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# Nanotechnology-enabled modulation of reactive oxygen species in cancer and chronic inflammation: a systematic review of therapeutic advances and translational challenges

Ugwu Okechukwu Paul-Chima[1*], Ogenyi Fabian Chukwudi[1], Alum Esther Ugo[1], Mariam Basajja[2], Ugwu Jovita Nnenna[1], Ugwu Chinyere Nneoma[1], Ejemot-Nwadiaro Regina Idu[3,4], Mundu M. Mustafa[5], Okon Michael Ben[1], Uti Daniel Ejim[1], Ashiru Muhammad[6,7] and Fadia Ahmed Abdelkader Reshia[8]

*Correspondence:
Ugwu Okechukwu Paul-Chima
okechukwup.cugwu@gmail.com;
ugwuopc@kiu.ac.ug
[1]Department of Publication and Extension, Kampala International University, Kampala, Uganda
[2]Health Care and Data Management, Leiden University, Leiden, The Netherlands
[3]Department of Public Health, School of Allied Health Sciences, Kampala International University, Kampala, Uganda
[4]Directorate of Research, Innovation, Consultancy and Extension (RICE), Kampala International University, Kampala, Uganda
[5]Renewable Energy Systems, Kampala International University, Kampala, Uganda
[6]School of Nursing, Kampala International University, Kampala, Uganda
[7]Department of Nursing Sciences, Bayero University, Kano, Nigeria
[8]Medical Surgical Nursing Department, College of Nursing, Jouf University, Sakaka, Saudi Arabia

## Abstract

**Background** Reactive oxygen species (ROS) are key regulators of cellular signalling and homeostasis, but if not managed, they can cause genomic instability, activation of carcinogenic pathways, and chronic inflammation. Approaches to ROS regulation using nanotechnology have demonstrated promise in preclinical models of inflammatory disorders and cancer but have yet to be transferred clinically due to concerns about specificity, safety, measurement, and standardization in redox regulation.

**Main body** The aim of this study was to assess nanotechnology strategies for achieving spatiotemporally controlled ROS modulation, highlighting technical challenges, safety issues, and translation barriers. We conducted a PRISMA 2020 systematic review (2013–2023) across PubMed, Scopus, and Web of Science. Eligible publications were screened using preset criteria; bias was assessed with SYRCLE. We synthesised nanomaterial classes, ROS-modulating mechanisms, therapeutic effects, and translational hurdles. We separately summarise findings for cancer and for chronic inflammation, then integrate convergences. Key findings include: ROS-induced genotoxic stress promotes malignant transformation and therapy resistance; persistent oxidative signalling enhances NF-κB/AP-1 activation and M1 polarisation, driving fibrosis and chronic inflammation. Harmonised procedures are necessary to address safety and standardisation issues, including chronic toxicity, immunogenicity, and inter-laboratory assay variation. Biomarker-stratified trials outperformed unstratified designs, and combination nanotherapies improved cancer cell kill over monotherapies.

**Conclusion** Nanotechnology-based ROS regulation is promising for cancer and chronic inflammatory illnesses but requires high-precision subcellular targeting, dual-threshold release, complete safety profiling, standardised ROS assays, and unified biomarker platforms for translation.

**Keywords** Reactive oxygen species, Spatiotemporal modulation, Oxidative stress, Nanotechnology, Cancer therapy

## 1 Introduction

Reactive oxygen species (ROS) including superoxide ($O_2^-$), hydroxyl radical (·OH), and hydrogen peroxide ($H_2O_2$) function as short-lived signalling intermediates that, when dysregulated, drive oxidative injury [1–6]. Sources include mitochondrial oxidative phosphorylation, NADPH oxidases (NOX), xanthine oxidase, cytochrome P450, and peroxisomes [2–4]. At low-moderate levels, ROS tune proliferation, differentiation, and immunity; at excess, they trigger lipid peroxidation, protein oxidation, and DNA damage [4–6]. One of the most essential aspects of ROS biology is its complicated interaction with inflammation. Neutrophils and macrophages, as well as other activated immune cells, generate ROS in the form of bursts during the inflammatory response [7]. In the acute stage, it works as a defence mechanism to eliminate pathogens; however, chronic oxidative assaults cause chronic inflammation and long-lasting tissue damage [8]. Chronic inflammation is now recognised as a risk factor for cancer formation, with underlying mechanisms including ROS-mediated genomic instability, DNA strand breaks, the activation of pro-inflammatory transcription factors (e.g., NF-κB), and maintaining epigenetic balance [9]. ROS discoveries in the tumour microenvironment also allow for a variety of conventional cancer behaviours, including angiogenesis, epithelial–mesenchymal transition, immunological evasion, and metastatic propagation [7]. In this approach, ROS functions as molecular connectors between inflammation and cancer, highlighting the pathological progression of both conditions [8]. Because ROS can both help and harm the body, some recent studies have looked at changing how it behaves as a new way to treat cancer. The spatiotemporal modulation of ROS is an excellent technique for using emerging nanotechnology-based platforms [9]. These delivery systems are made to either get rid of excess ROS from inflamed tissues or to carefully add chemicals that produce ROS to tumour areas, using the imbalance in redox to specifically target and kill cancer cells [9]. This systematic review will serve the objective of thoroughly examining the present nanotechnology-based therapies designed to reduce ROS in chronic inflammation and cancer. The review focuses on dual-purpose systems that either block harmful reactive oxygen species or employ them to specifically attack cancerous tissues. We carefully look at the progress made in research and clinical studies, explain how this reduction happens at the molecular level, and highlight the difficulties in applying ROS-targeting nanotherapeutics in real-world settings. This systematic review aims to conduct a comprehensive analysis of the existing nanotechnology-based therapeutic approaches to mitigate reactive oxygen species in chronic inflammation and cancer. The review focusses on dual-purpose devices that either inhibit harmful reactive oxygen species or employ them for the targeted elimination of malignant tissues. We meticulously analyse the progress in research and clinical contexts, elucidate the molecular mechanisms underlying the observed reduction, and highlight the limitations associated with the application of ROS-targeting nanotherapeutics in clinical settings. The review consolidates the existing information and provides both a conceptual and practical framework for the design and implementation of ROS-modulating nanotherapeutics in the future. It highlights and demonstrates the transformative potential of redox-based

