Eurasia Specialized Veterinary Publication

Entomological Research Letters

ISSN: 3108-639X

2025, Volume 5, Issue 2, Page No: 96-105
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Available online at: www.esvpub.com/

Redox Signaling Across Insect Immunity, Aging, Stress Tolerance, Metabolism, and Physiological Regulation

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ABSTRACT

Reactive oxygen species (ROS) in insects are commonly discussed as if they occupy a single continuum from low, beneficial signaling to high, damaging oxidative stress. Recent mechanistic studies instead indicate that biological meaning depends on where reactive species originate, where they act, how long they persist, the physiological state in which they arise, and the strength of evidence linking an oxidation event to function. This state-of-the-art review integrates redox regulation across immunity, aging, environmental stress, metabolism, antioxidant defense, and repair while preserving these distinctions. Insect studies show that hydrogen peroxide and mitochondrial ROS can transmit information in neural, regenerative, immune, developmental, and stress-response settings, whereas similar oxidant accumulation can also compromise barrier integrity, amplify inflammatory injury, or accompany reproductive decline. Antioxidant proteins likewise cannot be treated only as scavengers: thioredoxin, peroxiredoxin, glutathione-related enzymes, and redox-sensitive transcriptional systems can participate in signaling, detoxification, metabolism, autophagy, and repair. We therefore advance a proposed context-gated interpretation in which source identity, spatial compartment, temporal regime, biological state, and inference strength jointly determine what a redox measurement can support. The framework separates signaling from damage, acute response from evolutionary adaptation, and molecular perturbation from organismal consequence. Its main implication is methodological: insect redox biology will progress most reliably when chemically and spatially resolved measurements are connected to perturbation, rescue, identified molecular targets, and explicitly bounded organismal outcomes.

Keywords: Sexual satisfaction, Pregnant mothers, Healthy mothers, Candidate vaginitis

Received: 24 October 2025
Revised: 11 December 2025
Accepted: 13 December 2025

How to Cite This Article: Wiśniewski K, Nowak M, Adamczyk T. Redox Signaling Across Insect Immunity, Aging, Stress Tolerance, Metabolism, and Physiological Regulation. Entomol Appl Sci Lett. 2025;5(2):96-105. https://doi.org/10.51847/4o3bmmrkVJ

Introduction

Insect redox biology now spans thioredoxin-dependent regulation, pesticide-responsive CncC/Keap1 signaling, and thermal oxidative physiology, but these literatures frequently address different biological questions under overlapping terminology [1–3]. The problem is not whether ROS matter; it is what a particular redox observation is permitted to mean. A rise in an oxidation-sensitive signal can reflect localized information transfer, antimicrobial chemistry, compensatory defense, impaired homeostasis, or accumulated damage. General redox biology distinguishes regulated oxidative eustress from oxidative distress [4], but that distinction becomes useful in insects only when attached to taxon, tissue, life stage, exposure history, and measurement scale.

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This review therefore treats redox state as an inference problem rather than a single stress axis. We propose five context gates: reactive-species/source identity, spatial compartment, temporal regime, biological state, and inference strength. These gates do not constitute a validated universal pathway. They are an organizing architecture for asking when evidence supports signaling, when it supports damage, and when it supports only association. The following sections use mechanistic insect studies to test that distinction across neural signaling, immunity, aging, environmental challenge, metabolism, antioxidant systems, and repair.

Reactive species as signals

Direct evidence that ROS can transmit information is strongest when a defined source is experimentally manipulated and a functional consequence is rescued or reproduced. In Drosophila, astrocyte-to-neuron hydrogen peroxide signaling supports long-term memory formation, demonstrating that a reactive species can operate as intercellular information rather than merely as collateral oxidative burden [5]. Damage-induced regeneration provides a second form of specificity: ROS activate the Drosophila TNF receptor Wengen and downstream p38 signaling, whereas receptor context limits how broadly the result can be generalized [6].

