



REVIEW

Gut Microbiota, Oxidative Stress, and Extracellular Vesicles: Molecular Crosstalk in Inflammation and Disease and Therapeutic Interventions

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ABSTRACT: The gut microbiota, oxidative stress, and extracellular vesicles (EVs) form an interdependent triad essential for gastrointestinal homeostasis and systemic health. This narrative review summarizes the molecular crosstalk among these components in inflammation and disease. Literature was retrieved from PubMed and Scopus using relevant keywords and reference screening. Gut microbes regulate redox balance through metabolites such as short-chain fatty acids and modulation of host reactive oxygen species (ROS) production via mitochondrial pathways and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase. Dysbiosis has been associated with excessive ROS generation, impaired antioxidant defenses, and activation of redox-sensitive signaling pathways, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), NOD-like receptor pyrin domain containing 3 (NLRP3) inflammasome, and mitogen-activated protein kinase (MAPK), contributing to inflammatory and metabolic diseases. EVs act as mediators of host-microbe communication by transferring bioactive cargo that may influence oxidative stress, immune responses, and epithelial integrity. Host-derived EVs, shaped by redox status, may further contribute to systemic inflammation associated with chronic diseases. Therapeutic strategies include microbiota modulation, antioxidants, nuclear factor erythroid 2-related factor 2 (Nrf2) activators, NADPH oxidase inhibitors, and EV-based interventions. Integrated multi-omics and standardized EV profiling are needed for precision medicine approaches.

KEYWORDS: Gut microbiota; oxidative stress; reactive oxygen species; extracellular vesicles; inflammation; dysbiosis; redox signaling

1 Introduction

The gut microbiota is increasingly recognized as a critical determinant of human health, exerting broad influence over intestinal function, barrier integrity, metabolic regulation, and systemic physiological processes [1,2]. Disturbances in microbial composition or function, commonly referred to as dysbiosis, have been implicated in the development and progression of chronic inflammatory and metabolic disorders [3,4].

Oxidative stress has been proposed as a key molecular mechanism linking microbial imbalance to host tissue injury and inflammation. Under physiological conditions, reactive oxygen species (ROS) function as essential secondary messengers in intracellular signaling cascades and contribute to innate antimicrobial effector mechanisms; however, sustained or excessive ROS production disrupts redox homeostasis, leading to oxidative damage of lipids, proteins, and nucleic acids [5–7]. Emerging evidence suggests a bidirectional relationship in which microbial dysbiosis influences systemic oxidative stress, while oxidative stress reshapes microbial composition [8,9].

In recent years, extracellular vesicles (EVs) have emerged as important mediators of communication between host cells and microorganisms within the gut ecosystem [10,11]. Both mammalian cells and gut bacteria release membrane-bound vesicles containing bioactive molecules, including enzymes, metabolites, regulatory RNAs (ncRNAs), and immunomodulatory signaling proteins, that modulate immune, metabolic, and redox-related processes [12,13].

Importantly, while previous reviews have addressed gut microbiota, oxidative stress, and EVs separately or in parallel, they have rarely integrated these components into a unified mechanistic framework. In contrast, this review specifically conceptualizes a microbiota-oxidative stress-extracellular vesicle axis as an interconnected redox-inflammatory network, providing a systems-level perspective on their bidirectional interactions in disease progression.

This integrated microbiota-oxidative stress-extracellular vesicle axis is increasingly implicated in a wide range of inflammation-associated diseases, including inflammatory bowel disease, metabolic syndrome, cardiovascular disorders, and neuroinflammatory conditions. A schematic overview of this bidirectional network is provided in Fig. 1, illustrating how these components interact to regulate systemic homeostasis and disease progression. Despite growing interest, mechanistic links and the collective contribution of these components to disease pathogenesis remain incompletely understood; this review critically examines molecular crosstalk between gut microbiota, oxidative stress, and EVs in the context of inflammation and disease to provide a framework for future research and therapeutic development [14–16].

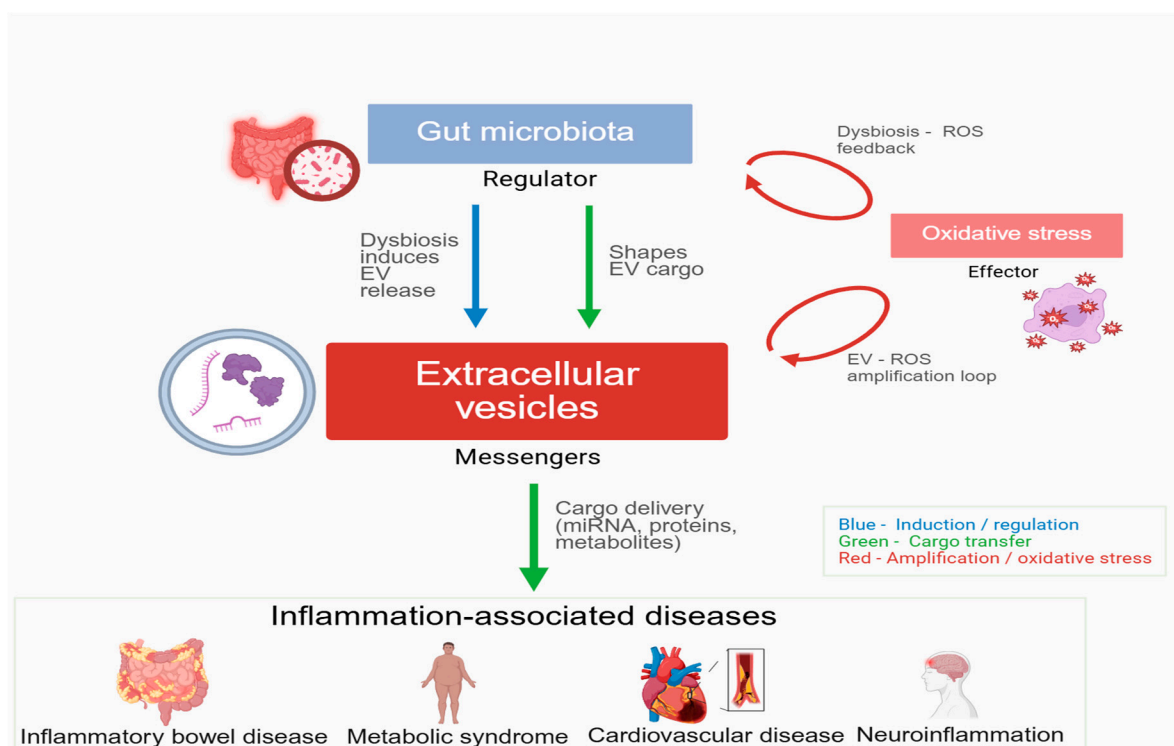


Figure 1: Molecular crosstalk between gut microbiota, oxidative stress, and extracellular vesicles (EVs). Gut microbiota, oxidative stress, and EVs form a bidirectional regulatory network involved in systemic homeostasis and disease. In this axis, Reactive Oxygen Species (ROS) act as central mediators; oxidative stress reshapes microbial communities, while gut dysbiosis, further promotes ROS generation. Created in BioRender, Velikova T (2026).

2 Literature Selection Strategy

This narrative review was conducted using literature retrieved from PubMed, Web of Science, and Scopus databases. Relevant studies were identified using combinations of the following keywords: ‘gut microbiota’, ‘oxidative stress’, ‘reactive oxygen species’, ‘extracellular vesicles’, ‘microbiota-derived extracellular vesicles’, ‘inflammation’, ‘redox signaling’, and ‘dysbiosis’. Additional references were identified through manual screening of reference lists from relevant articles. Priority was given to peer-reviewed original studies, mechanistic investigations, translational research, and high-impact review articles directly related to the microbiota-ROS-EV axis. Non-English publications, non-peer-reviewed sources, and studies lacking direct relevance to the central theme were excluded. Emphasis was placed on recent mechanistic and translational studies given the rapidly evolving nature of the field.

3 Gut Microbiota as a Regulator of Redox Homeostasis

The gastrointestinal tract maintains a tightly controlled redox equilibrium in which ROS production is balanced by antioxidant defenses to support epithelial integrity, immune signaling, and microbial homeostasis. The gut microbiota is an important regulator of this balance, modulating oxygen availability, epithelial metabolism, and antioxidant capacity. Disruption of microbial homeostasis or persistent inflammation may shift this equilibrium toward oxidative stress, leading to barrier dysfunction and amplified inflammatory responses [17]. Within the gastrointestinal tract, the redox balance is further shaped by the gut microbiota, which influences ROS production through microbial metabolism and modulation of host epithelial enzymes [18].

