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MOLECULAR MECHANISMS OF OXIDATIVE STRESS, INFLAMMATION AND CELLULAR INJURY IN PARASITIC INFECTIONS

Mamatyaqubova Malohat Sharof qizi

Andijan state medical institute,Andijan,Uzbekistan

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Abstract. Parasitic infections induce complex host responses in which reactive oxygen and nitrogen species (ROS/RNS) function both as antiparasitic effectors and as mediators of tissue damage. This narrative review examines the molecular interplay between phagocyte NADPH oxidase, mitochondrial redox signaling, NF-κB-dependent inflammatory transcription, NLRP3 inflammasome activation, and antioxidant defense systems. Lipid peroxidation, protein oxidation, and oxidative DNA lesions are discussed as plausible consequences of sustained redox imbalance. The interpretation of malondialdehyde, 8-hydroxy-2′-deoxyguanosine, glutathione, superoxide dismutase, and cytokine measurements is critically assessed. Parasite species, tissue tropism, disease stage, and host comorbidities substantially influence these pathways. The review synthesizes established mechanistic knowledge without presenting new clinical data and identifies priorities for prospective, parasite-specific biomarker studies.

Keywords: parasitic infections; oxidative stress; reactive oxygen species; inflammation; NF-κB; NLRP3; cellular injury; antioxidant defense.

INTRODUCTION

Parasitic diseases remain important causes of morbidity worldwide. Their manifestations depend on the infecting organism, parasite burden, tissue localization, duration of exposure, nutritional status, and host immune competence. Protozoa and helminths differ substantially in their life cycles and interactions with host tissues, yet both may induce inflammatory responses that alter cellular redox homeostasis. In this context, oxidative stress is not merely an incidental laboratory finding: it represents a dynamic imbalance between oxidant generation, antioxidant capacity, and the ability of redox-sensitive signaling networks to maintain cellular function (1, 2, 9).

Reactive oxygen species include superoxide anion, hydrogen peroxide, and hydroxyl radicals; reactive nitrogen species include nitric oxide-derived oxidants such as peroxynitrite. At controlled concentrations, these molecules participate in host defense, transcriptional regulation, cell differentiation, and adaptive signaling. Excessive or prolonged production, however, may oxidize membrane lipids, modify proteins, impair mitochondrial enzymes, and damage nucleic acids. Thus, the same biochemical machinery that restricts a parasite can contribute to collateral injury in surrounding host tissue (5, 6, 9).

Neutrophils, macrophages, eosinophils, dendritic cells, and lymphocyte subsets contribute to antiparasitic immunity. The phagocyte NADPH oxidase complex (particularly NOX2) produces superoxide during the respiratory burst. Inducible nitric oxide synthase can also generate nitric oxide, although its contribution varies by host species, parasite, and tissue microenvironment. Meanwhile, parasite-derived molecules and damage-associated signals activate innate immune receptors and downstream cytokine networks. Persistent stimulation may produce an inflammatory

feedback loop in which oxidative stress enhances inflammation and inflammation further increases oxidant production (3, 4, 11).

Several measurable indicators have been proposed to characterize these processes. Malondialdehyde (MDA) and 4-hydroxynonenal reflect aspects of lipid peroxidation; protein carbonyls indicate oxidative protein modification; 8-hydroxy-2′-deoxyguanosine (8-OHdG) is used to assess oxidative DNA damage; and glutathione, superoxide dismutase (SOD), and catalase provide information about antioxidant defenses. None is independently specific for parasitic infection. Diet, smoking, metabolic disease, sampling procedures, and assay platforms may affect results. Therefore, biomarker interpretation requires clinical context, parasite confirmation, and appropriate controls (7, 8, 10).

The aim of this article is to integrate the principal molecular mechanisms linking oxidative stress, inflammation, and cellular injury during parasitic infection; critically interpret commonly used indicators; and outline clinically relevant research priorities. The discussion emphasizes mechanistic plausibility and methodological limitations rather than unsupported claims of diagnostic accuracy or therapeutic efficacy.