Mitochondria add a temporal and energetic dimension. Complex-I-derived ROS produced through reverse electron transport contribute to acute heat-stress adaptation in Drosophila [7]. Yet aging uncouples ROS abundance from signaling competence: mitochondrial ROS can remain elevated while the capacity to generate the specific reverse-electron-transport signal is lost [8]. Thus, “high ROS” cannot itself distinguish maintained signaling from dysregulated oxidation. At the neuromuscular junction, experimentally increased mitochondrial ROS can potentiate presynaptic function, and catalase-sensitive manipulations support hydrogen peroxide as part of that signaling route [9]. The precise downstream redox target, however, remains less resolved than the causal involvement of the mitochondrial oxidant state.

Protein-resolved measurements further show why bulk oxidative labels are insufficient. Quantitative cysteine-redox proteomics in the Drosophila eye identified oxidation patterns that differed between blue-light exposure and aging, including changes in phototransduction machinery [10]. Oxidation of a cysteine is not automatically proof that the residue functions as a regulatory switch, but such measurements narrow the mechanistic search space. Across these examples, signal identity emerges from convergence among source localization, temporal control, perturbation, and function—not from ROS abundance alone.

Redox control of immunity

Insect immunity illustrates why redox effects cannot be classified as uniformly protective or damaging. In the Bactrocera dorsalis gut, bacterial induction of Duox-derived ROS interacts with the peritrophic matrix and Imd signaling, showing that epithelial redox control is coupled to barrier organization rather than operating as a free-standing antimicrobial output [11]. At another anatomical boundary, the opposite problem appears: during arboviral infection, excessive ROS can compromise blood-brain barrier integrity, while Sniffer-dependent control of ROS helps restrict infection in Drosophila and mosquitoes [12]. The direction of benefit therefore changes with compartment and host cost.

Spatial encounter with the pathogen is itself a boundary condition. Bacillus cereus spores can bypass stronger anterior intestinal defenses and germinate in posterior gut regions where immune activation is weaker, permitting persistence [13]. This study supports spatial heterogeneity of intestinal defense, but it does not by itself establish direct suppression of Duox-derived ROS by spores. Similarly, oxidative cell death can have mixed inflammatory consequences. Ferroptosis-like cell death in wounded Drosophila tissue recruits immune activity yet can also prolong inflammation [14]. The qualified term “ferroptosis-like” matters because phenotypic resemblance should not be inflated into universal identity with mammalian ferroptosis.

ROS also participate in temporally distinct immune functions. Intramacrophage hydrogen peroxide can prime JAK/STAT- and Toll-associated responses after injury, increasing resistance to a later challenge [15]. That phenomenon is innate priming rather than evidence of adaptive immunity. In antiviral defense, Nox-dependent ROS contributes to p38b/JAK-STAT protection against Invertebrate iridescent virus 6 [16]. In bacterial infection, hemocyte Duox-derived ROS can instead act directly as a microbicidal effector against Providencia alcalifaciens, and bacterial resistance to this oxidative attack contributes to virulence [17]. Together, these studies separate at least four redox roles—barrier-linked signaling, tissue-protective ROS restraint, immune priming, and direct microbial killing—that should not be compressed into a single “immune ROS” category.

Redox biology of aging

Aging exposes an especially important distinction between redox burden and redox regulation. In Drosophila, catalase overexpression can extend female lifespan through autophagy, and redox regulation of Atg4a at Cys102 is required for that effect [18]. The sex dependence is central: a mechanistically persuasive redox-longevity link in females does not establish a sex-independent rule. In the aging brain, mitochondrial functional state and active-zone plasticity are reciprocally coupled, indicating that early synaptic aging involves interactions among bioenergetic state, ROS, and plasticity rather than a one-directional accumulation of oxidative damage [19].

Environmental context can also accelerate age-associated pathology. Copper overload exacerbates testicular-aging phenotypes in male Drosophila when lncRNA CR43306 is deficient, with oxidative and ferroptosis-associated changes contributing to the phenotype [20]. This is evidence for a metal–redox interaction in reproductive aging, not a universal mechanism of normal aging. Peroxiredoxin studies likewise resist simple antioxidant narratives: mitochondrial peroxiredoxin influences intestinal barrier dysfunction and age-associated inflammation, but rescue of immune phenotypes does not necessarily produce equivalent rescue of lifespan [21]. Different downstream outcomes can therefore dissociate even when they share a redox regulator.

