Redox-Active Metabolites and their Role in Microbial Signalling

Karishma Singh, Suman Jayakumar Kankanwadi* and Vijay Kumar

Department of Microbiology, CCS Haryana Agricultural University, Hisar, Haryana

Corresponding Author
Suman Jayakumar Kankanwadi
Email: sumanjk2708@gmail.com

OPEN ACCESS

Keywords

Metabolites, Communication, Redox, Signalling, Ecological

How to cite this article:

Karishma, S., Kankanwadi, S. J. and Kumar, V. 2025. Redox-Active Metabolites and their Role in Microbial Signalling. *Vigyan Varta* 6 (12): 95-99.

ABSTRACT

Redox-active metabolites (RAMs) including phenazines, flavins, quinones, and emerging peptide-derived cofactors, have long been viewed through the narrow lens of toxicity or antimicrobial activity. However, recent studies have reframed these small molecules as integral agents of microbial communication. By undergoing reversible oxidation–reduction reactions, RAMs reshape environmental redox potentials and, in turn, modulate gene expression, biofilm development, nutrient acquisition, and interspecies interactions. This article highlights the evolving understanding of RAMs as signalling mediators, summarizes new discoveries from 2023–2025, and discusses future challenges in decoding their ecological and biomedical significance.

INTRODUCTION

Microbes are often portrayed as solitary chemical factories, quietly executing metabolic routines. Yet in reality, microbial communities function as densely interactive societies, constantly exchanging cues about stress, nutrient availability, population density, and environmental changes. Conventional quorum-sensing molecules like acyl-homoserine lactones or autoinducer peptides represent only one part of this communication repertoire.

Increasingly, researchers recognize that microbes also rely on **redox-active metabolites**, small molecules that shuttle electrons and influence the chemical landscape in ways that neighbouring cells can sense and respond to. These metabolites do not merely poison competitors or detoxify environments; they create **redox signals** that shape community behaviour. The past few years have brought significant new insights, reframing RAMs as multifaceted communication molecules central to microbial ecology, physiology, and evolution (Thalhammer *et al.,* 2023).

1. Redox-Active Metabolites: What They Are

RAMs are small organic molecules capable of **reversible electron transfer**. This property, long appreciated for its biochemical utility, now appears central to chemical messaging in microbial habitats.

Major classes include:

- **Phenazines** (e.g., pyocyanin) produced by *Pseudomonas* species (Thalhammer *et al.,* 2023).
- **Flavins** (riboflavin, FMN, FAD) often secreted by electrogenic microbes (as cofactors or secreted shuttles).
- **Quinones** (e.g., ubiquinone, menaquinone).
- **Emerging peptide-derived redox cofactors**, such as **Mycofactocin (MFT)**, recently characterized as a redox carrier in bacteria (Ellerhost *et al.,* 2025).

Rather than acting through classic ligand–receptor interactions, many RAMs influence cells by **modulating environmental redox potential**, thereby activating redox-responsive transcription factors or regulatory pathways (Rutbeek *et al.,* 2021).

2. RAMs as Signals in Population-Level Communication

Recent models suggest that RAMs function analogously to quorum-sensing molecules, but through **electron-based signaling**. When secreted, they create redox gradients that neighboring cells detect. These gradients can report:

- oxygen limitation
- metabolic stress
- community density
- availability of terminal electron acceptors

For example, phenazines from certain bacteria regulate gene networks tied to metabolism and survival under stress or oxygen-limitation (Rutbeek *et al.,* 2021). Flavin-mediated electron shuttling in EET-capable species helps coordinate extracellular electron transfer across populations, enabling cooperative respiration on mineral substrates (Salehi *et al.,* 2025).

Thus, RAMs serve as **diffusible redox signals** — not classical hormones, but chemical messengers embedded in the energy-flow architecture of microbial life (Salehi *et al.,* 2025).