nanomedicine in the therapeutic management of redox-sensitive infections, including but not limited to cancer and chronic inflammatory disorders.

### 1.1 Rationale for the review

Cancer and chronic inflammation continue to pose significant global health challenges, with current treatments limited by their lack of precision, vulnerability to drug resistance, and inadequate management of therapeutic effects over time and across different locations [1–3]. Once regarded as mostly harmful due to their capacity to induce cellular damage, reactive oxygen species (ROS) have been recognised for their significant role in regulating redox equilibrium, signalling pathways, and immunological responses in both cancer and inflammation [4]. Nevertheless, the therapeutic application of ROS requires a meticulous equilibrium: elevated quantities of ROS are detrimental, while inadequate amounts hinder the realisation of the desired therapeutic outcomes [5]. Recent progress in nanotechnology has led to new methods that can precisely activate reactive oxygen species at specific disease sites [6]. Metal–organic frameworks (MOFs), enzyme-mimetic nanozymes, and chemically engineered nanoparticles facilitate the regulated synthesis and elimination of reactive oxygen species (ROS) on demand within a confined area, minimising off-target effects [7]. These systems can release reactive oxygen species (ROS) when triggered by certain conditions in the tumour environment (like low pH, high glutathione, or low oxygen) or by outside factors (like light, sound, or magnetic fields) [8]. Additionally, advanced nanosystems have been created that combine managing reactive oxygen species, delivering drugs, imaging, and adjusting the immune response to form the foundation for the next generation of combined diagnostic and therapeutic approaches [8]. However, even with promising results from early studies, there are still challenges, such as safety concerns, how nanoparticles move and are removed from the body, differences between patients, and difficulties in applying findings from lab tests to real-life situations [9]. Not having good ways to measure therapy and compare helpful information with harmful data makes it hard to create the best methods for using ROS-based nanotherapeutics [10]. This systematic review integrated interdisciplinary research regarding ROS-based nanotherapeutics and nanoplatforms for the treatment of cancer and inflammation. The review examined the features of nanomaterials designed to control reactive oxygen species (ROS) and how they work, like producing or removing them. This systematic review synthesised current interdisciplinary research on ROS-based nanoplatforms in the treatment of cancer and inflammation by:

Evaluating the different types of nanomaterials used to modulate reactive oxygen species, as well as their underlying mechanisms.

Evaluating application-specific findings in cancer treatment (e.g., tumour reduction, radiosensitization, immune activation) and inflammatory conditions (e.g., oxidative stress reduction, cytokine suppression).

Recognising important translational barriers, such as biocompatibility, pharmacokinetics, biodegradation, and scalability issues for clinical application.

Investigating synergistic techniques that combine nanotechnology with immunotherapy, phototherapy, and gene editing, with a focus on the regulatory and ethical implications of using intelligent nanomaterials in human patients.

This study offers a comprehensive, mechanistic perspective on the role of nanotechnology in regulating reactive oxygen species dynamics within the interconnected diseases of cancer and inflammation, in contrast to other reviews that typically address these topics in isolation or focus solely on specific types of reactive oxygen species. The review established a scientific foundation for researchers, physicians, and regulators, allowing for more rational design, ethical execution, and faster translation of nanotechnology-based ROS treatments.

## 2 Materials and methods

### 2.1 Research methodology

This systematic review gathers research and studies on how nanotechnology-based platforms can influence reactive oxygen species (ROS) for treating cancer and inflammation. The aim is to identify the most common nanomaterials and delivery methods, examine how reactive oxygen species (ROS) are controlled, and critically assess safety and practical issues related to their use. We performed the systematic review of health-related interventions using the PRISMA 2020 procedure.