The intestinal stem-cell compartment provides a complementary non-monotonic example. Manipulating intracellular ROS in Drosophila stem cells produces different proliferative consequences depending on cellular state and the range of ROS alteration [22]. Aging biology should consequently avoid a one-dimensional model in which progressively increasing ROS produces progressively increasing dysfunction. The more defensible interpretation is state dependent: oxidant source, target availability, compensatory capacity, tissue context, and duration together determine whether an age-associated redox change remains signaling-competent, becomes maladaptive, or reflects damage.

Environmental stress

Environmental stress is where redox terminology most easily slides from observation to unsupported adaptation. During pupal diapause in Helicoverpa armigera, ROS-associated AKT/GSK3β signaling participates in regulation of an endocrine developmental cascade [23]. Here ROS are embedded in a life-stage-specific state transition. In Bactrocera dorsalis and Aedes aegypti, perturbing AANAT1 alters midgut ROS, CncC/Maf-associated detoxification responses, and insecticide susceptibility [24]. That result supports a redox-linked detoxification mechanism in defined laboratory systems, but it does not by itself demonstrate evolved field resistance.

Heavy-metal and insecticide studies reinforce the need to specify both stressor and inference level. Lead exposure in Drosophila increases ROS and recruits MTF-1/Nrf2/JNK-linked metallothionein regulation, connecting oxidative state to metal handling [25]. In Helicoverpa armigera, insecticide exposure increases hydrogen-peroxide-associated CncC signaling and inducible P450 expression; scavenging and RNA interference support functional involvement of the ROS–CncC axis [26]. The evidence does not require the stronger claim that ROS directly oxidizes a particular CncC sensor or that this inducible response universally explains inherited resistance.

Heat represents a further caution. Across insect studies, heat commonly alters ROS and antioxidant responses, but increased antioxidant activity is not automatically evidence that oxidative damage was prevented or that heat tolerance improved [3]. Acute survival, inducible detoxification, developmental arrest, and compensatory antioxidant responses are all physiological responses. Evolutionary adaptation requires heritable change across generations. Experimental evolution of Drosophila under extreme oxygen conditions demonstrates that such multigenerational genomic adaptation can be detected [27], but it does not identify a universal redox mechanism for adaptation. The essential boundary is therefore between stress-linked redox response and evidence of inherited evolutionary change.

Because these environmental cases differ simultaneously in duration, life stage, tissue, stressor identity, and inferential scale, prose alone obscures the point at which similar ROS observations cease to be biologically equivalent. **Table 1** therefore separates the observable redox pattern from the interpretation it can support and from the test needed to move beyond that interpretation.

Table 1. Environmental stress states separated by redox meaning, context, and inference boundary

Critical boundary and decisive check	Stress-linked state with evidential standing	Biological context with observed basis	Recorded evidence

