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Editorial

Redox Remodeling as a Natural Product Strategy in Cancer Therapy: Lessons from Arnicolide C

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Cancer remains a leading cause of mortality worldwide despite major advances in surgery, radiotherapy, targeted therapy, and immunotherapy. Although these approaches have improved outcomes in selected malignancies, durable responses are still limited by tumor heterogeneity, adaptive signaling, and treatment-related toxicity.[1] As a result, increasing attention has turned toward identifying biological vulnerabilities shared across cancer types rather than relying solely on single-target inhibition. Among these vulnerabilities, oxidative homeostasis has emerged as an increasingly attractive therapeutic target.[2]

Reactive oxygen species (ROS) occupy a complex and often paradoxical position in cancer biology.[3] At physiological or moderately elevated levels, ROS support tumor initiation and progression by promoting genomic instability, metabolic adaptation, and oncogenic signaling. In contrast, excessive oxidative stress disrupts cellular integrity and activates cell death programs. Because cancer cells generally maintain chronically elevated ROS while depending heavily on antioxidant systems to sustain survival, they exist within a precarious redox balance. This dependence creates a form of redox vulnerability that may be selectively exploited for therapeutic benefit. Consequently, strategies aimed at manipulating oxidative homeostasis have gained increasing attention in anticancer drug development.

The significance of ROS extends beyond oxidative damage itself. Growing evidence indicates that ROS function as signaling intermediates capable of reshaping oncogenic networks and influencing therapeutic responsiveness.[4] This role becomes particularly relevant in therapy-resistant tumors characterized by marked signaling plasticity. Canonical pathways such as PI3K/Akt and MAPK remain central regulators of proliferation, metabolism, and survival, yet therapeutic inhibition of these pathways is often undermined by compensatory rewiring and incomplete responses. This raises a broader therapeutic question: could more durable benefit arise from modulating higher-order regulatory systems, such as redox homeostasis, rather than focusing exclusively on individual signaling nodes?

Natural products offer a useful framework for exploring this possibility. Historically, medicinal plant-derived compounds have served not only as sources of anticancer agents but also as valuable tools for uncovering therapeutically relevant biology.[5] Many natural products are now recognized as regulators of oxidative signaling and cellular redox balance. Among them, sesquiterpene lactones have attracted particular interest because of their electrophilic characteristics and ability to engage redox-sensitive pathways.[6] Yet important mechanistic questions remain unresolved. While ROS induction is commonly reported, how oxidative perturbation translates into coordinated remodeling of oncogenic signaling remains insufficiently understood.

Recent work on Arnicolide C (AC), a sesquiterpene lactone isolated from *Centipeda minima*, provides an informative example of this therapeutic paradigm.[7] Unlike conventional kinase inhibitors, AC appears to act as a natural product-derived ROS inducer whose activity has been investigated in experimental models of hepatocellular carcinoma. Multi-level investigations demonstrated oxidative stress induction following AC treatment, whereas attenuation of ROS markedly reduced its biological effects. These findings identify oxidative signaling as a driving component of AC activity rather than a secondary consequence of treatment. In this context, AC serves not only as an anticancer agent but also as a mechanistically informative model for understanding ROS-directed therapeutic intervention.

Notably, the consequences of AC-induced redox remodeling extended beyond generalized cytotoxicity. ROS accumulation coordinated broad changes in oncogenic signaling, including suppression of PI3K/Akt and ERK activity together with activation of JNK signaling. These signaling changes ultimately converged on MYC downregulation, a finding of particular interest given the longstanding challenge of directly targeting MYC. As a master regulator of proliferation, metabolism, and survival, MYC remains one of the most difficult oncogenic drivers to therapeutically control across multiple malignancies, including hepatocellular carcinoma.[8] From this perspective, the findings surrounding AC encourage reconsideration of MYC-directed therapy, not necessarily through direct inhibition of MYC itself, but through disruption of the signaling environments that sustain MYC-dependent oncogenic programs.

The implications of this work extend beyond MYC biology

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alone. ROS should not be viewed simply as damaging metabolites or nonspecific mediators of cytotoxicity. Instead, oxidative signaling may function as a higher-order regulator capable of coordinating interconnected oncogenic pathways. Such regulation may be especially relevant in cancers characterized by pathway redundancy and adaptive rewiring, where single-target strategies often encounter therapeutic resistance. In this regard, AC illustrates how redox remodeling can reshape oncogenic signaling networks rather than merely suppress isolated molecular targets.

At the same time, the therapeutic potential of redox-based intervention should be interpreted with appropriate caution. Oxidative signaling is inherently context-dependent. Insufficient ROS induction may fail to destabilize malignant signaling networks, whereas excessive oxidative stress carries the risk of collateral tissue injury and inflammatory toxicity. Moreover, the influence of redox modulation on stromal and immune components within the tumor microenvironment remains incompletely understood. Whether ROS-inducing agents consistently enhance antitumor immunity or produce competing biological consequences warrants further investigation.

This perspective also aligns with broader concepts in integrative medicine. Therapeutic benefit may arise not only from inhibition of individual molecular targets but also from coordinated regulation of interconnected biological systems. This view is consistent with the concept of holistic integrative medicine, which advocates understanding disease and therapy through interconnected biological systems rather than isolated targets.[9] Such a systems-oriented perspective may provide a useful framework for interpreting the multitarget and network-regulating properties of natural products, particularly in the context of integrative cancer therapy.[10] Owing to their structural diversity and pleiotropic pharmacology, natural products are particularly well suited to this paradigm and are increasingly recognized as modulators of signaling networks and disease susceptibility. Viewed in this context, the study of AC reflects contemporary efforts to bridge traditional medicine–derived compounds with precision oncology.

Nevertheless, several challenges must be addressed before ROS-targeted strategies can be realistically translated into clinical practice. Long-term toxicological evaluation, pharmacokinetic characterization, and comprehensive tissue safety assessment remain essential. Orthotopic and immunocompetent tumor models will also be required to clarify the relationship between redox remodeling and antitumor immunity. Combination strategies deserve further investigation, as modulation of redox homeostasis may have the potential to improve responsiveness to targeted therapy or immunotherapy while delaying therapeutic resistance.

Whether AC itself ultimately advances to clinical application remains uncertain. Yet the broader therapeutic implications emerging from this work may prove widely relevant. Exploiting redox vulnerability to reshape oncogenic signaling represents more than a mechanism restricted to a single compound; it reflects an evolving therapeutic concept in cancer treatment. In this sense, natural product research and integrative medicine may contribute not only new anticancer candidates but also fresh mechanistic insights and conceptual foundations for precision oncology.

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Conflict of interest

The author declares no financial conflict of interest. The author is a co-author of the original Arnicolide C study cited as Ref. 7 and discussed in this Editorial.

Author contributions

GQC is the sole author of the manuscript.

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