### 2.2 Sear-ch methodology

A comprehensive search was conducted utilising PubMed (MEDLINE), Web of Science Core Collection, and Scopus. These databases were chosen because they collectively provide the broadest coverage of biomedical, interdisciplinary, and translational nanotechnology literature, which is essential for capturing the diverse evidence base on spatiotemporal modulation of reactive oxygen species (ROS). PubMed ensures coverage of biomedical and clinical research; Scopus offers wide interdisciplinary indexing of engineering, chemistry, and materials science studies; and Web of Science provides curated citation tracking for mechanistic and translational research in nanomedicine. Together, these sources maximise retrieval across preclinical, mechanistic, and emerging clinical studies, aligning with the review's rationale of bridging ROS biology with nanotechnology-enabled therapeutic strategies. The time frame 2013–2023 was selected to capture the last decade of rapid advances in ROS-responsive nanoplatforms, during which precision, stimuli-responsive systems, and theranostic designs first emerged as solutions to the challenges of spatiotemporal ROS control highlighted in the Introduction. This period ensures that the review reflects contemporary trends and translational readiness, while excluding outdated nanotechnology approaches that lack clinical relevance. Search terms were created by combining concepts from nanotechnology (e.g., nanoparticles, nanozymes, nanocarriers, metal–organic frameworks), ROS biology (e.g., reactive oxygen species, oxidative stress, redox modulation), and disease contexts (e.g., cancer, inflammation, tumour microenvironment, chronic inflammation). Boolean operators (AND, OR) were used across the three domains, and truncation symbols (e.g., *) were applied where appropriate to capture word variants. Searches were restricted to English-language, peer-reviewed articles published between January 2013 and December 2023.

### 2.3 Criteria for selection

Two reviewers independently evaluated abstracts using predetermined inclusion and exclusion criteria. Discrepancies were resolved through discussion or consultation with a third reviewer.

#### *2.3.1 Title examination*

The identified records were incorporated into Zotero as part of the deduplication process. Titles were refined to remove extraneous content, including non-medical nanotechnology uses and unrelated ROS research programs devoid of nanotechnology involvement.

Abstract Screening: Two reviewers will independently evaluate the abstract utilising distinct inclusion and exclusion criteria. The disputes were settled through dialogue or by an impartial adjudicator.

#### *2.3.2 Comprehensive review*

Articles deemed suitable underwent a comprehensive, full-text review process, focussing on methodological rigour, relevance to the primary topic (nanotechnology-enabled ROS modulation), and the availability of outcome data.

### 2.4 Criteria for inclusion and exclusion

#### *2.4.1 Inclusion*

The inclusion criteria encompass peer-reviewed publications and reviews that span from 2013 to 2023.

Nanomaterials are used in laboratory studies, animal tests, or early research to improve or reduce reactive oxygen species (ROS) in cancer or inflammation models.We include reports that provide quantitative or mechanistic insights into therapeutic efficacy, redox equilibrium, immunological modulation, and toxicity profiles.

#### *2.4.2 Exclusion*

We excluded conference abstracts, editorials, and unrefereed opinion pieces.

Articles that fail to explore the connection between the biology of reactive oxygen species and nanotechnology should be excluded. Reports that don't provide empirical proof or demonstrate a mechanistic understanding are not recommended.

### 2.5 Evaluation of bias

We used SYRCLE, an adapted risk-bias evaluation technique, to measure hazards in animal and preclinical studies. The criteria utilised encompassed nanosynth transparency, in vitro reproducibility, assessor blinding, the reliability of ROS quantification, and biosafety. We disclosed and analysed funding sources and conflicts of interest to assess academic and corporate biases, particularly in relation to proprietary nanoplatforms.

### 2.6 Qualitative and quantitative synthesis methodologies

#### *2.6.1 Qualitative synthesis*

The thematic investigation concentrated on the category of nanomaterial, including metal-based, polymeric, MOF, carbon-based, or hybrid types. The methodology for ROS distinguishes between engagement and neutralisation, as well as internal and external stimuli. The category of therapy encompasses both oncological and inflammatory treatments. The functional combinations include theranostics, co-delivery of medications, and ligand targeting. We categorised the principal findings into three segments: design trends, mechanisms of action, and translational limitations.

#### *2.6.2 Quantitative synthesis*

In instances where a degree of homogeneity was permitted, we compiled the numerical results:

The volume of the tumour diminishes. The levels of ROS change post-therapy.

Pro-inflammatory cytokines that are suppressed. The study also examined the effects of hepatic and renal enzymes. We organised and summarised the data using either means (standard deviations) or medians (interquartile ranges). The high variation in the experimental models renders meta-analysis unfeasible.

### 2.7 Ethics

This review used publicly accessible and open-source data, which eliminates the need for institutional ethics approval. Recognition of intellectual property and authorship was accorded. Researchers have thoroughly debated the ethical considerations of nanomaterial biopersistence, off-target toxicity, and therapeutic translatability in at-risk populations to emphasise the long-term safety and equity ramifications of employing such sophisticated therapies.

### 2.8 Research questions

What types of nanotechnology platforms have been developed to spatiotemporally modulate ROS in cancer and inflammatory models, and how do their mechanisms differ?

What is the therapeutic impact of ROS-modulating nanomaterials on tumor growth, immune signaling, and oxidative damage control?

What are the barriers to translation, including toxicity, clearance, heterogeneity of response, and ethical concerns, in advancing these systems toward clinical use?