Antioxidant induction does not establish protection or improved tolerance **Pair redox measurements with damage, performance, and recovery endpoints**	Heat-associated ROS/antioxidant response Evidence-based distinction	Multiple insect taxa; thermal exposure Heat perturbs redox physiology	Altered ROS, antioxidant activity, or oxidative-damage markers
Taxon and life-stage specificity **Perturb pathway components across stages and species**	Diapause-linked ROS signaling Evidence-based distinction	H. armigera pupal brain; developmental transition ROS participates in a stage-specific developmental signaling context	ROS-associated AKT/GSK3β and endocrine-cascade changes
Laboratory susceptibility is not field-evolved resistance **Test field genotypes, tissue specificity, and causal redox targets**	Xenobiotic-induced detoxification control Evidence-based distinction	B. dorsalis/A. aegypti midgut Gut redox state contributes to inducible detoxification regulation	AANAT1 perturbation alters ROS, CncC/Maf output, and susceptibility
Exposure-specific laboratory model **Resolve source-specific oxidants and organismal costs across realistic exposures**	Metal-triggered redox homeostasis Evidence-based distinction	D. melanogaster under lead exposure Redox signaling participates in metal handling	ROS elevation with MTF-1/Nrf2/JNK-linked metallothionein response
Direct molecular redox sensor and inherited resistance remain unresolved **Identify modified sensor residues and test resistant field populations**	Insecticide-induced ROS–CncC–P450 response Evidence-based distinction	H. armigera larvae ROS-associated CncC activity contributes to inducible xenobiotic response	ROS modulation and CncC perturbation alter inducible P450 expression/tolerance
Not direct evidence for a specific ROS pathway **Connect selected loci to redox phenotypes with functional validation**	Multigenerational oxygen adaptation Evidence-based boundary	Experimental Drosophila populations Heritable evolutionary response can be distinguished from acute physiology	Repeatable genomic change under long-term extreme-O_2 selection
Architecture itself is not prospectively validated **Test whether the gates improve prediction across taxa and environments**	Context-gated stress interpretation Proposed synthesis	Cross-domain synthesis from the states above Similar ROS readouts may represent different biological processes	Joint consideration of source, compartment, duration, life state, and inheritance

Note: Evidence-derived entries summarize distinctions established in the immediately preceding section. “Proposed synthesis” identifies the article’s new interpretive organization rather than an empirically validated classification. No numerical scores or certainty grades are implied.

The same distinctions can be compressed visually only if transient signaling, damage-associated states, compensatory regulation, and heritable change remain separated. **Figure 1** therefore treats environmental stress as a nested field of context gates and feedbacks rather than a linear stress-to-ROS-to-outcome sequence.