Antioxidant defense systems, comprising both enzymatic and non-enzymatic components, are essential for maintaining redox homeostasis by regulating ROS and limiting oxidative stress, a process closely linked to aging and chronic disease, including gastrointestinal disorders [19]. Non-enzymatic antioxidants such as glutathione and thioredoxin buffer intracellular redox fluctuations and regulate redox-sensitive signaling, while their activity is tightly controlled by thioredoxin-interacting protein (TXNIP), whose age-associated upregulation promotes oxidative damage and cellular senescence [20]. Enzymatic antioxidants, including superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase, act sequentially to detoxify superoxide and hydrogen peroxide, preserving cellular macromolecules from oxidative injury [21,22]. In the gastrointestinal tract, where epithelial tissues are continuously exposed to oxidative challenges, disruption of these antioxidant systems contributes to barrier dysfunction, inflammation, and diseases such as inflammatory bowel disease and colorectal cancer, highlighting redox regulation as a key therapeutic target [23,24]. Table 1 provides an overview of common ROS, reactive nitrogen species (RNS), and key cellular antioxidants.

Table 1: Common reactive oxygen and nitrogen species and the cellular antioxidant defenses that regulate redox homeostasis.

Type	Examples	Source/Generation	Primary Function	Antioxidant Defense	References
Reactive Oxygen Species (ROS)	Superoxide ($O_2^{\bullet-}$), Hydrogen peroxide (H_2O_2), Hydroxyl radical ($\bullet OH$), Singlet oxygen ($^1O_2$)	Mitochondrial electron transport chain, NADPH oxidases, peroxisomal reactions	Signal transduction, immune defense, and oxidative damage at high levels	SOD, CAT, GPx, GSH, TRX	[25–27]
Reactive Nitrogen Species (RNS)	Nitric oxide ($NO\bullet$), Peroxynitrite ($ONOO^-$), Nitrogen dioxide ($\bullet NO_2$)	Nitric oxide synthases (NOS); reaction of NO with ROS	Vasodilation, immune modulation, biomolecule nitration	GSH, TRX, peroxiredoxins	[28–30]

Table 1: *Cont.*

Type	Examples	Source/Generation	Primary Function	Antioxidant Defense	References
Enzymatic antioxidants	Superoxide dismutase (SOD), Catalase (CAT), Glutathione peroxidase (GPx), Glutathione reductase (GR), Peroxiredoxins (Prx)	Endogenous cellular production	Detoxification of ROS and redox balance maintenance	Maintain cellular redox homeostasis	[31–33]
Non-enzymatic antioxidants	Glutathione (GSH), Thioredoxin (TRX), Vitamins C and E, Uric acid, Flavonoids	Dietary intake or endogenous synthesis	Free radical scavenging and redox signaling modulation	Support enzymatic systems and prevent oxidative damage	[20,34,35]

Note: ROS, Reactive Oxygen Species; $O_2^{\bullet-}$, superoxide anion; H_2O_2 , hydrogen peroxide; $\bullet OH$, hydroxyl radical; $^1O_2$, singlet oxygen; RNS, Reactive Nitrogen Species; $NO\bullet$, nitric oxide; $ONOO^-$, peroxynitrite; $\bullet NO_2$, nitrogen dioxide; NOS, nitric oxide synthase; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; GR, glutathione reductase; Prx, peroxiredoxins; GSH, glutathione; TRX, thioredoxin.

The gastrointestinal tract relies on the antioxidant system to maintain redox homeostasis and protect epithelial tissues from oxidative stress-induced damage. This balance is strongly influenced by the gut microbiota and its metabolites, as commensal bacteria contribute to antioxidant defenses primarily through short-chain fatty acids and other bioactive signaling molecules that support barrier integrity and modulate immune responses (Table 2) [36,37]. Disruption of microbial composition can impair redox homeostasis, elevate oxidative stress, and promote gastrointestinal pathology. In addition to microbial factors, dietary micronutrients, particularly vitamin D, play a critical role in shaping microbial composition, regulating immune function, and maintaining epithelial integrity through vitamin D receptor-dependent pathways [38,39]. Bidirectional interactions between microbial metabolites, host antioxidant systems, and nutrient-sensing receptors collectively determine redox equilibrium, highlighting the importance of an integrated microbiota-nutrient-host axis in preserving gastrointestinal health and preventing inflammation-driven disease.

Table 2: Functional overview of gut microbiota-induced ROS regulation: mechanisms and biological effects.

Gut Microbiota	Mode of ROS Induction	Major ROS Species	Enzymes Involved	Cellular Sites	ROS-Mediated Effects	Host Antioxidant Systems	References
SCFA-producing microbiota (<i>Faecalibacterium</i> , <i>Roseburia</i> , <i>Coprococcus</i>)	Indirect via SCFAs (butyrate-mediated signaling)	$\downarrow$ H_2O_2 , $\downarrow$ $O_2^{\bullet-}$	The bacterial butyryl-CoA: acetate CoA-transferase pathway produces butyrate, which activates the host Nrf2/KEAP1 pathway and enhances antioxidant defense	Intestinal epithelium, immune cells, colonocytes	Anti-inflammatory; restoration of redox homeostasis; improved epithelial energy metabolism	Activation of Nrf2 pathway; induction of SOD, CAT, GPx; increased GSH	[40–42]
Barrier-protective commensal (<i>Akkermansia muciniphila</i>)	Indirect via mucus layer strengthening and reduced endotoxin translocation	$\downarrow$ systemic ROS (H_2O_2 , HOCl)	Bacterial: Mucin-degrading enzymes (support its niche). Host: Endocannabinoid system modulation ($\uparrow$ 2-OG, 2-AG, 2-PG)	Gut lumen, intestinal mucus layer, epithelial interface (lamina propria)	Reduced metabolic endotoxemia; decreased chronic inflammation and oxidative stress; improved metabolic balance	Upregulation of SOD and CAT; increased GSH availability	[43–45]
Pathogenic Enterobacteriaceae (<i>Escherichia coli</i> , <i>Salmonella Typhimurium</i>)	Host NOX/DUOX activation and mitochondrial dysfunction via virulence factors	$O_2^{\bullet-}$, H_2O_2 , HOCl ($\uparrow$ ROS)	NADH dehydrogenase, extracellular demethylmenaquinone.	Epithelial mitochondria, phagocytes	Oxidative stress; epithelial damage; inflammation; barrier disruption	Consumption/depletion of GSH; activation of Nrf2 stress response	[46–48]
Probiotic ROS-modulating bacteria (<i>Lactobacillus</i> , <i>Bifidobacterium</i>)	Controlled redox signaling and mild ROS generation	Low-level H_2O_2 , $O_2^{\bullet-}$	Bacterial: NADH oxidases, flavin reductases Host: NADPH oxidase, myeloperoxidase	Intestinal lumen, immune interface	Immune modulation; antimicrobial defense; maintenance of redox balance	Balanced activity of SOD, CAT, GPx systems	[49–51]
Opportunistic pro-oxidant bacteria (<i>Enterococcus faecalis</i>)	Extracellular electron transfer-associated ROS production	$O_2^{\bullet-}$, H_2O_2	Host mitochondrial electron transport chain (ETC) complexes	Gut lumen, epithelial surface	DNA damage; chronic inflammation; carcinogenic potential	Overwhelms SOD/CAT detoxification capacity	[52–54]

Note: SCFAs, short-chain fatty acids; ROS, reactive oxygen species; H_2O_2 , hydrogen peroxide; $O_2^{\bullet-}$, superoxide anion; HOCl, hypochlorous acid; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; GSH, glutathione; Nrf2, nuclear factor erythroid 2–related factor 2; NOX, NADPH oxidase; DUOX, dual oxidase. $\uparrow$, increase; $\downarrow$, decrease or reduced levels. SCFA, short-chain fatty acid-mediated effects include butyrate-driven Nrf2 activation and metabolic signaling.