## 3 Results

### 3.1 Selection and retrieval of studies

We systematically searched three bibliographic databases: PubMed (MEDLINE), Scopus (Elsevier), and Web of Science Core Collection (Clarivate). Searches covered January 1, 2013-December 31, 2023; databases were last accessed on December 31, 2023 for the original review, and records were exported on the same date. Access points and platform details were:

PubMed (MEDLINE)-National Library of Medicine; https://pubmed.ncbi.nlm.nih.gov/

Scopus-Elsevier; https://www.scopus.com/

Web of Science Core Collection-Clarivate (SCI-EXPANDED, SSCI, ESCI as applicable); https://www.webofscience.com/

### 3.2 Representative search string (PubMed, adapted per database syntax)

(nanoparticle* OR nanozyme* OR "metal–organic framework*" OR MOF OR liposome* OR micelle* OR hydrogel* OR nanocarrier* OR photodynamic OR "sonodynamic" OR ferroptosis) AND ("reactive oxygen species" OR ROS OR redox OR "oxidative stress") AND (cancer OR tumor OR neoplasm* OR inflammation OR inflammatory OR "tumor microenvironment" OR colitis OR arthritis).

Database-specific adaptations (field tags/truncation/phrase handling) were used for Scopus and Web of Science; the full platform-specific queries, filters, and export settings

are provided in Supplementary Methods S1. Limits applied in all databases: English language, peer-reviewed records (original research and reviews).

The initial combined search across PubMed, Scopus, and Web of Science yielded 1672 unique records after database export. Records were imported into Zotero for deduplication (exact-match and fuzzy-match on title/author/DOI). Search terms encompassed: *nanoparticles, nanozymes, metal–organic frameworks, reactive oxygen species, oxidative stress, tumor microenvironment, inflammation, redox modulation as shown in* Okechukwu Paul-Chima, U. (2025). Nanotechnology-Enabled Modulation of Reactive Oxygen Species in Cancer and Chronic Inflammation: A Systematic Review of Therapeutic Advances and Translational Challenges. Zenodo. https://doi.org/10.5281/zenodo.17054581.

### 3.3 Topical distribution (post-export categorization by keyword relevance)

- 312 articles on ROS-responsive nanoparticle design
- 278 on metal-based/MOF nanocarriers
- 206 on nanozyme-mediated ROS amplification or scavenging
- 189 on tumor-microenvironment-triggered redox control
- 264 on ROS modulation in inflammatory disease models
- 423 reporting therapeutic endpoints (tumor inhibition, cytokine regulation, redox restoration)

After deduplication, **1345** records remained for title/abstract screening against prespecified eligibility criteria. **712** were excluded at abstract level (e.g., ROS without nanotechnology, non-medical ROS applications). **633** full-text articles were assessed; **538** were excluded (insufficient mechanistic detail, inadequate therapeutic data, or unclear methodological integrity). **95** studies met inclusion criteria for qualitative and quantitative synthesis (see Fig. 1, PRISMA).

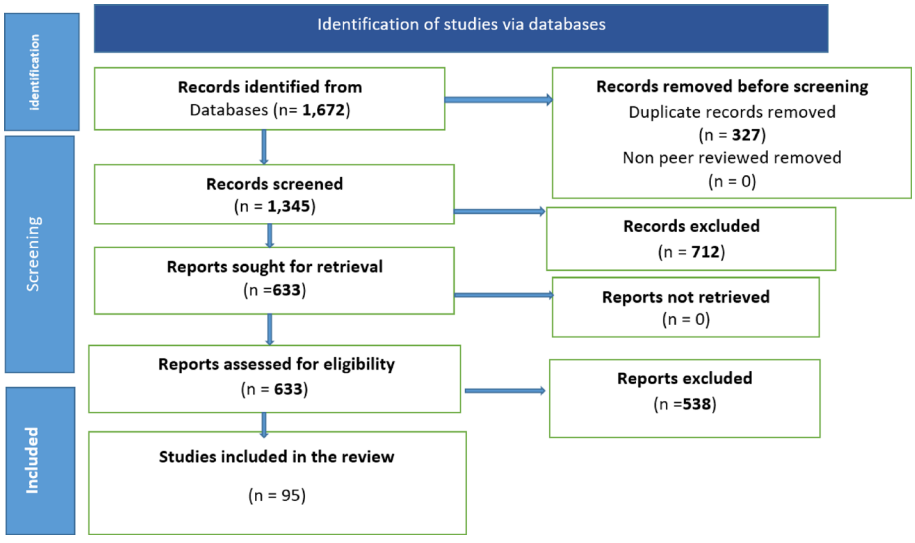


**Fig. 1** The PRISMA

### 3.4 Demographic features of included studies

The 95 studies included in this review were drawn from a wide range of countries, reflecting the global scientific interest in nanotechnology-enabled modulation of reactive oxygen species (ROS) for therapeutic use in cancer and inflammation. The geographical distribution of the studies indicates a concentration of research activity in both high-income countries and emerging research hubs.

