and phenotypic levels. Furthermore, the authors proposed that butyrate production by the gut microbiota is directly related to OS through the NO_2-dependent IL-12 signaling pathway in NK cells (61). On the other hand, short-chain fatty acids are found in higher concentrations in the serum of RA patients than in those healthy people (62,63), while they have been found to be decreased in the faeces of patients with RA (64). In fact, a study in mice showed the role of butyrate in the homeostasis of B-reg cells in RA, which has been reviewed in previous articles (64). In addition, it has been shown that the components of the intestinal microbiota are key aspects in the differentiation of effector T cells, which impacts susceptibility to autoimmune diseases and to RA (64).

Other molecules produced by the bacteria that make up the intestinal microbiota and that have been found to be associated with RA are terpenoids, which are chemically modified terpenes. Terpenoids are known to be capable of suppressing the NF-κB signaling pathway, a fundamental transcription factor for the pathogenesis of multiple inflammatory diseases, including RA (62). Specifically, Kisikawa T et al. conducted a shotgun metagenomics study in which they found that the R6FCZ7 gene is decreased in the intestinal microbiota of RA patients compared to healthy subjects. The protein encoded by this gene carries out different functions, including redox catalysis. The authors attributed this decrease to the diminished abundance of some bacterial species of the *Bacteroides* genus (62). This evidence, together with those previously described, supports the notion that the role of the intestinal microbiota in the susceptibility to or the development of RA is not only related to the homeostasis of the immune system but also OS. On the other hand, the microbiota of the oral mucosa has been extensively evaluated in RA patients due to the role of periodontitis in the disease (65).

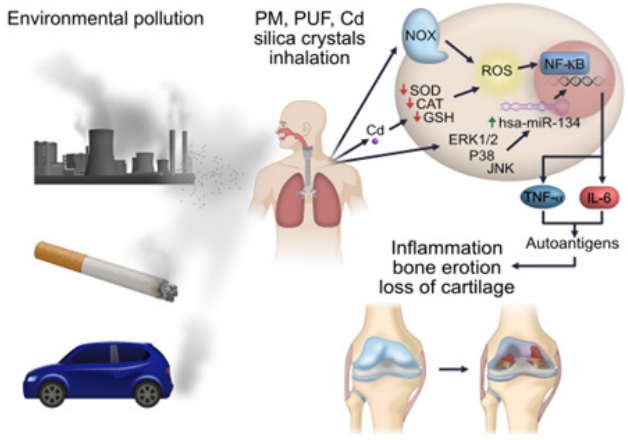

Figure 3. Contribution of pollution to RA development through OS.

There is already evidence related to the use of prebiotics and/or probiotics as an adjuvant treatment for RA patients. Approximately 9% of the studies focused on the evaluation of some type of dietary intervention with prebiotics or probiotics. In this regard, studies in mice have shown that supplementation with short-chain fatty acids, and in particular butyrate, has an immunosuppressive effect on RA (64). In addition, it is thought that the association between the use of antibiotics a greater risk of RA is related to the alterations in the microbiota that this entails, regardless of the underlying infection (66).

In a randomized, double-blind, placebo-controlled clinical trial, RA patients who were supplemented for 8 weeks with *Lactobacillus acidophilus* ($2x10^9$ CFU/g), *Lactobacillus casei* ($2x10^9$ CFU/g), and *Bifidobacterium bifidum* ($2x10^9$ CFU/g) had a decrease in disease activity, as measured with DAS-28, and they observed an improvement in their insulin levels, HOMA-B index, and serum CRP levels (67). These results are consistent with the study by Vaghef-Mehrabany et al. from 2019, in which they observed that supplementing RA patients with *L. casei* (10^8 CFU) for two months resulted in a decrease in CRP and the DAS-28 score. They also observed a significant decrease in proinflammatory cytokines (TNF-α, IL-12, IL-1β) and an increase in IL-10 in the serum of the supplementation group (68). All this evidence suggests that the human microbiota is a decisive factor in the alteration of the immune response, inflammation, redox mechanisms, and metabolism, all of which are processes of vital importance in the pathophysiology of RA. Due to the intrinsic nature of the human microbiota, its modification is a highly plausible adjuvant treatment option for modulating the development and progression of the disease.

Oxidative stress regulation as a new complementary strategy for treatment

The main objective of the treatment strategies for RA is to achieve remission, mainly by controlling swelling and pain, thus improving the quality of life of patients. The challenge lies in detecting and diagnosing RA at early stages, which will allow for prompt and assertive treatment, preventing irreversible damage so that the loss of joint function can be avoided or delayed and reducing disability. There are different methods of treatment for RA, including therapies with nonsteroidal anti-inflammatory drugs (NSAIDs) as the preferential method to relieve pain and decrease inflammation (69) and disease-modifying antirheumatic drugs (DMARDs), which are involved in delaying the progression of joint damage and deformity, as recommended by EULAR (70). In severe cases, the joint can be replaced (71).