4 Sources of ROS Generation

Mitochondria and NADPH oxidases constitute the principal cellular sources of ROS. Within mitochondria, ROS generation occurs primarily along the electron transport chain, where single-electron transfer to molecular oxygen produces superoxide ($O_2^{\bullet-}$), predominantly at ubisemiquinone intermediates of coenzyme Q. Seminal studies demonstrated that mitochondrial hydrogen peroxide (H_2O_2) formation is tightly coupled to ubiquinone content, as depletion of ubiquinone markedly reduces ROS production, whereas reconstitution restores and enhances peroxide generation [55]. The rate of mitochondrial ROS production is strongly influenced by metabolic state and can be amplified by electron transport inhibitors, uncouplers of oxidative phosphorylation, or elevated oxygen tension, underscoring the capacity of mitochondria to become a major source of oxidative stress under pathological conditions [5,56,57]. Beyond stochastic electron leakage during aerobic respiration, the mitochondrial electron transport chain generates ROS primarily at complexes I and III. This regulated ROS production enables mitochondria to function as redox-signaling hubs, critically regulating physiological processes such as T-cell activation and adaptive immune responses [55,58,59]. The major intracellular and extracellular sources of ROS are summarized in Fig. 2. Importantly, microbial dysbiosis and microbiota-derived metabolites directly influence mitochondrial ROS generation and NOX activation, thereby linking microbial composition to oxidative stress-dependent inflammatory and EV signaling pathways. The gut microbiota critically regulates host redox homeostasis, in part through microbial metabolites that modulate major cellular sources of ROS. Short-chain fatty acids influence NADPH oxidase activity, while microbial dysbiosis alters mitochondrial and endoplasmic reticulum-derived ROS production, promoting oxidative stress (Table 3).

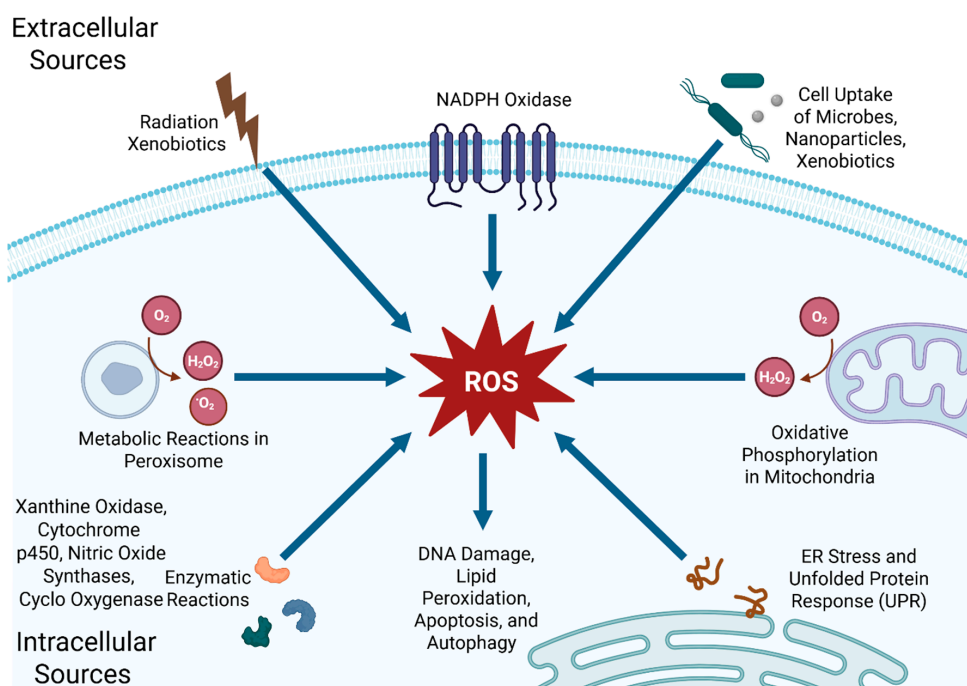


Figure 2: Intracellular and extracellular sources of oxidative stress. Oxidative stress arises from excessive ROS production generated extracellularly by radiation, xenobiotics, NADPH oxidases and the uptake of microbes and nanoparticles, and intracellularly by mitochondrial oxidative phosphorylation, peroxisomal metabolism, enzymatic reactions involving Xanthine Oxidase and Cytochrome p450, and endoplasmic reticulum stress, leading to cellular damage. Created in BioRender, Velikova T (2026) and adapted from [8].

NADPH oxidases are specialized multicomponent enzymes that generate ROS through the controlled one-electron reduction of molecular oxygen using NADPH. The phagocytic isoform NADPH oxidase 2 (NOX2) is the best-characterized member and a major inducible source of ROS in immune cells, where it produces superoxide ($O_2^{\bullet-}$) that is rapidly converted to hydrogen peroxide (H_2O_2), a diffusible redox signaling molecule. In contrast, NOX1 is predominantly expressed in non-phagocytic cells, particularly the intestinal epithelium, where microbiota-modulated ROS production regulates epithelial signaling, migration, and mucosal repair; however, dysregulated NOX1 activity contributes to inflammation and tumorigenesis [60–62].

Table 3: Major cellular sources of ROS regulated by the gut microbiota and their functional roles.

Subcellular Location	Major ROS-Producing System	ROS	Mode of ROS Generation	Oxidative Stress-Related Pathologies	Modulatory Role of Gut Microbiota	References
Mitochondria	Electron Transport Chain (ETC) Complexes I & III	$O_2^{\bullet-}$, H_2O_2	Electron leakage during oxidative phosphorylation	Neurodegenerative diseases (Alzheimer's, Parkinson's), cardiovascular diseases, diabetes, cancer, ageing	SCFAs associated with improved mitochondrial efficiency; dysbiosis linked to increased mtROS production	[63–65]
Peroxisomes	Fatty Acid β -Oxidation; Xanthine Oxidase (XOR)	H_2O_2 , $O_2^{\bullet-}$	Fatty acid and purine oxidation	Metabolic syndromes (gout, hyperuricemia), neurodegenerative disorders, Zellweger syndrome	SCFAs modulate lipid metabolism and uric acid pathways	[66–68]
Endoplasmic Reticulum (ER)	Cytochrome P450 Enzymes (CYP); ERO1	H_2O_2 , $O_2^{\bullet-}$	Protein folding and detoxification reactions	ER stress-related diseases: diabetes, fatty liver disease, neurodegenerative disorders, inflammatory conditions	Microbial metabolites may modulate ER stress and CYP activity	[69–71]
Plasma Membrane (Phagocytic & Non-Phagocytic)	NADPH Oxidase 2 (NOX2/Phox)	$O_2^{\bullet-}$, H_2O_2	Activated in phagocytes after pathogen recognition, transferring electrons from NADPH to O_2 .	Chronic granulomatous disease (CGD), atherosclerosis, autoimmune disorders, chronic inflammation	Microbiota modulates NOX2 activity, boosting pathogen killing while limiting excessive activation by commensals.	[72–74]
Extracellular Space/Lumen	Secreted Peroxidases (e.g., Lactoperoxidase); DUOX2	H_2O_2 , HOCl, OSCN ⁻	DUOX2 produces H_2O_2 at epithelial surfaces, and peroxidases convert it into bactericidal hypohalous acids.	Hypothyroidism (DUOX2 defects), gastrointestinal inflammation, cystic fibrosis	Microbiota regulates DUOX2, and metabolites support peroxidase activity, shaping microbial balance.	[75–77]

Note: HOCl, hypochlorous acid; mtROS, mitochondrial reactive oxygen species; SCFAs, short-chain fatty acids; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; Nrf2, nuclear factor erythroid 2-related factor 2; 2-OG, 2-oleoylglycerol; 2-AG, 2-arachidonoylglycerol; 2-PG, 2-phosphoglycerate; T3SS, type III secretion system; iNOS, inducible nitric oxide synthase; TLR2, toll-like receptor 2; HDAC, histone deacetylase; GPCR, G protein-coupled receptor; KEAP1, kelch-like ECH-associated protein 1; PSA, polysaccharide A; LPS, lipopolysaccharide; Th1/Th17, T-helper 1/17 cells; IL-10, interleukin-10; NOX2, NADPH oxidase 2; DUOX2, dual oxidase 2; HO-1, heme oxygenase-1; NQO1, NAD(P)H:quinone oxidoreductase 1; GST, glutathione S-transferase; NAC, N-acetyl-L-cysteine.

5 Oxidative Stress-Mediated Inflammatory Signaling in the Gastrointestinal Tract

Oxidative stress is considered a key driver and amplifier of inflammatory signaling within the gastrointestinal (GI) tract, where epithelial cells, immune cells, and resident microbiota coexist in a highly reactive environment [17,78]. Under physiological conditions, low levels of ROS function as signaling molecules that regulate epithelial renewal, immune surveillance, and host-microbe interactions. However, excessive or sustained ROS production disrupts redox homeostasis and initiates pro-inflammatory signaling cascades that contribute to mucosal injury and chronic intestinal inflammation [22,78,79]. Sustained activation of this redox-inflammatory axis promotes disruption of epithelial tight junctions, increased intestinal permeability, and translocation of luminal antigens, features that are central to the pathogenesis of inflammatory bowel disease and colitis-associated colorectal cancer [21,80].