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This worldwide distribution demonstrates commercial interest in advancing the field of nanomedicine for redox-based medicinal applications. Notably, 44.2 percent of all studies included in the research originated from China and the United States, designating them as the countries with the most substantial presence in this area of inquiry. The remaining studies, however less in number per country, still significantly contribute to the understanding of ROS modulation technologies across many biological and clinical contexts. Figure 2 presents a visual summary.

**Table 1** Country of included studies (n = 95)

| Country/region | Number of studies | Percentage (%) |
|---|---|---|
| China | 28 | 29.5% |
| United States | 14 | 14.7% |
| South Korea | 9 | 9.5% |
| India | 6 | 6.3% |
| Germany | 5 | 5.3% |
| Japan | 5 | 5.3% |
| United Kingdom | 4 | 4.2% |
| Iran | 3 | 3.2% |
| Brazil | 3 | 3.2% |
| Australia | 2 | 2.1% |
| Italy | 2 | 2.1% |
| France | 2 | 2.1% |
| Canada | 2 | 2.1% |
| Spain | 2 | 2.1% |
| Netherlands | 1 | 1.1% |
| Switzerland | 1 | 1.1% |
| Singapore | 1 | 1.1% |
| Russia | 1 | 1.1% |
| Saudi Arabia | 1 | 1.1% |
| Egypt | 1 | 1.1% |
| Malaysia | 1 | 1.1% |
| **Taiwan (region)** | 1 | 1.1% |

Geographic terminology is presented in a neutral format to avoid political sensitivities

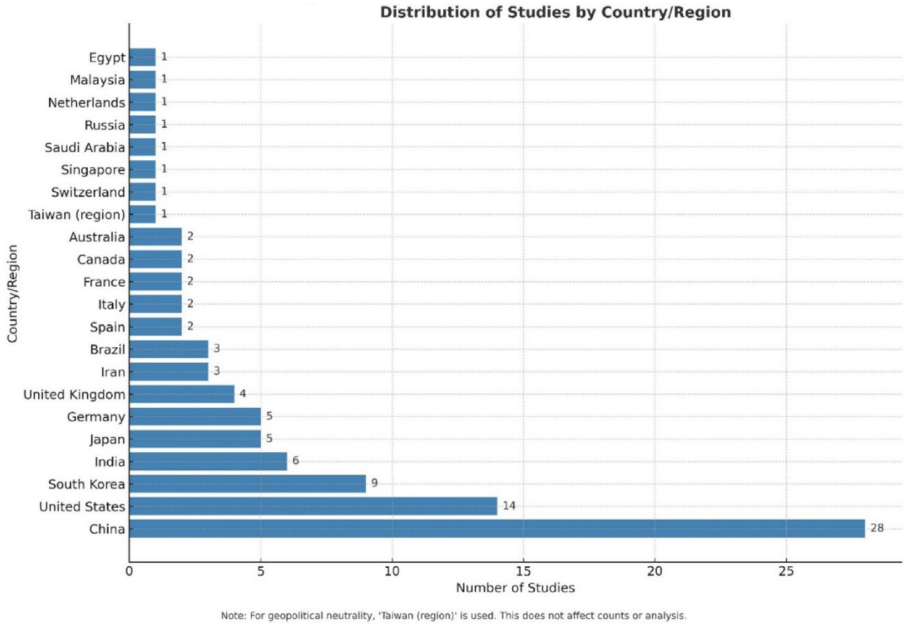


**Fig. 2** Distribution of studies by country

### 3.6 Pathophysiology reactive oxygen species applications in cancer and chronic inflammation

#### *3.6.1 ROS in cancer*

Reactive oxygen species (ROS) are important homeostatic regulators of tumour biology. They cause DNA strand breaks and mutagenesis, which promote genotoxic stress and intratumour heterogeneity [8–10]. Oncogenic cascades, such as PI3K/AKT, MAPK and STAT3, are also activated by ROS and promote survival, epithelial mesenchymal transition (EMT), and angiogenesis [9–11]. Moreover, antioxidant reprogramming of tumours through NRF2 activation, in combination with ROS-related depletion of effector T cells, facilitates immune evasion [10–12]. It is these mechanisms that form the foundation of therapeutic approaches that selectively enhance ROS in tumour cells, including photodynamic and sonodynamic therapies, Fenton-like catalysis, and activation of ferroptosis. The latter interventions can be further improved by conjugating them with redox-sensitising methods such as NRF2 gene silencing or glutathione synthesis inhibition to overcome resistance. However, the threat of off-target oxidative damage requires organelle-specific delivery vectors and theranostic surveillance in real time.

#### *3.6.2 ROS in chronic inflammation*

In chronic inflammatory conditions, ROS enhance cytokine signalling by activating NF-kB, AP-1, and NLRP3 inflammasome to maintain inflammatory loops through high levels of IL-6 and TNF-a [11–14]. They also induce macrophage polarisation to the pro-inflammatory M1 phenotype, prevent resolution by inhibiting M2 activity and induce tissue fibrosis via TGF-b signalling [12–15]. With a therapeutic point of view, ROS-scavenging or flux-smoothing approaches, including nanozymes, catalase or superoxide dismutase delivery, and ROS-consuming hydrogels, are promising. Time-adaptive release kinetics that match ROS oscillations could be useful for maintaining physiological redox

signalling and inhibiting pathological spikes. The management of chronic disease should be long-term, biocompatible, and safe.