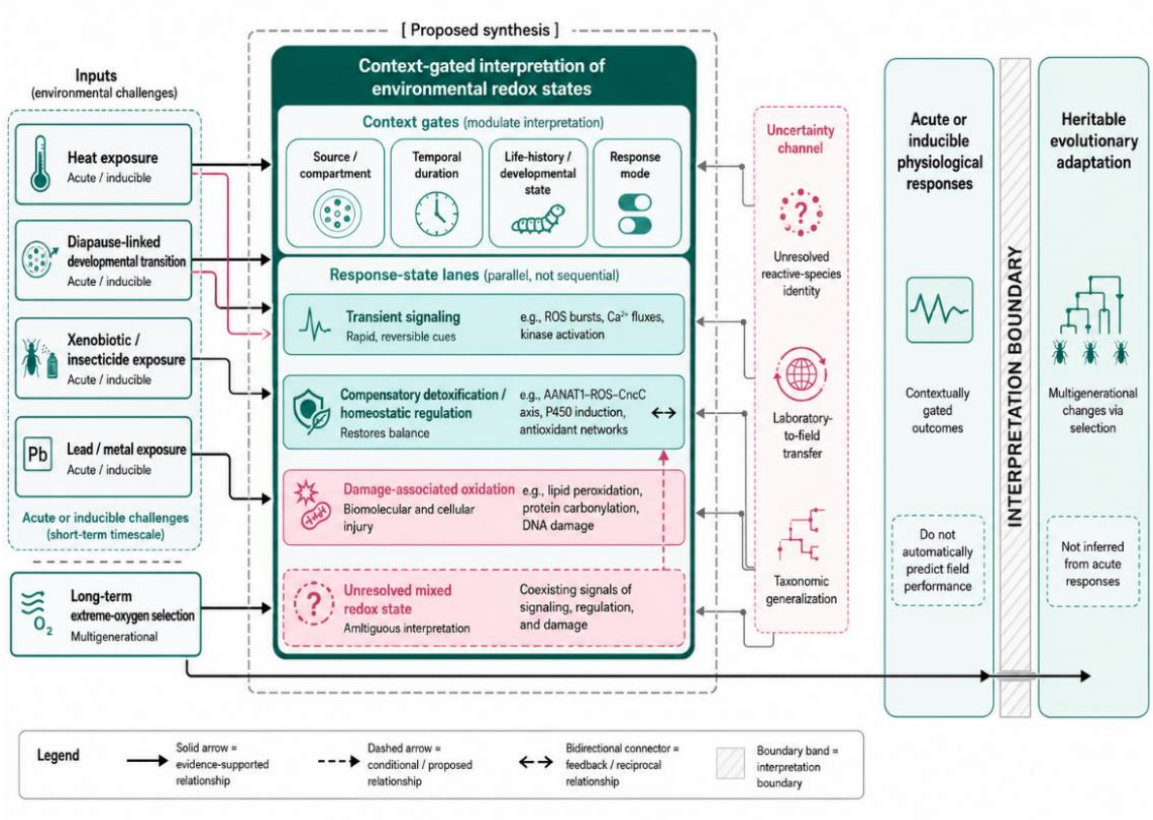


Figure 1. Context gates separating insect stress-linked redox signaling from oxidative burden and evolutionary adaptation

Metabolic regulation

Redox regulation intersects metabolism most convincingly when a redox-active protein is linked to a defined metabolic function rather than inferred from antioxidant activity alone. In Bombyx mori, peroxiredoxin 6 is required for post-translational activation of xanthine dehydrogenase and consequently influences uric-acid synthesis [28]. This establishes a metabolic regulatory role that cannot be reduced to generic peroxide removal.

Endocrine state can likewise redirect redox output. In Spodoptera exigua, 20-hydroxyecdysone and juvenile hormone exert opposing effects on DUOX-ROS immunity during Bacillus thuringiensis challenge [29]. The result demonstrates endocrine modulation of redox-dependent gut defense in a defined larval infection system, not a universal polarity of juvenile hormone and ecdysteroid effects across insects. Reproductive physiology provides another boundary: in the adult male Drosophila testis, Maf-S/Keap1/Nrf2-associated redox regulation contributes to germline stem-cell maintenance, whereas elevated ROS favors differentiation [30]. Together, these studies show that metabolism, endocrine signaling, immunity, and reproduction can share redox regulators while retaining tissue- and state-specific outputs.

Antioxidant and repair systems

The term “antioxidant system” becomes misleading when proteins assigned to it also control xenobiotic metabolism, signaling, or repair. In Spodoptera litura, GSTe16 supports pyrethroid detoxification while also displaying antioxidant activity, and multiscale genetic and biochemical evidence links the enzyme to insecticide tolerance [31]. These functions coexist but should not be interpreted as evidence that every detoxification phenotype is mediated through antioxidant chemistry.

Repair systems show similar integration. A Drosophila GPX4 ortholog connects lipid-peroxidation defense with O-GlcNAc regulation and DNA-damage responses in intestinal stem-cell homeostasis during aging and oxidative challenge [32]. Thioredoxin-system evidence likewise supports regulatory roles beyond bulk antioxidant defense [1], while peroxiredoxin phenotypes in aging flies demonstrate that immune, barrier, and lifespan consequences can diverge even when a common redox protein is perturbed [21]. Peroxiredoxin 6 regulation of xanthine dehydrogenase further illustrates that a nominal antioxidant protein can control metabolism [28].

Broader ROS–FOXO–xenosensor literature provides a useful comparative precedent for feedback between xenobiotic sensing and redox-responsive transcription [33], but this non-insect evidence cannot substitute for direct insect validation. The central interpretive problem is therefore functional assignment: increased antioxidant activity may signify scavenging, compensatory stress response, detoxification, metabolic regulation, repair, or several processes simultaneously.

Table 2 distinguishes these possibilities by asking what level of evidence is needed before an antioxidant-associated observation can be assigned a specific physiological function.