Over the last few years, new contributions have been made to improve the results of the standard medications (methotrexate, hydroxychloroquine, sulfasalazine, and prednisolone) used in RA treatment. New strategies based on the regulation of pro-oxidant and antioxidative enzymes have been proposed. This is not necessarily an isolated therapy, as recent investigations show a synergistic effect between complementary or alternative medicine and conventional RA treatment. The alternative treatments to regulate OS in RA and manage disease activity include vitamins, antioxidant agents, dietary supplements, probiotics, and a variety of physical therapies (Table 1).

Leon Fernandez et al. (2016) (72) proposed an ozone-mediated strategy. Rectal insufflations of medical ozone (5/week, Monday to Friday), combined with methotrexate (12.5 mg, intramuscular), decreased pain intensity and injury redox markers, such as NO and MDA, and increased the capacity of the antioxidant endogenous system, such as SOD, CAT, and GSH.

Vitamin and antioxidant supplements contribute largely to improving inflammation and OS. In 2015 Abdollahzad (73) showed that a dose of 100 mg/day coenzyme Q10 (CoQ10) for 2 months significantly decreased MDA in serum and suppressed the overexpression of TNF-α, but no changes were found in the total antioxidant capacity (TAC)

Table 1. Proposed synergistic treatments that reduce OS and improve health in RA patients.

Synergic treatments	Effects	Reference
Rectal insufflation of medical-grade ozone	↓ Pain intensity and injury redox markers, such as NO and MDA ↑ Capacity of the antioxidant endogenous system, including SOD, CAT, and GSH	72
Coenzyme Q10 (CoQ10)	↓ MDA in serum, suppression of the overexpression of TNF-α	73
N-acetylcysteine (NAC)	Improvements in global health and pain relief analysed by VAS and HAQ	74
Pomegranate (POMx)	↑ Paraoxonase 1 (PON1) activity in serum prevents the oxidation of low-density lipoprotein cholesterol (LDL-C) ↓ Free radical-induced lipid peroxidation	75
Saffron	↓ DAS28 index scores, TNF-α, interferon-gamma and MDA	78
Sesamin	↓ Serum levels of MDA and increased TAC and high-density lipoprotein cholesterol (HDL-C) levels	77
Allium sativum (garlic)	↑ TAC and decreased MDA at the serum level	79
Lactobacillus acidophilus, L. casei, and *Bifidobacterium bifidum*	Improved DAS28 scores, decreased serum insulin levels and high-sensitivity CRP concentrations	67,80,81
Exercise training	↑ Serum protein carbonyls and NO, and decreased the 3-nitrotyrosine (3-NT), which was related to a decreased DAS28 score	82
Yoga session	↓ DAS28 and HAQ scores	83
Acupuncture	↑ SOD, GR, CAT plasma activity, GSH blood levels, and ATP concentrations ↓ Serum MDA, nitrate and nitrite, CRP, IL-6 levels, GPx activity and the ESR	84

or IL-6 in the group of RA patients. Batooei et al. (2018) (74) demonstrated that oral N-acetylcysteine (NAC) (600 mg) twice a day for 12 weeks is a good adjuvant therapy that affects the clinical outcomes of RA patients, revealing significant improvements in their global health, pain relief analyzed with the visual analogue scale (VAS), and functional status (disability) measured with the Health Assessment Questionnaire (HAQ) Disability Index. However, they found no significant differences in DAS28 and ESR as indicators of the presence of inflammation.