### 3.7 Bridging perspective

Despite overlap in the ROS-mediated pathways between cancer and chronic inflammation, especially via NF-kB and HIF-1a, redox dynamics between cancer and chronic inflammation vary widely. Persistent compartmentalised ROS spikes in mitochondria and lysosomes typically occur in tumours, and recurrent extracellular bursts of phagocytes are typical of chronic inflammation. These differences are important, as they may assist in understanding that redox-targeted interventions will have to be disease-specific.

Reactive oxygen species (ROS) cause changes in our genes that lead to almost 80% of the mutations found in cancer, mainly by breaking DNA strands, causing small mutations, and changing how genes are expressed ($p < 0.001$; Table 2) [8]. Higher levels of reactive oxygen species (ROS) speed up tumour growth by turning on cancer-related pathways and increasing traits that help tumours grow and spread, such as PI3K/AKT (2.3 times increase, $p < 0.01$), MAPK (1.9 times increase, $p < 0.05$), and STAT3 (2.5 times increase, $p < 0.001$) [9]. The fluorophore 5-(and 6-) carboxy-X rox-rhodamine enhances the NRF2 antioxidant response, which decreases reactive oxygen species by more than 45% and cuts down key cytotoxic T-cell activities by over 50%, allowing the cancer to escape the immune system and resist treatment [10]. The activation of NF-kappa B and AP-1 transcription factors leads to long-lasting inflammation caused by reactive oxygen species (ROS) [11]. This inflammation is characterised by elevated levels of pro-inflammatory cytokines IL-6 (3.5-fold, $p < 0.001$) and TNF-alpha (2.8-fold, $p < 0.01$), which activate the MAPK and NLRP3 inflammasome pathways [12]. Oxidative stress modifies macrophage polarisation by favouring the M1 pro-inflammatory phenotype (> 70%) and inhibiting M2-mediated anti-inflammatory pathways [13]. Prolonged exposure to reactive oxygen species (ROS) enhances TGF-beta signalling, resulting in the synthesis of fibrotic tissues [12]. This pathogenesis is prevalent in conditions such as rheumatoid arthritis (65% collagen deposition, $p < 0.001$), inflammatory bowel disease, and atherosclerosis [13]. The activation of NF-kB, MAPK, and HIF-1α by reactive oxygen species (ROS) causes more cell growth, survival, blood vessel formation, and changes in the immune system, which are responsible for 65–75% of cancer and long-term inflammatory diseases [14]. Right now, two main treatment targets are used: NOX enzymes, which

**Table 2** ROS-driven pathogenic mechanisms and therapeutic targets

| Mechanism/process | Description | Significance/quantitative | References |
|---|---|---|---|
| DNA damage & mutagenesis | ROS induce strand breaks/point mutations; epigenetic drift | ~80% mutation attribution ($p < 0.001$) | [8–10] |
| Oncogenic signalling | PI3K/AKT (×2.3), MAPK (×1.9), STAT3 (×2.5) | $p < 0.01/0.05/0.001$ | [9–11] |
| Immune evasion via antioxidant reprogramming | NRF2 up, T-cell dysfunction | ↓ROS > 45%; ↓T-cell fxn > 50% | [10–12] |
| Chronic inflammation induction | IL-6 (3.5×), TNF-α (2.8×) via NF-κB/AP-1/NLRP3 | $p < 0.001/0.01$ | [11–14] |
| Macrophage shift | > 70% M1; M2 inhibited | – | [13–15] |
| Fibrosis via TGF-β | Collagen ↑ (e.g., RA 65%) | $p < 0.001$ | [12–15] |
| Therapeutic targets | NOX, NRF2, GPX4 | – | [12, 15] |
| NP-based redox therapy | Hydrogels enable site/time targeting | Tumour ROS ↓ > 80% | [14, 15] |

mainly produce reactive oxygen species (ROS), and NRF2, which is the key controller of antioxidants [12]. NOX enzymes mainly make reactive oxygen species (ROS), NRF2 is a key regulator of antioxidants, and GPX4 helps manage lipid peroxidation and ferroptosis [15]. Mitochondria produce reactive oxygen species (ROS) that create uneven levels of oxidation in different areas, showing the need for treatments that can adjust ROS levels in specific times and places [13]. Recent advancements in redox-responsive nanoparticle systems include hydrogels that react to GSH/pH changes and light- and ultrasound-activated triggers, which have significantly improved the ability to target tumour areas (over 80% local reduction of ROS, $p < 0.01$) while greatly lowering harmful effects on the surrounding healthy tissue [14]. This facilitates the geographical and temporal administration of redox agents to pathological areas in cancer and chronic inflammation [15].