In the intestinal epithelium, elevated ROS has been shown to activate redox-sensitive transcription factors, most notably nuclear factor- κ B (NF- κ B) and activator protein-1 (AP-1) [81]. Mitochondria and NADPH oxidases, particularly NOX1 and NOX2, represent major sources of ROS that link metabolic stress and microbial stimuli to inflammatory signaling in intestinal epithelial and immune cells [82,83]. The inflammatory microenvironment disrupts redox homeostasis by recruiting neutrophils that generate excessive ROS via the respiratory burst, thereby sustaining a feed-forward cycle of oxidative stress and inflammation [84–86]. This imbalance is amplified during gut dysbiosis, where diminished production of antioxidant metabolites such as butyrate and expansion of pro-inflammatory pathobionts exacerbate redox perturbations. Chronic epithelial ROS exposure induces DNA damage, cellular senescence, and impaired mucosal repair, linking it to persistent inflammatory conditions [87–89].

Oxidative stress also plays a critical role in inflammasome activation. Excess ROS has been implicated in promoting NLRP3 inflammasome assembly, leading to caspase-1 activation and subsequent maturation of IL-1 β and IL-18 [90]. This mechanism contributes to the pathogenesis of inflammatory bowel disease (IBD), where persistent inflammasome signaling exacerbates epithelial damage and disrupts barrier integrity [91,92]. In parallel, ROS-induced lipid peroxidation and oxidative DNA damage further contribute to epithelial dysfunction and sustained inflammatory responses [6].

Oxidative stress additionally alters EV biogenesis and cargo composition, promoting the release of EVs enriched in oxidized lipids, mitochondrial DNA, and pro-inflammatory mediators that may further amplify NF- κ B signaling and inflammasome activation in recipient cells.

The gut microbiota strongly modulates oxidative stress-driven inflammation. Dysbiosis is associated with increased luminal oxygen tension, altered microbial metabolism, and enhanced ROS production from both host and microbial sources. Loss of beneficial anaerobic bacteria and reduced production of short-chain fatty acids impair antioxidant defenses and favor pro-inflammatory redox signaling [93,94]. Conversely, commensal microbes and their metabolites can attenuate oxidative stress by activating antioxidant pathways, such as nuclear factor erythroid 2-related factor 2 (Nrf2), thereby limiting inflammatory damage [95,96]. These key oxidative stress-mediated inflammatory signaling pathways in the gastrointestinal tract are summarized in Table 4.

Persistent redox imbalance promotes disease progression in conditions such as IBD, colorectal cancer, and metabolic-associated intestinal disorders. Targeting redox-dependent inflammatory pathways, therefore, represents a promising strategy for restoring intestinal homeostasis and limiting chronic inflammation [85,97,98].

Table 4: Oxidative stress-mediated inflammatory signaling pathways in the gastrointestinal tract.

Signaling Pathway	Major ROS Source	Key Molecular Targets	Downstream Inflammatory Mediators	Pathophysiological Outcomes	References
NF-κB pathway	Mitochondria, NOX1/NOX2	IκB kinase (IKK), p65	TNF-α, IL-6, IL-1β, COX-2	Chronic intestinal inflammation; epithelial injury	[99–101]
MAPK signaling (ERK, JNK, p38)	Mitochondria, ER stress	MAPK kinases (MEK, MKK)	AP-1 activation, cytokines	Immune activation; barrier dysfunction	[102,103]
NLRP3 inflammasome	Mitochondria, NOX-derived ROS	NLRP3, ASC, caspase-1	IL-1β, IL-18	Immune activation; barrier dysfunction	[104–106]
JAK/STAT pathway	ROS-induced cytokine signaling	STAT3, STAT1	IL-6-dependent transcription	Chronic inflammation; tumorigenesis	[107–109]
Nrf2 antioxidant pathway	Mitochondrial and cytosolic ROS	Keap1–Nrf2 complex	HO-1, GPx, SOD, CAT	Antioxidant response; redox homeostasis	[95,110, 111]
ER stress/UPR signaling	ER-derived ROS	PERK, IRE1α, ATF6	CHOP, NF-κB crosstalk	Epithelial apoptosis; inflammation	[112,113]
TLR-mediated signaling	Microbiota-induced ROS	TLR4/MD2, MyD88, TRIF, IRAK4	NF-κB, cytokines	Innate immune activation; dysbiosis-associated inflammation	[114–116]
PI3K/Akt/mTOR pathway	Growth factor-induced ROS, mitochondrial leakage	PI3K, PDK1, Akt, mTORC1, FOXO	mTOR activation, cytokines	Cell survival; inflammation-associated tumor growth	[117–119]
HIF-1α signaling	Mitochondrial ROS	HIF-1α stabilization	VEGF, glycolytic genes	Hypoxia adaptation; inflammatory angiogenesis	[120–122]
p53 stress response	Mitochondrial and nuclear ROS	p53, ATM/ATR	Cell-cycle arrest, apoptosis	Genomic instability; cancer risk	[123–125]
Autophagy signaling	Mitochondrial ROS	AMPK, mTOR	LC3, Beclin-1	Barrier maintenance; inflammation resolution	[126–128]
Wnt/β-catenin pathway	ROS-modulated redox signaling	β-catenin, GSK-3β	Proliferation-associated genes	Dysregulated epithelial renewal; carcinogenesis	[129–131]

Note: IKK, IκB kinase; TNF-α, tumor necrosis factor-alpha; IL, interleukin; COX-2, cyclooxygenase-2; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; ER, endoplasmic reticulum; MEK, MAPK/ERK kinase; MKK, MAPK kinase; AP-1, activator protein-1; NLRP3, NOD-like receptor family pyrin domain-containing 3; ASC, apoptosis-associated speck-like protein containing a CARD; IBD, inflammatory bowel disease; JAK/STAT, Janus kinase/signal transducer and activator of transcription; STAT3/1, signal transducer and activator of transcription 3/1; UPR, unfolded protein response; PERK, protein kinase RNA-like ER kinase; IRE1α, inositol-requiring enzyme-1 alpha; ATF6, activating transcription factor 6; CHOP, C/EBP homologous protein; TLR, Toll-like receptor; MyD88, myeloid differentiation primary response 88; TRIF, TIR-domain-containing adaptor-inducing interferon-β; IRAK4, interleukin-1 receptor-associated kinase 4; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; PDK1, phosphoinositide-dependent kinase-1; mTOR, mechanistic target of rapamycin; FOXO, fork-head box O; HIF-1α, hypoxia-inducible factor-1 alpha; VEGF, vascular endothelial growth factor; ATM/ATR, ataxia telangiectasia mutated/ATM and Rad3-related kinase; AMPK, AMP-activated protein kinase; LC3, microtubule-associated protein 1 light chain 3; GSK-3β, glycogen synthase kinase-3 beta.

6 EVs as Mediators of Microbiota-Host Communication

EVs are membrane-bound nanoparticles released by most cell types and serve as key mediators of intercellular communication. Based on biogenesis and size, EVs are broadly classified into small EVs (sEVs <200 nm) and large EVs (lEVs >200 nm). sEVs, often termed exosomes, originate from the endosomal pathway and are formed as intraluminal vesicles within multivesicular bodies that fuse with the plasma

membrane for release. In contrast, IEVs, including microvesicles and apoptotic bodies, are generated by direct outward budding of the plasma membrane or during apoptosis [132–134]. By comparison, prokaryotes lack endomembrane systems; Gram-negative bacteria form OMVs via outer membrane blebbing, while Gram-positive bacteria release MVs through cell wall remodeling and turgor-driven extrusion [135]. These EV subtypes exhibit distinct molecular signatures. sEVs are enriched in endosomal markers such as tetraspanins (CD9, CD63, CD81), ESCRT-associated proteins (TSG101, Alix), and heat shock proteins. IEVs preferentially express plasma membrane-associated proteins, including integrins, actinin-4, and ARF6, and frequently expose phosphatidylserine on their surface [136–138]. Functionally, sEVs facilitate long-range signaling through the transfer of proteins, lipids, and nucleic acids (e.g., miRNAs and mRNAs), influencing immune regulation, neuronal communication, and tumor progression. IEVs are more commonly implicated in rapid physiological and pathological processes, including coagulation, inflammation, and tissue remodeling [139–141]. To ensure rigor and reproducibility in EV research, the MISEV2023 guidelines provide standardized recommendations for EV isolation, characterization, and functional validation. Adherence to these guidelines is essential as EV-based diagnostics and therapeutics, particularly in oncology, advance toward clinical translation.

Oxidative stress has been shown to regulate and is also thought to influence EV release through ROS-sensitive pathways involving ceramide signaling, calcium flux, mitochondrial dysfunction, and ESCRT-associated membrane remodeling [142,143]. Under dysbiotic conditions, excessive ROS production promotes the release of EVs enriched in oxidized lipids, inflammatory cytokines, mitochondrial DNA, and redox-sensitive microRNAs, which propagate inflammatory signaling and epithelial dysfunction locally and systemically [144].