Table 2. Cross-scale evidence requirements for assigning function to insect antioxidant and repair systems

Biological scale and context, observable evidence, and functional interpretation	Boundary or discordance	Decisive next test
GST-linked xenobiotic response		
Evidence-based distinction		
Enzyme to larval tolerance **Genetic and biochemical detoxification with antioxidant activity** **Detoxification and redox functions can coexist**	Antioxidant activity alone does not explain resistance	Separate catalytic detoxification from redox-protective effects
GPX-linked epithelial maintenance		
Evidence-based distinction		
Stem cell to aging intestine **Lipid-peroxidation defense coupled to nutrient and DNA-damage signaling** **Repair, redox control, and nutrient sensing can intersect**	Effects remain cell-state dependent	Cell-specific rescue and target validation
Thioredoxin-system regulation		
Evidence-based distinction		
Protein to physiological network **Redox-dependent regulatory functions across insect systems** **Thioredoxin activity extends beyond peroxide defense**	Taxonomic coverage remains uneven	Resolve tissue-specific substrates and redox targets
Peroxiredoxin-dependent aging phenotypes		
Evidence-based distinction		
Organelle to barrier, immunity, lifespan **Divergent phenotypic rescue after peroxiredoxin perturbation** **Shared regulator can generate non-equivalent outcomes**	Immune rescue does not guarantee lifespan rescue	Partition organelle-, tissue-, and phenotype-specific mechanisms
Peroxiredoxin-dependent metabolism		
Evidence-based distinction		
Protein to uric-acid synthesis **Requirement for metabolic-enzyme activation** **Redox protein can directly regulate metabolism**	Demonstrated in a specific silkworm pathway	Test conservation and molecular activation mechanism
Functional-assignment triage		
Proposed synthesis		
Cross-system interpretation **Convergence of localization, perturbation, rescue, target identity, and phenotype** **Functional labels should follow evidence strength rather than protein class**	Architecture is not prospectively validated	Compare its classification performance across taxa and tissues

Note: Evidence-derived rows summarize mechanisms developed in Section 7. The final row identifies the article's proposed interpretive rule; no numerical evidence score or certainty grade is implied.

Discordance among antioxidant abundance, redox state, molecular target, and organismal phenotype is more informative than forcing all observations into a single defense category. **Figure 2** therefore triages such discordance before assigning antioxidant-associated changes to scavenging, detoxification, metabolism, repair, or broader regulation.