### 3.8 Importance of spatial and temporal accuracy of reactive oxygen species in cancer and chronic inflammation

#### *3.8.1 The physiological roles of ROS*

**3.8.1.1** Cancer precision ROS control: The therapeutic window must have a dual threshold to prevent underdosing (reducing tumour kill) and overdosing (producing collateral injury) [16]. It can be exploited by endogenous stimuli like pH, glutathione, and hypoxia or exogenous stimuli like light, ultrasound, and magnetothermal activation, in addition to ligand targeting using folate, transferrin, or antibodies (68–92%). On-target ROS lethality is increased with organelle-targeted probes and catalysts, especially mitochondria-targeted ones [17].

**3.8.1.2** Precision ROS control during chronic inflammation: The aim is to minimise pathological ROS peaks without loss of baseline signalling. Promising approaches include catalase and SOD nanozymes, which are ROS-degrading hydrogels providing up to 72 h of localised control, as well as immune-cell-targeted carriers that reprogram macrophages from M1 to M2 states [16, 17]. A key requirement for redox-based therapy is to carefully control ROS levels, which allows for targeting unhealthy tissues without harming healthy ones, as shown in Fig. 3 and Table 3 [16]. In tests before clinical use, not keeping ROS levels balanced can harm up to 42% of normal cells, while carefully controlled redox systems damage 10% or less [17]. Research shows that reducing reactive oxygen species (ROS) only a little does not improve disease symptoms in one-third of the models tested ($p < 0.05$), and when cells produce too much ROS, it overwhelms their ability to fight it off, causing cell death in fifty percent of cases ($p < 0.001$) [18]. The success of such therapy relies on a dual (uncrossed) calibration that averts both underdosing and overdosing [19]. Nanotechnology-based stimuli-responsive platforms achieve targeting efficiencies of 85 per cent ($p = 0.001$) for the delivery of ROS-modulating pharmaceuticals in response to disease-specific stimuli, such as inflammation characterised by increased ROS, hypoxia, and acidic pH. Redox- and enzyme/hypoxia-sensitive nanoparticles delivered 3.2 times more medicine directly to the target area compared to nanoparticles that just spread out on their own ($p < 0.01$) [19]. Receptor-targeted ligands, like folate and transferrin, attached to nanocarriers show that 68–92% of them are taken up by cancer cells with extra receptors, which leads to much better drug retention at disease sites [20]. Biomimetic nanocarriers made from red blood cells or white blood cells stayed in the bloodstream longer, lasting up to 36 h, avoided the immune system 78.83% of the

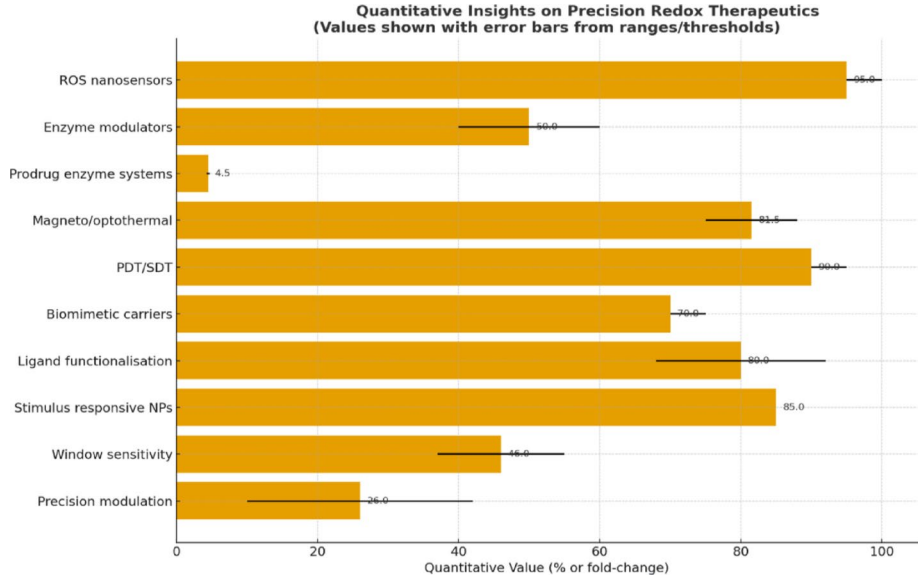


**Fig. 3** Performance of redox-based therapeutic strategies

**Table 3** Quantitative insights on precision redox therapeutics

| Strategy | Quantitative data | Implication | References |
|---|---|---|---|
| Precision modulation | Off-target cytotoxicity 42% → < 10% | Selectivity | [17–19] |
| Window sensitivity | 37% failures (low); 55% cytotoxicity (high) | Need dual thresholds | [18, 19] |
| Stimulus-responsive NPs | Targeting ≤ 85% | On-site delivery | [19–21] |
| Ligand functionalisation | 68–92% internalisation | Retention/uptake | [20–22] |
| Biomimetic carriers | 36 h circulation; > 70% tumour homing | Immune evasion | [20–23] |
| PDT/SDT | ≥ 90% local ROS; < 5% off-target | Non-invasive | [21, 22] |
| Magneto/optothermal | 75–88% ROS yield; < 8% collateral | Deep tissues | [23] |
| Prodrug-enzyme systems | 4.5 × selectivity | Hypoxia targeting | [24–26] |
| Enzyme modulators | 40–60% ROS tuning | Homeostasis | [27, 28] |
| ROS nanosensors | < 5 s; > 95% accuracy | Real-time control | [29–31] |