In this review, the term EVs refers collectively to both host-derived EVs and bacteria-derived vesicles unless otherwise specified. Host-derived EVs include exosomes, microvesicles, and apoptotic bodies released by mammalian cells, whereas bacterial vesicles include outer membrane vesicles (OMVs) from Gram-negative bacteria and membrane vesicles (MVVs) from Gram-positive bacteria. Although these vesicle populations differ in biogenesis, composition, and cellular origin, both participate in intercellular communication and modulation of oxidative stress and inflammatory signaling pathways [145–147].

Bacterial OMVs contribute to colorectal cancer progression through delivery of virulence factors that induce oxidative DNA damage, inflammatory signaling, and epithelial dysfunction. Beyond pathogenic interactions, microbial-derived extracellular vesicles (MDEVs) from commensal gut bacteria play essential roles in maintaining intestinal homeostasis. These nanoscale vesicles transport proteins, nucleic acids, lipids, and metabolites that regulate microbial community dynamics, preserve epithelial barrier integrity, and modulate local and systemic immune responses [148,149]. MDEVs also mitigate oxidative stress by influencing redox-sensitive pathways and delivering antioxidant microbial factors, positioning them as key regulators of gut health and promising biomarkers and therapeutic targets in inflammatory and metabolic diseases [150]. MDEVs attenuate oxidative stress in the gut by delivering antioxidant enzymes and regulatory molecules to intestinal epithelial cells. Their cargo activates redox pathways, particularly the Kelch like ECH associated protein 1 (Keap1)–Nrf2 axis, inducing endogenous antioxidants such as heme oxygenase-1 and glutathione. This enhances epithelial resistance to oxidative damage, suppresses inflammation, and preserves barrier integrity [151,152].

MDEVs deliver short-chain fatty acids (SCFAs) from commensal bacteria to intestinal epithelial cells, facilitating their stability and uptake. SCFAs, particularly butyrate, support colonocyte metabolism, reduce oxidative stress, and activate cytoprotective pathways via HDAC inhibition, GPR41/43 signaling, and Nrf2 activation. Moreover, SCFAs enhance tight junction protein expression (ZO-1, occludin, claudins), strengthening epithelial barrier function and limiting microbial translocation and inflammation, thereby

supporting gut and systemic homeostasis [153–155]. MDEVs from commensal and probiotic gut bacteria modulate intestinal immunity and oxidative stress in IBD. Microbiota-derived EVs modulate intestinal inflammation through TLR- and NF- κ B-dependent signaling pathways, influencing cytokine production, epithelial barrier integrity, and oxidative stress responses in inflammatory bowel disease [156]. Collectively, microbiota-derived EVs represent promising therapeutic targets for restoring intestinal homeostasis in IBD [156–158].

Oxidative stress-modified host EVs and microbiota-derived EVs are key mediators of gut-brain communication in neurodegenerative diseases, linking gut dysbiosis to blood-brain barrier (BBB) dysfunction and neuroinflammation. Bacterial OMVs enriched in lipopolysaccharide activate TLR4 signaling in microglia and astrocytes, amplifying pro-inflammatory responses, while dysbiosis-associated reductions in SCFA-associated microbiota-derived EVs weaken neuroprotective and anti-inflammatory signaling [159–161]. These EVs can cross a compromised blood-brain barrier and propagate neuroinflammatory signaling through delivery of pro-oxidative and inflammatory cargo. Together, EV-mediated transport of inflammatory and neurotoxic cargo integrates gut microbial imbalance, oxidative stress, BBB disruption, and chronic neurodegeneration [162–164].

The molecular pathways through which MDEVs influence oxidative stress in the gut remain incompletely defined, and their potential as therapeutic tools for oxidative stress-associated diseases has yet to be fully investigated (Table 5) [165,166].

Table 5: Extracellular vesicles as mediators of gut microbiota-oxidative stress-inflammation crosstalk.

EV Source	Major Triggers	Key Cargo	Effects on Oxidative Stress & Inflammation	Disease Relevance	References
Pathobiont-derived EVs (<i>E. coli</i> , Enterobacteriaceae)	Dysbiosis, host ROS	LPS, toxins, bacterial DNA/sRNAs	Activate TLR2/4–NOX signaling; increase ROS; activate NLRP3; disrupt tight junctions	IBD exacerbation; metabolic endotoxemia; neuroinflammation	[13,167,168]
Commensal/Probiotic EVs (<i>Faecalibacterium</i> , <i>Bacteroides</i> , <i>Lactobacillus</i>)	Homeostasis	SCFAs, PSA, antioxidant enzymes	Activate TLR2/Nrf2; inhibit NF- κ B; enhance barrier integrity	Gut homeostasis; anti-inflammatory effects	[169–171]
Inflamed IEC-derived EVs	LPS, cytokines, ROS	miR-21, miR-155, HMGB1, NOX enzymes	Amplify ROS; promote M1 macrophage polarization; spread epithelial injury	IBD; gut-liver axis inflammation; colorectal cancer progression	[172–174]
Immune cell-derived EVs (macrophages, neutrophils, DCs)	Inflammasome oxidative burst	IL-1 β , IL-18, NLRP3, MPO	Propagate inflammasome signaling; increase ROS; enhance NETosis	Acute colitis; systemic inflammation; autoimmunity	[175–177]
MSC-derived EVs	Inflammatory injury	miR-146a, let-7, SOD, catalase	Suppress TLR/NF- κ B signaling; restore redox balance; promote repair	Therapeutic potential in inflammatory diseases	[178–180]

Note: EVs, extracellular vesicles; sRNAs, small RNAs; IECs, intestinal epithelial cells; HMGB1, high-mobility group box 1; M1, classically activated macrophages; DCs, dendritic cells; MPO, myeloperoxidase; NETosis, neutrophil extracellular trap formation; MSCs, mesenchymal stem cells; CRC, colorectal cancer; miR, microRNA.

7 Role of the Microbiota-Oxidative-Stress-EV Axis in Systemic Diseases

Oxidative stress (OS) and the gut microbiota are tightly interconnected and jointly influence disease development. A healthy gut microbiota maintains redox homeostasis by regulating immune responses, metabolic processes, and antioxidant production. Dysbiosis disrupts redox balance and promotes systemic inflammation. These effects, mediated via microbial metabolites, disrupt cellular homeostasis and contribute to metabolic and inflammatory disorders [85,88,181]. This is particularly relevant in intestinal diseases [78,182,183].

Gut microbiome dysbiosis disrupts microbial metabolite production relevant to cardiovascular homeostasis [184,185]. Under normal conditions, commensal bacteria ferment dietary fibers to produce short-chain fatty acids (SCFAs), primarily acetate, propionate, and butyrate, which exert cardioprotective effects by modulating inflammation, regulating blood pressure, and maintaining intestinal barrier integrity. Dysbiosis is associated with decreased SCFA availability, leading to impaired gut barrier function and increased translocation of bacterial endotoxins into the circulation. This phenomenon, referred to as metabolic endotoxemia, promotes chronic low-grade inflammation and contributes to the development and progression of cardiovascular disease [186–188]. Mechanistically, SCFAs exert these effects through activation of G-protein coupled receptors (e.g., GPR41, GPR43) and inhibition of histone deacetylases (HDACs), thereby modulating NF- κ B signaling, mitochondrial function, and antioxidant gene expression. These SCFA-mediated signaling pathways further interact with EV-based intercellular communication, which extends their regulatory influence beyond the gut microenvironment. Beyond the gut and cardiovascular system, the microbiota-oxidative stress-extracellular vesicle (EV) axis has emerged as a critical mediator of systemic disease. Both host- and microbiota-derived EVs act as important signaling vehicles, transporting redox-active molecules, inflammatory mediators, microbial components, and nucleic acids to distant organs [189,190]. Dysbiosis-driven oxidative stress has been associated with alterations in EV biogenesis, cargo composition, and release, thereby amplifying inflammatory signaling and oxidative damage beyond the intestinal environment [191,192].

MDEVs enriched in lipopolysaccharides, toxins, and small RNAs can penetrate epithelial barriers and enter systemic circulation, where they modulate immune cell activation and endothelial function [193,194]. Concurrently, oxidative stress enhances the release of host EVs carrying oxidized lipids, mitochondrial DNA, and pro-inflammatory cytokines, reinforcing redox imbalance and immune dysregulation. Of particular relevance, oxidative stress-induced mitochondrial dysfunction further promotes the release of mitochondrial-derived vesicles and mitochondrial DNA-containing EVs, which act as potent damage-associated molecular patterns (DAMPs), intensifying innate immune activation. This bidirectional EV-mediated communication contributes to the propagation of chronic inflammation and tissue injury in metabolically active and immune-sensitive organs, including the liver, heart, brain, and lungs, where tissue-specific microenvironmental conditions determine the extent of EV-driven dysfunction [195–197].