3. Biofilm Organization and Community Metabolism

Biofilms, surface-attached microbial communities are strongly shaped by redox-active molecules. RAMs can:

- promote or inhibit biofilm formation,
- influence biofilm matrix production,
- govern the transition between growth and dispersal,
- enable collective energy harvesting.

Phenazines, for example, help maintain redox balance deep within oxygen-limited biofilms, preventing stagnation of reducing equivalents and allowing continued metabolic flux.

Moreover, quinones, flavins and other redox-active cofactors can act as **electron shuttles**, enabling cells inside biofilms to respire using distant electron acceptors (e.g., oxygen at the biofilm surface, or mineral oxides in the environment) (Willets, 2023).

This community-scale electron sharing provides a survival advantage under challenging or resource-limited conditions, and reveals a form of **distributed metabolism** coordinated via redox chemistry (Willets, 2023).

4. Interspecies and Cross-Kingdom Communication

RAMs influence not only bacteria, but also fungi and host cells. In co-culture biofilms of bacteria and filamentous fungi, redox-active metabolites such as phenazines have been shown to modulate fungal development: for instance, shifting fungal growth toward sporulation rather than vegetative proliferation (Willets, 2023).

In that study, phenazine-mediated redox cycling generated reactive oxygen species (ROS), which triggered a conserved oxidative stress response *via* a transcription factor homologous to mammalian AP-1, leading to morphological changes in fungi.

Such findings highlight that RAMs are **ecological mediators**, shaping not only bacterial communities, but also interactions across domains of life (bacteria ↔ fungi ↔ possibly even host) (Chen *et al.,* 2023).

5. Expanding the RAM Repertoire: New Discoveries (2023–2025)

Recent research highlights that the universe of RAMs is far more diverse than previously appreciated:

- The discovery and biochemical characterization of Mycofactocin (MFT), a **peptide-derived redox cofactor**, indicates that microbes may deploy previously unknown redox-active molecules. In many mycobacteria and related actinobacteria, MFT supports specialized oxidoreductases that recycle NAD(P)H, thus linking secondary metabolism, redox balance, and respiration (Zhang *et al.,* 2023).
- A landmark experimental study showed that deletion of the gene encoding a flavoprotein dehydrogenase, MftG, abrogates ethanol-dependent growth in *Mycolicibacterium smegmatis*. This demonstrated that MFT is not just a static cofactor, it participates dynamically in electron transfer from metabolic substrates to the electron transport chain (ETC) (Saldivar *et al.,* 2024).
- A conceptual framework recently proposed outlines how to systematically identify biological functions of RAMs beyond phenazines, by combining chemical, physical, and ecological analyses of microbial microenvironments.

These results suggest that microbial communication via redox chemistry may be more pervasive and ancient than previously assumed.

Challenges and Future Perspectives

1. **Distinguishing Signals from Stress Artifacts:** Because RAMs often generate reactive oxygen species (ROS), separating intentional signalling from incidental oxidative damage remains challenging. Many responses attributed to "toxicity" may in fact be finely tuned regulatory behaviours.

2. **Mapping Spatiotemporal Redox Microenvironments:** Microbial habitats, especially biofilms, contain microscale chemical gradients that evolve in minutes. Currently, we lack high-resolution tools to visualize redox states *in situ*. Progress will require the integration of microelectrodes, redox-sensitive biosensors, fluorescent reporters, and

computational modelling to capture redox dynamics over space and time.

A suggested research direction is to couple chemical measurements (e.g., redox potentials, ROS levels), physical parameters (diffusion, biofilm architecture), and biological outputs (gene expression, community structure), in the spirit of the framework proposed by Thalhammer & Newman (Deng *et al.,* 2022)

3. **Untangling Interactions in Mixed Communities:** Most RAM studies focus on single species. Yet in natural settings, RAMs interact with dozens or hundreds of taxa simultaneously. Understanding how mixed species interpret shared redox cues and how different organisms modulate, intercept, or exploit those signals — remains largely unexplored.