There are a few reports about dietary supplements and their effect on RA activity. In 2011, Balbir-Gurman et al. (2011) (75) demonstrated that the intake of pomegranate (POMx) as a potent antioxidant due to its content of flavonoids and polyphenols has a good effect on the disease activity of RA patients compared to the baseline. They observed that a dose of 10 ml/day POMx juice for 12 weeks decreased the DAS28 score and the tender joint count. The clinical improvement was linked to the decrease in serum oxidative status, a small yet significant increase in serum paraoxonase 1 (PON1) activity that prevents oxidation of low-density lipoprotein cholesterol (LDL-C), and a decrease in free radical-induced lipid peroxidation. In 2016, Ghavipour et al. (76) showed that the intake of two capsules of POMx (250 mg) significantly reduced the DAS28 score and was related to a decrease in the swollen, tender joint count, pain intensity, and ESR. POMx intake also decreased the HAQ score and morning stiffness. In serum, GPX levels were improved, but no variations were observed in MMP3, CRP, or MDA levels. These data indicate that POMx improves disease activity (75). Helli et al. (2016) (77) validated that sesame supplementation works as an antioxidant and anti-inflammatory factor, showing that it not only improved the protective effect on cardiovascular risk but also significantly decreased the serum levels of MDA and increased the TAC and high-density lipoprotein cholesterol (HDL-C) levels in RA patients. Saffron (dried stigmas of Crocus sativus L) is another dietary complement that contains different antioxidant compounds. In 2019, Hamidi et al. (78) described that saffron supplementation significantly decreased the DAS28 index, the number of tenders and swollen joints, the pain intensity using VAS, and the CRP. The authors also described that those clinical improvements might be related to the decrease in TNF-α, interferon-gamma and MDA and the increase in the TAC. Recently, garlic (Allium sativum, Alliacea family) has taken relevance due to the antioxidant feature of diverse compounds, such as allicin, diallyl sulfide, saponins, etc., and its involvement in the regulation of the nuclear factor ertythrobia-2 related factor antioxidant response element pathway. Moosavian et al. (2020) (79) observed that garlic as a supplement affects OS biomarkers, increases TAC, and decreases MDA at the serum level; therefore, garlic influences the quality of life of RA patients.

Regarding probiotics and their antioxidant properties, in 2015, Vaghef-mehrabany et al. (80) found no significant changes after 8 weeks of treatment with *Lactobacillus casei* (*L. casei*) strains (daily capsule containing 10^8 CFU) as a complement to the traditional treatment, finding no significant difference in serum MDA, TAC levels or CAT activity between the studied groups. Furthermore, they found no significant changes in SOD and GPX activities. However, in 2016, Zamani et al. (67) described the effects of probiotic supplementation on the metabolic status of RA patients, concluding that the combination of *Lactobacillus acidophilus*, *L. casei*, and *Bifidobacterium bifidum* improved DAS28 and decreased serum insulin levels and high-sensitivity CRP concentrations but had no effect on inflammation and OS. In 2017, Zamani et al. (81) analyzed symbiotic supplementation and its relation to biomarkers of inflammation and OS. The results showed a decrease in serum high-sensitivity CRP levels, improvement in DAS28 and VAS scores, and a significant elevation in plasma NO and GSH. These data demonstrate that the symbiotic capsule (*Lactobacillus acidophilus*, *L. casei*, and *Bifidobacterium bifidum* plus 800 mg inulin) has a beneficial effect on RA patients after 8 weeks of intake.

Interestingly, another adjuvant in RA treatment is the use of alternative physical therapy. Wadley et al. (82) reported the effect of exercise training on markers of OS in RA, describing those weekly exercise sessions (30–40 min) for 3 months significantly increased the serum protein carbonyls and NO and decreased the 3-nitrotyrosine (3-NT), which was related to a decreased DAS28. In 2019, Gautam et al. (83) recommended yoga as a complementary mind-body therapy. A 120-minute daily yoga session and 5 sessions per week for 8 weeks significantly decreased the severity of RA, reducing the participants' DAS28 and HAQ values. It also significantly reduced OS due to the decrease in ROS and the increase in TAC. It has been suggested that acupuncture may be an adjuvant for RA treatment. Atiia et al. (84) described that laser acupuncture (904 nm, 100 mW power output for 1 minute) for 3 days a week for 4 weeks significantly increased SOD, GR, CAT plasma activity, GSH blood levels, and ATP concentrations and reduced oxidative markers, such as serum MDA, nitrate and nitrite, CRP, IL-6 levels, GPx activity, and the ESR, in laser-exposed patients compared to those before treatment. In 2017, Hirvonen et al. (85) proposed the use of whole-body cryotherapy (dry air from −110 °C to −160 °C) for 1–3 min as a complement to the classical treatment for RA. Cryotherapy was associated with a decrease in pain, and it increased the total peroxyl radical trapping antioxidant capacity of plasma (TRAP); these findings led to the conclusion that cryotherapy increases the antioxidant defense in the short term.

In summary, OS, inflammation, and RA disease activity are closely related, and supplementary therapies targeting oxidative damage have a synergic effect when used in combination with conventional treatment; together, they enhance the clinical outcomes of RA patients, as described previously.

Conclusions

RA is an autoimmune disease that affects approximately 1% of the worldwide population. In the past decade, more evidence has emerged suggesting that oxidative stress can be generated by pollution and microbiota imbalances and that such factors are therefore associated with RA progression. For that reason, it is important to consider comprehensive treatments that decrease oxidative stress and help reduce disease activity in patients with RA.

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