In metabolic and neuroinflammatory disorders, aberrant EV signaling driven by gut dysbiosis and oxidative stress has been implicated in insulin resistance, endothelial dysfunction, blood-brain barrier disruption, and altered immune cell polarization [198–200]. Collectively, these findings highlight the microbiota-OS-EV axis as a central integrator of local gut perturbations and systemic disease processes, underscoring its potential as a therapeutic target for redox- and inflammation-driven pathologies.

A schematic overview of systemic diseases associated with oxidative stress is presented in Fig. 3, which illustrates how chronic ROS accumulation contributes to neurodegenerative, cardiovascular, metabolic, pulmonary, reproductive, inflammatory, and neoplastic disorders.

Oxidative stress, chronic inflammation, and EVs form a self-perpetuating cycle that drives sustained cellular damage and progressive organ dysfunction (Table 6 and Fig. 3). From a systems biology perspective, this axis may represent a unified signaling network integrating microbial ecology, redox regulation, and intercellular communication, thereby providing a mechanistic framework for multi-organ disease progression. Targeting this interconnected microbiota-oxidative stress-EV axis may offer promising therapeutic opportunities for effective disease management and the development of therapeutic strategies aimed at redox- and inflammation-driven pathologies.

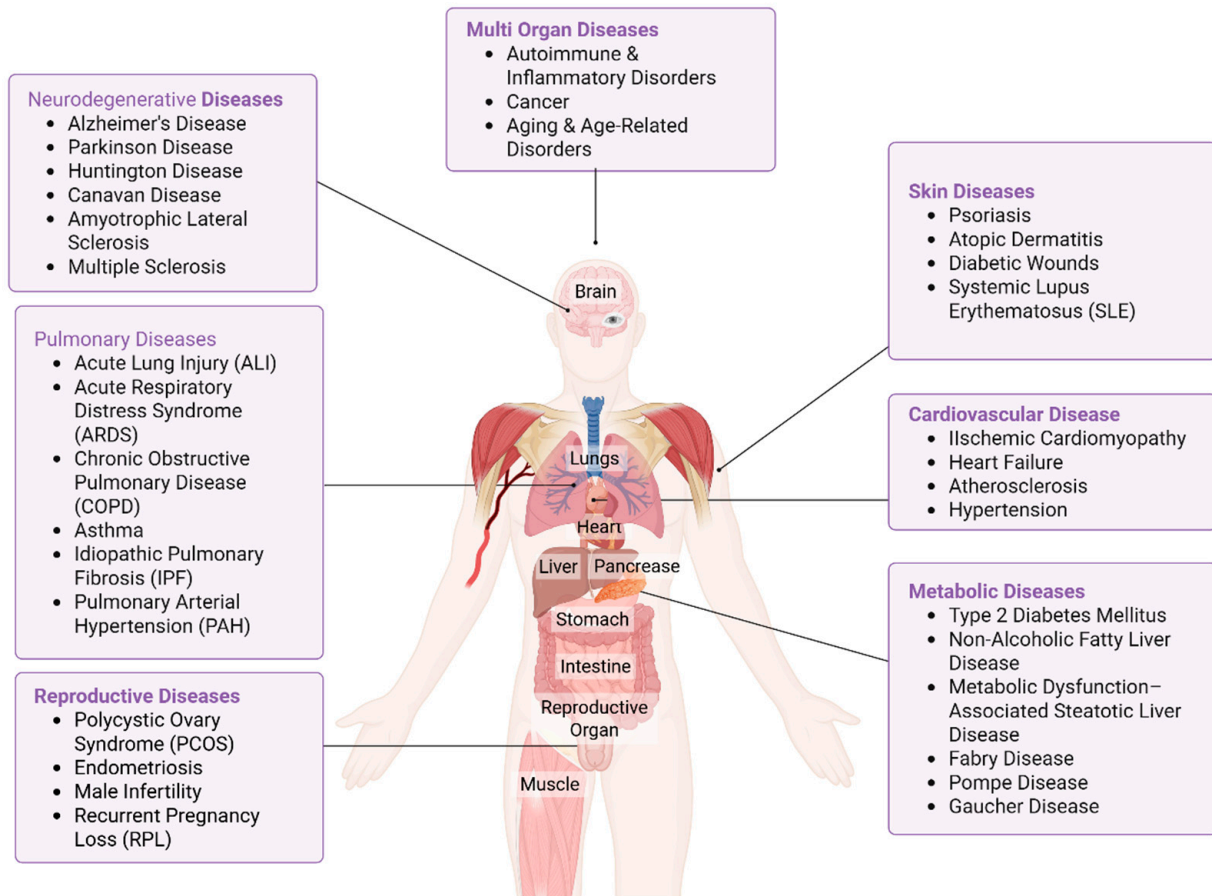


Figure 3: Human diseases associated with oxidative stress. Oxidative stress contributes to the pathogenesis of neurodegenerative, cardiovascular, metabolic, pulmonary, reproductive, inflammatory, and neoplastic diseases through chronic ROS-mediated tissue injury and inflammation. Created in BioRender, Velikova T (2026) and adapted from [201].

Table 6: Role of oxidative stress, chronic inflammation, and EVs in systemic diseases.

Disease Category	Key Roles of Oxidative Stress	Key Roles of Chronic Inflammation	EV-Mediated Mechanisms	References
Cardiovascular Diseases	ROS associated with endothelial dysfunction, lipid oxidation, and vascular injury	Immune activation, plaque instability, vascular remodeling	EVs implicated in endothelial dysfunction, smooth muscle activation, and thrombosis; regulate cardiac remodeling	[202–204]
Metabolic Disorders	Hyperglycemia- and lipid-induced ROS causing mitochondrial and vascular damage	Low-grade inflammation, cytokine release, adipose tissue dysfunction	EVs mediate inter-organ metabolic crosstalk and insulin resistance	[205–207]
Neurodegenerative Diseases	Mitochondrial dysfunction, protein oxidation, neuronal injury	Microglial activation and neuroinflammation	EVs may contribute to propagation of toxic protein aggregates and neuroinflammatory signaling	[208–210]

Table 6: *Cont.*

Disease Category	Key Roles of Oxidative Stress	Key Roles of Chronic Inflammation	EV-Mediated Mechanisms	References
Autoimmune & Inflammatory Disorders	ROS-driven tissue damage and immune activation	Persistent cytokine production and immune dysregulation	EVs regulate antigen presentation and immune cell signaling in autoimmunity	[211–213]
Cancer	ROS-induced DNA damage, genomic instability, and tumor progression	Tumor-promoting inflammation and immune evasion	EVs promote metastasis, immune suppression, and therapy resistance	[214–216]
Pulmonary Diseases	Oxidative injury from hypoxia, smoke, and inflammation	Chronic immune cell activation and tissue remodeling	EVs regulate airway inflammation, fibrosis, and vascular remodeling	[217–219]
Renal Diseases	ROS-mediated tubular and glomerular injury	Cytokine-driven fibrosis and immune activation	EVs mediate kidney injury progression and serve as biomarkers	[220–222]
Liver Diseases	ROS from lipid metabolism and mitochondrial dysfunction	Kupffer cell activation and inflammatory fibrosis	EVs regulate inflammation, fibrosis, and hepatocarcinogenesis	[223–225]
Skin Disorders	Oxidative damage to keratinocytes and fibroblasts	Immune dysregulation and cytokine imbalance	EVs regulate inflammation, wound healing, and immune signaling	[226–228]
Aging & Age-Related Disorders	Mitochondrial ROS accumulation and senescence	“Inflamming” via SASP factors	EVs propagate senescence and redox imbalance	[229–231]
Reproductive Disorders	ROS-induced gamete and tissue dysfunction	Hormonal and immune imbalance	EVs regulate fertility, implantation, and reproductive inflammation	[232–234]

Note: ROS, reactive oxygen species; EVs, extracellular vesicles; SASP, senescence-associated secretory phenotype; DNA, deoxyribonucleic acid.