Table 1. Major pathways of oxidative injury during parasitic infections

Biological component	Principal mechanism	Potential consequence
Phagocytes	NOX2-mediated ROS generation	Parasite restriction and collateral tissue injury
Mitochondria	Electron transport perturbation	Reduced ATP production; increased mitochondrial ROS
Lipid membranes	Lipid peroxidation	Altered membrane integrity and permeability
Nucleus and DNA	Oxidative modification	DNA repair response and altered cell-cycle regulation

LITERATURE REVIEW

Parasitology literature describes transmission, parasite development, and host–parasite interactions as essential foundations for clinical reasoning (1–4). Epidemiological prevention resources emphasize the diversity of exposure routes and the need to identify the responsible organism. Such sources provide a practical framework but generally do not establish causal relationships between specific redox biomarkers and disease severity. Mechanistic interpretation therefore also requires contemporary research in cellular biochemistry and immunology.

Sies and Jones (9) characterize ROS as pleiotropic physiological signaling agents, arguing against an overly simplistic view in which every increase in oxidant production is necessarily pathological. Forman and Zhang (10) similarly discuss why indiscriminate antioxidant treatment may fail: oxidants participate in protective signaling, and the biological effect of an antioxidant depends on

its localization, dose, and timing. These concepts are especially relevant to parasitic infections, in which oxidative mechanisms may be required for microbial control.

Research on inflammatory signaling provides a complementary perspective. Liu and colleagues (11) detail how NF-κB controls the transcription of inflammatory mediators, whereas Swanson and colleagues (12) explain the molecular regulation of the NLRP3 inflammasome and maturation of IL-1β and IL-18. These pathways may contribute to host responses during infection, but the degree of activation cannot be generalized across all parasites. Taken together, the literature supports an integrated model of redox–immune interaction while underscoring the need for species-specific clinical validation.

MATERIALS AND METHODS

This study was designed as a narrative literature review. The synthesis drew on background materials in Uzbek concerning parasitic diseases, cell biology, and immunity (1–8), together with four peer-reviewed international reviews addressing ROS signaling, antioxidant therapy, NF-κB, and the NLRP3 inflammasome (9–12). The evidence was organized into five analytical domains: oxidant sources, inflammatory signaling, macromolecular injury, parasite-specific variation, and diagnostic or therapeutic implications.

No patient recruitment, experimental intervention, original laboratory measurement, systematic meta-analysis, or statistical hypothesis testing was performed. The line and bar charts are explicitly conceptual teaching illustrations; their arbitrary values are not observed patient measurements, pooled effect estimates, or evidence of clinical efficacy. Accordingly, the findings below represent a qualitative synthesis and should not be interpreted as a primary clinical study.

RESULTS AND DISCUSSION

1. Sources of ROS and redox imbalance

Parasite antigens, tissue disruption, and host-derived danger signals can recruit and activate innate immune cells. In professional phagocytes, NOX2 transfers electrons to molecular oxygen and generates superoxide. Subsequent reactions produce additional oxidants, including hydrogen peroxide. Although these reactions contribute to pathogen restriction, extracellular oxidant release can also affect neighboring epithelial, endothelial, and stromal cells. The net outcome depends on compartmentalization, duration of exposure, and the efficiency of antioxidant recycling (3, 9).

Mitochondria are a second important source of redox signals. Electron leakage from the respiratory chain generates mitochondrial ROS under both physiological and pathological conditions. Inflammatory mediators, hypoxia, altered substrate availability, and damage to mitochondrial membranes may increase this production. Conversely, mitochondrial dysfunction may reduce ATP generation and impair ion homeostasis, thereby amplifying tissue injury. Mitochondrial ROS should therefore be understood as part of a bidirectional signaling system rather than as a universal marker of irreversible damage (6, 9).

2. Inflammatory signaling pathways

Pattern-recognition receptors detect microbial structures and molecules released by damaged host cells. Their activation can engage kinase cascades that stimulate NF-κB, resulting in transcription of cytokines, chemokines, adhesion molecules, and additional inflammatory mediators. Oxidative modifications may influence this network at multiple levels, while cytokine signaling can further stimulate oxidant-generating enzymes. Consequently, inflammatory amplification may persist even when the initial parasite-associated trigger has changed (11).

The NLRP3 inflammasome is a multiprotein platform that, in appropriate cellular contexts, activates caspase-1 and promotes maturation of IL-1β and IL-18. Ion flux, mitochondrial perturbation, and cellular stress can contribute to its regulation. However, inflammasome involvement differs across infectious agents, host cell types, and experimental systems. It would be inaccurate to infer that every parasitic infection is NLRP3-driven; instead, its contribution must be tested with parasite-specific models and validated human specimens (12).