4. **Applications in Synthetic Biology and Biotechnology:** Engineers are beginning to use RAMs as "wires" for coordinating multi-strain microbial consortia. However, designing predictable, safe systems is complicated by redox noise, metabolite promiscuity, and context-dependent behaviour. Careful design and environmental control will be essential.

5. **Ecological and Biomedical Implications:** Manipulating RAMs in soils, sediments, or microbiomes may enhance nutrient cycling, bioremediation, or suppression of pathogens. But this also raises risks: altering redox landscapes could destabilize delicate ecological networks or shift microbial community composition in unintended ways. Responsible application requires deep mechanistic understanding and long-term ecological assessment.

CONCLUSION

Redox-active metabolites offer a radically new perspective on microbial life. Far from acting solely as toxins or metabolic byproducts, these molecules serve as **dynamic communication signals**, helping microbes coordinate metabolism, negotiate territory, build biofilms, and interact with hosts. Recent discoveries including peptide-derived redox cofactors like Mycofactocin and complex redox-based signaling circuits reveal that the microbial world communicates in a chemical language written in electrons.

As we develop better tools to observe and interpret redox landscapes, we may come to appreciate RAMs not as simple chemical curiosities, but as the foundation of microbial sociobiology. Ultimately, listening to these redox whispers may reshape our understanding of ecosystems, infectious disease, and the deep evolutionary strategies of the smallest organisms on Earth.

REFERENCES

Chen, N., Du, N., Shen, R., He, T., Xi, J., Tan, J., ... & Yuan, Q. (2023). Redox signaling-driven modulation of microbial biosynthesis and biocatalysis. *Nature Communications*, *14*(1), 6800.

Deng, Y., Zhang, K., Zou, J., Li, X., Wang, Z., & Hu, C. (2022). Electron shuttles enhanced the removal of antibiotics and antibiotic resistance genes in anaerobic systems: A review. *Frontiers in Microbiology*, *13*, 1004589.

Ellerhorst, M., Nikitushkin, V., Al-Jammal, W. K., Gregor, L., Vilotijević, I., & Lackner, G. (2025). Recent insights into the biosynthesis and biological activities of the peptide-derived redox cofactor mycofactocin. *Natural Product Reports*.

Rutbeek, N. R., Rezasoltani, H., Patel, T. R., Khajehpour, M., & Prehna, G. (2021). Molecular mechanism of quorum sensing inhibition in Streptococcus by the phage protein paratox. *Journal of Biological Chemistry*, *297*(3).

Saldivar, A., Ruiz-Ruiz, P., Revah, S., & Zuñiga, C. (2024). Genome-scale flux balance analysis reveals redox trade-offs in the metabolism of the thermoacidophile Methylacidiphilum fumariolicum under auto-, hetero-and methanotrophic conditions. *Frontiers in Systems Biology*, *4*, 1291612.

Salehi, M., Campillo-Balderas, J. A., Paalme, T., & Künzler, M. (2025). *The chemical ecology of coumarins and phenazines affects iron acquisition by pseudomonads*. Environmental Microbiology Reports, 17(1), 45–58. https://doi.org/10.1111/1758-2229.13095

Thalhammer, K. O., & Newman, D. K. (2023). A phenazine-inspired framework for identifying biological functions of microbial redox-active metabolites. *Current opinion in chemical biology*, *75*, 102320.

Willetts, A. (2022). Inter-Species Redox Coupling by Flavin Reductases and FMN-Dependent Two-Component Monooxygenases Undertaking Nucleophilic Baeyer–Villiger Biooxygenations. *Microorganisms*, *11*(1), 71.

Zhang, J., Liu, H., Zhang, Y., Fu, B., Zhang, C., Cui, M., ... & Chen, C. (2023). Enhanced CO2 reduction by electron shuttle molecules via coupling different electron transport processes in microbial electrosynthesis. *Fermentation*, *9*(7), 679.