8 Clinical Implications and Translational Relevance of the Microbiota-ROS-EV Axis

The gut microbiota-ROS-EV axis represents a tightly interconnected regulatory network central to the development and persistence of chronic inflammatory, metabolic, and neoplastic disorders. Microbial dysbiosis shifts the gut ecosystem from an anti-oxidative to a pro-oxidative gut microbial profile, characterized by depletion of antioxidant-supporting commensals and enrichment of pro-oxidative opportunistic taxa. This functional transition in microbial ecology drives redox imbalance and excessive ROS generation, which in turn alters EV biogenesis, molecular cargo, and intercellular signaling properties [88,235]. These EVs subsequently disseminate inflammatory and regulatory signals systemically, potentially contributing to amplification of disease-associated pathways. A schematic overview of gut microbial taxa associated with pro-oxidative and anti-oxidative gut environments is presented in Fig. 4.

From a clinical perspective, modulation of the gut microbiota represents a foundational and currently applicable approach to restoring redox homeostasis. The gut microbiota plays a central role in host redox balance and EV-mediated communication [236]. Probiotic supplementation, particularly with *Lactobacillus* and *Bifidobacterium* species, has demonstrated clinical and translational benefits in improving intestinal barrier integrity and promoting the production of antioxidant metabolites, including SCFAs such as butyrate, thereby reducing local oxidative stress and inflammatory signaling [237,238]. Complementary prebiotic fiber intake supports expansion of beneficial microbial populations, while dietary patterns such as the Mediterranean diet and polyphenol-rich foods are associated with improved redox balance and favorable modulation of microbiota composition and host signaling pathways [239–241]. These interventions are already widely used as dietary or adjunctive strategies in human populations.

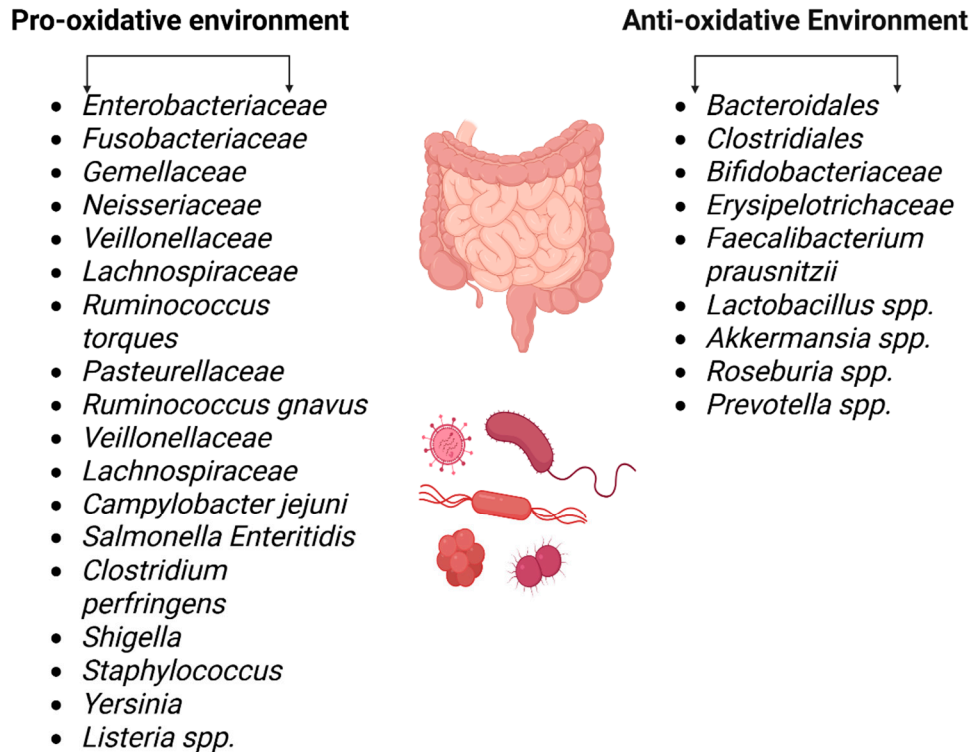


Figure 4: Gut microbial taxa associated with pro-oxidative and anti-oxidative environments. Dysbiosis-driven shifts in gut microbial composition alter redox homeostasis by promoting either pro-oxidative or anti-oxidative conditions. Opportunistic and pathogenic taxa are associated with ROS generation and inflammation, whereas beneficial commensals support antioxidant balance through metabolite production and immune regulation. Created in BioRender, Velikova T (2026).

In addition, several clinically used pharmacological agents indirectly modulate this axis through antioxidant and anti-inflammatory effects. Compounds such as sulforaphane, N-acetylcysteine, statins, and metformin activate endogenous antioxidant pathways, particularly Keap1-Nrf2 signaling, leading to upregulation of cytoprotective enzymes and reduced intracellular ROS burden [242–244]. These interventions are associated with modulation of systemic redox balance and inflammatory signaling in clinical and experimental studies, although direct effects on EV biology in humans remain insufficiently characterized.

Table 7 summarizes current antioxidant and anti-inflammatory therapies used in clinical practice or as adjunctive interventions in oxidative stress- and inflammation-driven diseases, highlighting both therapeutic benefits and limitations, including limited ROS specificity, variable efficacy, and pharmacokinetic constraints.

Despite these available interventions, clinical translation remains limited by several interconnected challenges. A major barrier is the lack of target specificity, as most antioxidant and anti-inflammatory agents act systemically rather than selectively modulating disease-relevant ROS sources or EV subpopulations [245,246]. This is compounded by limited predictive validity of current preclinical models, inter-individual variability in microbiota composition and redox status, and incomplete understanding of EV-mediated signaling in humans [247]. Additional limitations include poor bioavailability, rapid metabolism, and insufficient tissue targeting. Safety concerns, including potential disruption of physiological redox signaling and off-target immunological effects, further restrict optimization [248,249].

Table 7: Approved and adjunct therapies for the management of oxidative stress and chronic inflammation.

Therapeutic Class	Approved Clinical Indications	Key Therapeutic Agents	Preclinical Evidence	Clinical Trial Evidence	Major Limitations and Variability	References
Classical Small-Molecule Antioxidants	COPD, deficiency states, acute toxicity, cardiovascular disease	Vitamin C, Vitamin E, NAC, CoQ10, statins, carbocysteine	ROS scavenging, antioxidant enzyme support, mild anti-inflammatory effects	Mixed efficacy; clear benefit in deficiency and select acute settings	Limited efficacy in chronic disease; bioavailability issues; potential adverse effects	[250–252]
Anti-inflammatory Biologics	RA, IBD, psoriasis, CAPS, cardiovascular inflammation	Infliximab, Adalimumab, Canakinumab, Tocilizumab	Cytokine inhibition (TNF- α , IL-1 β , IL-6) $\rightarrow$ reduced inflammatory signaling	Strong efficacy in autoimmune and inflammatory diseases (RCT-supported)	High cost, infection risk, parenteral administration	[253–255]
Conventional Anti-inflammatories (NSAIDs & Corticosteroids)	Pain, arthritis, asthma, autoimmune flares	NSAIDs, corticosteroids	COX inhibition (NSAIDs); NF- κ B suppression (steroids)	Effective symptom control; widely validated in clinical use	GI, metabolic, immune side effects; no direct ROS targeting	[256–258]
Immunometabolic Modulators	T2DM, dyslipidemia, CVD, metabolic inflammation	Metformin, statins	AMPK activation, potential NOX inhibition, mitochondrial protection	Strong cardiometabolic benefit in RCTs/meta-analyses	Drug intolerance, contraindications in CKD, variable effects	[259–261]
Small-Molecule Immune Pathway JAK Inhibitors (JAKinibs)	RA, UC, PsA, AD, myeloproliferative disease	Tofacitinib, Baricitinib, Upadacitinib	JAK/STAT inhibition $\rightarrow$ reduced cytokine-driven inflammation and ROS	FDA/EMA approved for multiple inflammatory diseases	Infection risk, hematologic effects, safety concerns	[262–264]
Dietary & Nutraceutical Interventions (Mediterranean Diet & Polyphenols)	CVD prevention, IBD support, metabolic inflammation	Mediterranean diet, curcumin, resveratrol, EGCG, NAC	Nrf2 activation, possible microbiota modulation, antioxidant effects	Moderate evidence; mostly adjunctive benefit	Bioavailability and standardization issues	[265–267]

Notes: COPD, chronic obstructive pulmonary disease; ROS, reactive oxygen species; NAC, N-acetylcysteine; CoQ10, coenzyme Q10; RCTs, randomized controlled trials; RA, rheumatoid arthritis; IBD, inflammatory bowel disease; CAPS, cryopyrin-associated periodic syndromes; TNF- α , tumor necrosis factor-alpha; IL, interleukin; IL-1 β , interleukin-1 beta; IL-6, interleukin-6; NSAIDs, non-steroidal anti-inflammatory drugs; COX, cyclooxygenase; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus; CVD, cardiovascular disease; AMPK, AMP-activated protein kinase; JAK/STAT, Janus kinase/signal transducer and activator of transcription; UC, ulcerative colitis; PsA, psoriatic arthritis; GI, gastrointestinal; AD, atopic dermatitis; FDA, U.S. Food and Drug Administration; EMA, European Medicines Agency; EGCG, epigallocatechin gallate; Nrf2, nuclear factor erythroid 2-related factor 2; NOX, NADPH oxidase.