3. Membrane, protein, and DNA injury

Polyunsaturated membrane fatty acids are vulnerable to chain reactions of lipid peroxidation. Reactive aldehydes such as MDA and 4-HNE may arise during these processes and can modify cellular proteins. Depending on intensity and tissue location, lipid oxidation may change membrane fluidity, permeability, receptor behavior, and organelle function. Although MDA is frequently measured, it is not a parasite-specific marker and can be affected by sample handling and analytical methodology (7, 10).

Oxidation of amino acid side chains and formation of protein carbonyls may reduce enzyme activity, alter cytoskeletal stability, and disrupt signaling complexes. Oxidative DNA lesions can trigger repair pathways, cell-cycle arrest, or programmed cell death when damage is severe. Apoptosis, necrotic injury, and regulated inflammatory cell death may coexist, but their relative importance depends on the affected tissue and the host–parasite interaction. Mechanistic markers must therefore be interpreted alongside histopathology and clinical findings rather than in isolation (5, 9).

4. Differences among parasite species

In malaria, erythrocyte destruction, heme metabolism, and systemic inflammation may contribute to oxidative burden. In toxoplasmosis, intracellular parasite–host interactions and cellular immunity shape tissue responses. Helminth infections often involve type 2 immune responses, eosinophil activation, and chronic tissue remodeling. These examples illustrate why a single redox model cannot adequately describe all parasitic diseases. The direction and magnitude of biomarker changes can differ by organism, tissue, infection stage, and host nutritional or metabolic condition (1–4).

Chronic exposure may sustain low-grade inflammatory signaling, but some parasites also modulate host immunity and may dampen particular inflammatory pathways. Thus, parasite persistence does not automatically imply continuously rising ROS concentrations. Repeated sampling, well-defined infection stages, and careful measurement of parasite burden are necessary to distinguish transient

protective responses from sustained pathological injury. Confounding by concurrent bacterial infection, anemia, and metabolic disorders should be addressed explicitly (2, 3, 10).

5. Diagnostic and therapeutic implications

Combined assessment of MDA, 8-OHdG, glutathione, SOD, catalase, and selected cytokines may help characterize redox–inflammatory phenotypes in research. Yet these measurements are neither substitutes for parasitological diagnosis nor universally validated severity scores. A useful diagnostic panel would require standardized specimen collection, reproducible assays, prespecified clinical outcomes, and external validation in independent patient populations. Diagnostic discrimination should be reported with confidence intervals and evaluated against appropriate reference standards (8–10).

Adjunctive antioxidant strategies remain biologically plausible but require careful evaluation. Because ROS also contribute to antiparasitic defense, indiscriminate suppression could have unintended consequences. Any therapeutic trial should specify parasite species, antiparasitic treatment, antioxidant agent, dose, timing, safety outcomes, and clinically meaningful endpoints. At present, the molecular rationale alone does not justify recommending antioxidant supplementation as a standard treatment for parasitic infections (9, 10).

Table 2. Molecular mechanisms and research biomarkers

Process	Candidate marker	Interpretive limitation
Lipid peroxidation	MDA, 4-HNE	Nonspecific; sensitive to preanalytical conditions
DNA oxidation	8-OHdG	Also increased in other oxidative conditions
Antioxidant defense	SOD, catalase, GSH	Depends on tissue, timing, and assay
Inflammation	IL-6, TNF, IL-1β	Not specific to parasite species