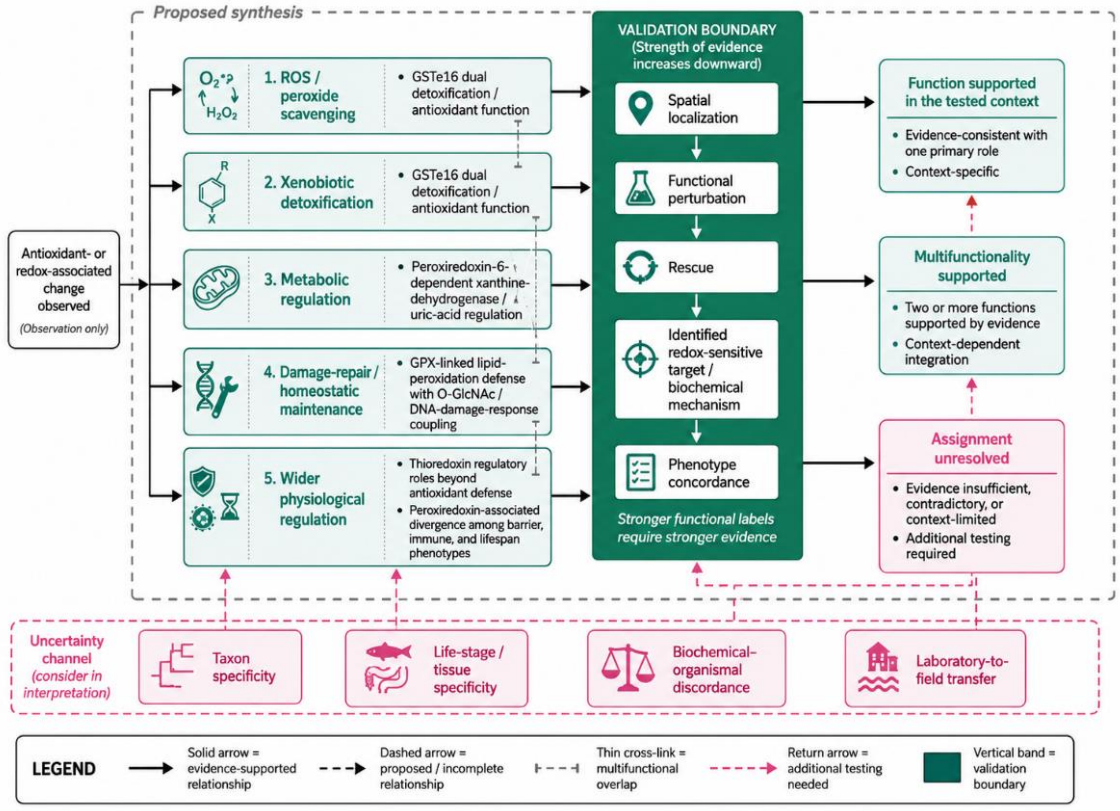


Figure 2. Functional triage of discordant antioxidant, repair, and physiological redox evidence

System-level redox integration

System-level integration requires keeping oxygen availability, ROS production, redox sensing, and downstream phenotype analytically distinct. Drosophila crystal cells and PPO2 contribute to oxygen transport and homeostasis [34]; this constrains the physiological environment in which redox reactions occur but is not itself evidence of ROS signaling.

Across the reviewed insect systems, integration is instead visible where context-specific mechanisms intersect. Gut redox control can couple barrier function with immunity [11]; redox regulation of autophagy can alter longevity [18]; developmental ROS signaling can interface with diapause pathways [23]; and endocrine state can alter DUOX-dependent immunity [29]. These observations support cross-system coupling but not a single conserved master circuit.

We therefore define the article's principal proposed context-gated architecture as an interpretive layer linking source, compartment, duration, biological state, and inference strength. Its purpose is to prevent molecular observations from being promoted automatically to organismal or evolutionary conclusions. A relationship can be mechanistically strong within one tissue and still remain uncertain across sex, stage, species, or environment.

New molecular tools and open questions

Progress now depends less on measuring more undefined "ROS" and more on identifying chemically and spatially specific redox events. Consensus guidance emphasizes that common probes cannot be assumed to quantify a universal ROS pool, while spatial redox models predict that peroxiredoxin/thioredoxin organization can generate localized microdomains [35, 36]. The latter remains a theoretical, non-insect framework and should motivate testing rather than be imported quantitatively into insects.

Insect redox proteomics already demonstrates the value of cysteine-resolved measurements [10], but oxidation alone does not establish functional regulation. Stronger inference requires combinations of localization, targeted perturbation, rescue, redox-insensitive or redox-mimetic variants, and phenotype measurement. The Atg4a redox-site experiment provides one such target-level benchmark [18], whereas genetic manipulation of AANAT1 [24], peroxiredoxin 6 [28], and GSTe16 [31] illustrates how pathway assignment can be strengthened across molecular and organismal scales.

Important gaps remain outside Drosophila, in field environments, across sexes and developmental stages, and at interfaces where redox signaling may vary over minutes while phenotypic consequences emerge over days or generations. Future studies should therefore specify reactive species, source, compartment, temporal regime, target, biological state, and transfer boundary. Testing whether the proposed context gates improve cross-study interpretation is itself an empirical priority.

Conclusion

Insect redox biology is not adequately represented by a continuum running from antioxidants to oxidative damage. Reactive species can function as localized signals, immune effectors, developmental regulators, metabolic modifiers, or damaging oxidants, and the same nominal ROS measurement can support different interpretations in different biological states. Antioxidant proteins likewise participate in signaling, detoxification, metabolism, and repair beyond bulk scavenging.

The proposed context-gated architecture therefore treats source, compartment, duration, biological state, and inference strength as prerequisites for redox interpretation. Its value is not in claiming a universal insect pathway, but in enforcing boundaries between observation and mechanism, laboratory response and field generalization, acute physiology and adaptation, and molecular change and organismal consequence. Future progress will depend on chemically resolved measurements, target-level validation, taxonomic expansion, and experiments that connect redox mechanisms to explicitly bounded physiological outcomes.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

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