9 Emerging Strategies and Perspectives—Innovative Solutions Targeting Chronic Oxidation-Inflammation Related Diseases

Despite extensive preclinical evidence supporting antioxidant efficacy across diverse pathologies, clinical translation remains limited by pharmacokinetic and biological constraints, including poor bioavailability, rapid clearance, insufficient tissue targeting, and failure to sustain local redox modulation. These limitations are particularly evident in certain acute neurological conditions such as spinal cord injury (SCI), where the blood-spinal cord barrier restricts drug penetration and the evolving secondary injury cascade necessitates precise spatial and temporal control of redox modulation [268].

In parallel, more targeted pharmacological approaches are being explored, notably the inhibition of specific NADPH oxidase (NOX) isoforms, which represent major enzymatic sources of pathological ROS. Targeted inhibition of NOX reduces ROS production, thereby attenuating oxidative stress-dependent alterations in EV biogenesis and limiting the downstream release of pro-inflammatory and disease-propagating EVs [62].

Extracellular vesicles themselves constitute a dual therapeutic target, functioning both as mediators of pathology and as vehicles for intervention. On one hand, inhibition of EV biogenesis or cellular uptake has emerged as an effective strategy to disrupt the propagation of inflammatory signals. In preclinical settings, agents such as GW4869, a neutral sphingomyelinase inhibitor, are widely used to suppress EV formation, supporting a contributory role of EVs in inflammation driven by microbial imbalance and oxidative stress [269,270]. On the other hand, EVs—particularly those derived from mesenchymal stem cells—are increasingly exploited as therapeutic nanocarriers. These vesicles naturally transport antioxidant enzymes, anti-inflammatory proteins, and regulatory microRNAs, and can be engineered to deliver targeted cargo to inflamed tissues, offering lower immunogenicity, intrinsic homing capacity, and multifunctional properties consistent with off-the-shelf biologic potential. EV-based therapies therefore represent a promising means to restore redox balance and immune homeostasis within the microbiota-ROS-EV axis [271,272].

Beyond EV-centered approaches, more advanced strategies focus on system-level modulation of redox biology. Catalytic antioxidant mimetics and mitochondria-targeted antioxidants aim to overcome limitations of conventional scavengers by providing sustained ROS regulation at primary sites of generation. Despite strong preclinical efficacy across cardiovascular, neurodegenerative, and metabolic disease models, their clinical translation remains limited by pharmacokinetic constraints and insufficient large-scale human trials [273].

In parallel, activation of endogenous cytoprotective pathways, particularly through Nrf2 signaling, and immunometabolic reprogramming strategies such as itaconate derivatives, represent a paradigm shift toward restoring redox-immune homeostasis at transcriptional and metabolic levels [274]. However, these approaches remain constrained by off-target effects, safety concerns, and limited human validation.

Nanoparticle-based delivery systems are also being developed to enhance stability, tissue targeting, and bioavailability of redox-active compounds. While these systems show promise in overcoming pharmacological barriers, long-term safety and regulatory scalability remain unresolved [275].

Finally, combination and synergistic therapies targeting multiple nodes of ROS generation, redox signaling, and immune activation are emerging as a rational strategy to improve therapeutic durability and dose efficiency. However, optimized trial designs and robust regulatory frameworks are still required for clinical translation [269,276]. These and other emerging therapeutic strategies are comprehensively summarized in Table 8.

Collectively, these emerging strategies reflect a shift from conventional antioxidant supplementation toward precision, pathway-integrated modulation of the microbiota-ROS-EV axis. Future clinical translation will require validated targeting strategies, robust biomarker-driven patient stratification, and rigorous human trial confirmation of efficacy and safety.

Table 8: Emerging and translational therapeutic strategies targeting oxidative stress and inflammation within the microbiota-ROS-EV axis.

Therapeutic Modality	Clinical Development Status	Representative Agents	Mechanistic Advantages	Evidence from Preclinical Models	Evidence from Clinical Studies	Key Translational Challenges	References
Catalytic Antioxidant Mimetics	Phase I–III (limited)	Calmangafodipir, Tempol, EUK-134, nanozymes	Catalytic ROS scavenging (SOD/CAT mimetic activity)	Demonstrated strong protection in oxidative injury and neurodegeneration models	Limited clinical efficacy; safety concerns in late trials	Short half-life, off-target effects, toxicity risk	[277–279]
Metabolic Intermediates/Derivatives	Preclinical	Itaconate derivatives	Nrf2-mediated immunometabolic regulation	Anti-inflammatory effects in immune and neuro models	No clinical data	Unknown safety and pharmacokinetics	[280–282]
Mitochondria-Directed Antioxidants	Phase I–II	MitoQ, SkQ1	Reduction of mitochondrial ROS	Shown to improve vascular and metabolic function in preclinical studies	Early safety and modest efficacy signals	Limited RCTs, variable uptake	[283–285]
Nanoparticle & Advanced Delivery Systems	Preclinical-Phase I/II	Curcumin NPs, nanoceria	Targeted ROS modulation and drug delivery	Antioxidant and tissue-protective effects	Early safety signals in selected trials	Toxicity, scalability, regulation	[286–288]
Nrf2 Activators	Phase II–III/preclinical	DMF, sulforaphane, bardoxolone	Nrf2 pathway activation	Neuroprotection and antioxidant effects	Approved or mixed clinical outcomes	Safety concerns, bioavailability	[289–291]
Stem Cell-Derived Therapies & Exosomes	Early clinical	MSCs, MSC-EVs	Paracrine antioxidant and anti-inflammatory effects	Associated with reduced oxidative stress and tissue injury in experimental studies	Early feasibility trials	Standardization and manufacturing	[292–294]
Combination Therapies	Preclinical-clinical	Omega-3 + statins, antioxidant cocktails	Multi-target metabolic and redox modulation	Improved metabolic and cardiac outcomes	Mixed clinical benefit in meta-analyses	Patient stratification, translation gap	[295–297]

Note: SOD, superoxide dismutase; CAT, catalase; ROS, reactive oxygen species; Nrf2, nuclear factor erythroid 2-related factor 2; DMF, dimethyl fumarate; EUK-134, synthetic superoxide dismutase/catalase mimetic; MSCs, mesenchymal stem cells; EVs, extracellular vesicles; NPs, nanoparticles; MitoQ, mitochondrial-targeted coenzyme Q10; SkQ1, plastoquinone derivative; EUK-134, synthetic SOD/catalase mimetic; RRMS, relapsing-remitting multiple sclerosis; CKD, chronic kidney disease; PD, Parkinson's disease; RCTs, randomized controlled trials.

10 Conclusion and Future Perspectives

The microbiota-oxidative stress-extracellular vesicle (EV) axis has emerged as an integrated signaling network linking dysbiosis-driven oxidative stress to local and systemic inflammatory disease progression. Increasing evidence indicates that oxidative stress not only disrupts microbial and epithelial homeostasis but it is also associated with remodeling of EV biogenesis and cargo composition, thereby amplifying inflammatory signaling across organ systems. Although therapeutic strategies targeting microbiota composition, ROS signaling, and EV-mediated communication show promise, major mechanistic and translational barriers continue to limit clinical application.

Future research should prioritize four major areas. First, mechanistic studies are needed to define how dysbiosis-induced oxidative stress regulates EV biogenesis, cargo remodeling, and intercellular signaling, particularly through ROS-sensitive pathways involving mitochondrial dysfunction, NOX activation, and inflammatory transcriptional networks. Second, standardized characterization of EV subpopulations, cargo profiles, and cell-specific origins under oxidative stress conditions is essential to improve reproducibility and biomarker discovery. Third, translational studies using germ-free and defined microbiota animal models, organoid platforms, and other physiologically relevant *in vivo* systems are required to establish causality within the microbiota-ROS-EV axis and improve the predictive value of preclinical research. Finally, future therapeutic development should focus on precision strategies integrating microbiome signatures, redox biomarkers, and engineered EV platforms to enable targeted modulation of inflammatory and oxidative signaling pathways.

Clarifying the mechanistic crosstalk within the microbiota-ROS-EV axis will be critical for the development of targeted diagnostics and precision therapies capable of interrupting chronic oxidative-inflammatory signaling in gastrointestinal and systemic disease.

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