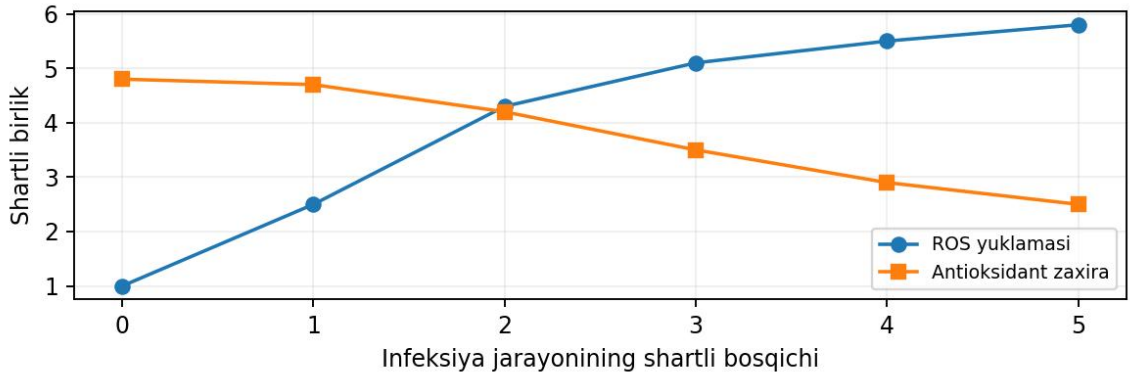


Figure 1. Conceptual trajectories of ROS burden and antioxidant reserve (illustrative values, not clinical measurements).

The opposing trends shown in Figure 1 illustrate how a theoretical imbalance may emerge when oxidant production outpaces adaptive antioxidant capacity. The axes represent relative, arbitrary units rather than measured concentrations or an empirically established time course. The diagram is intended to clarify the underlying biological concept and should not be used to infer patient prognosis or treatment response.

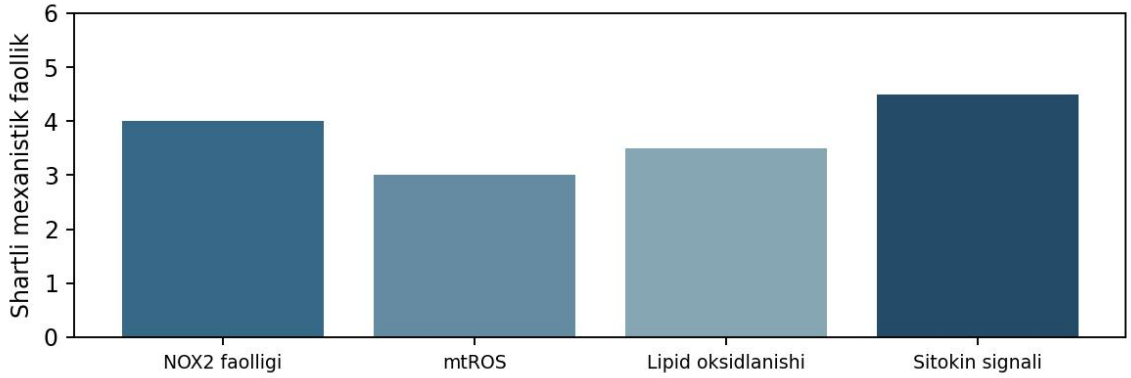


Figure 2. Conceptual comparison of pathogenic pathways (illustrative values, not empirical measurements).

Figure 2 depicts the possibility that multiple processes—oxidant generation, inflammatory signaling, mitochondrial dysfunction, and molecular injury—operate concurrently. The heights of the bars do not represent measured activity, effect sizes, or relative clinical importance. Actual pathway contributions must be established in appropriately designed studies of defined parasitic infections.

Table 3. Practical methodological priorities for future studies

Research question	Recommended approach	Factors to control

ROS and disease severity	Prospective repeated-measures study	Age, comorbidities, medications
Inflammatory pathways	Cytokine panels and cellular models	Parasite species and burden
Diagnostic biomarker utility	ROC analysis and external validation	Reference standard and sample storage

CONCLUSION

Oxidative stress and inflammation are interdependent components of host responses to parasitic infections. Their effects are context dependent: reactive species may support pathogen control at regulated levels but contribute to tissue injury when production is excessive, prolonged, or poorly compartmentalized. NOX2-dependent oxidant generation, mitochondrial redox signaling, NF-κB activation, and inflammasome pathways provide a coherent framework for understanding these interactions (9, 11, 12).

Lipid peroxidation, protein oxidation, and oxidative DNA damage are plausible downstream consequences of redox imbalance. Nevertheless, biomarkers such as MDA, 8-OHdG, and antioxidant enzyme activity lack parasite specificity and may be affected by preanalytical and clinical confounders. Their interpretation should therefore complement, not replace, validated parasitological testing and patient assessment (7, 8, 10).

Future investigations should prioritize prospective parasite-specific cohorts, standardized biomarker panels, repeated measurements, and links between molecular findings and clinically meaningful outcomes. Carefully controlled mechanistic studies and independent validation are needed before redox markers or adjunctive antioxidant interventions can be incorporated into routine clinical pathways.

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