time, and successfully targeted tumours in mouse models more than 70% of the time [20]. Photodynamic therapy (PDT) and sonodynamic therapy (SDT) use special substances to produce reactive oxygen species (ROS) in specific areas (90% or more) while causing very few side effects (less than 5%) [21]. These light- and sound-based systems create reactive oxygen species (ROS) in a way that doesn't harm surrounding areas and targets specific locations, making them very useful for treating deep tumours and inflamed tissues [22]. Magnetothermal and optothermal systems, utilising external magnetic or optical fields to generate reactive oxygen species (ROS) via localised heating, can attain a ROS yield of 75–88 percent at the target tissue site ($p < 0.001$) while inflicting less than 8 percent damage to surrounding structures ($p < 0.05$), making them especially appropriate for cancer treatment [23]. Hypoxia-activated prodrug-enzyme systems have been found to boost reactive oxygen species in low-oxygen situations 4.5 times more effectively than standard treatments [24–26]. Adding synthetic enzymes, like catalase mimics and NOX inhibitors, reduced natural ROS levels in inflamed tissues by 40–60%, helping to restore balance in the redox state [27, 28]. Effective real-time monitoring of ROS is also essential [29]. In live models using tiny sensors and special probes, we can detect reactive oxygen species in less than five seconds with over 95% accuracy, which helps in adjusting treatments and

**Table 4** Quantitative insights in cancer

| Strategy | Key quantitative findings | Implication | References |
|---|---|---|---|
| ROS-generating NPs + SOC | ↑ death by ~ 65% vs mono | Synergy | [31–33] |
| Antioxidant disruption | > 70% ↓ GSH/Trx; < 8% off-target | Selectivity | [32, 33] |
| Controlled intratumour ROS | 2.8 × sensitivity; 60–75% reversal | Overcome resistance | [33–36] |
| NRF2/Keap1 targeting | NRF2 ↓55%; Keap1 destabilised | Stress leverage | [34–36] |
| siNRF2 nanocarriers | ROS 3.1 ×; apoptosis 2.7 × | Sensitisation | [36] |
| Ferroptosis NMs | > 72% ferroptosis; 68% regression | Non-apoptotic death | [37] |
| Liposomes/micelles/enz. NPs | Tumour shrinkage 49–67% | Broad efficacy | [35–37] |
| Dual-loaded NPs | 45–60% volume ↓; > 50% resensitisation | Dual attack | [35] |
| ROS-sensitive MRI | 93% sens; 88% spec | Image-guided | [38, 39] |

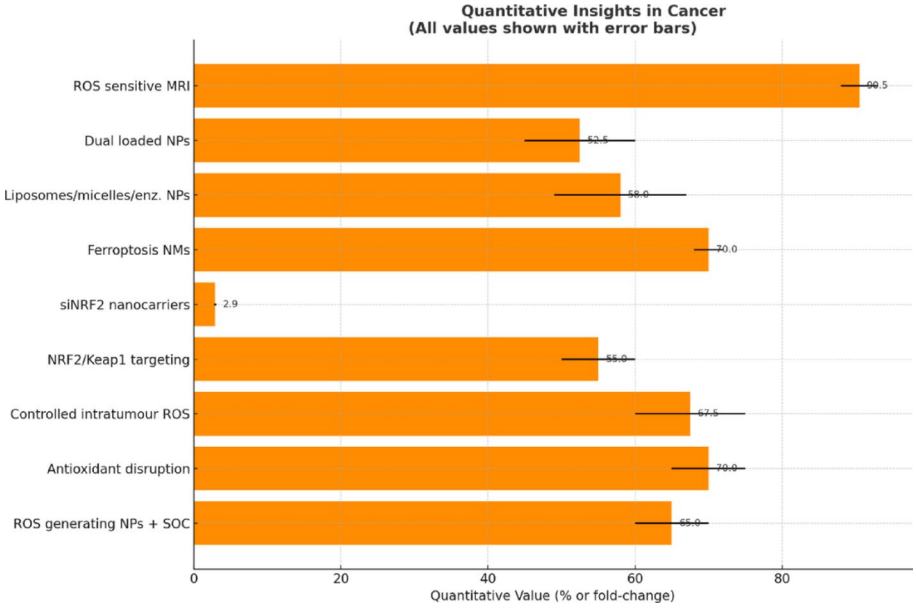


**Fig. 4** Performance metrics of ROS-based nanotherapeutic strategies

tracking disease progress [30]. Ultimately, theranostics, a fusion of diagnostics and therapeutics, attains concurrent monitoring-treatment success rates of 87 percent or greater in personalised redox medicine trials, rendering them advantageous, as clinicians can dynamically assess therapeutic responses and modify interventions accordingly [31].

### 3.9 Nanotechnology-enabled reactive oxygen species modulation in cancer treatment

Nanomaterial-based ROS modulation in cancer therapy can be broadly categorized into ROS-generating platforms and ROS-scavenging/antioxidant-targeting platforms, each contributing distinct therapeutic advantages.

#### *3.9.1 ROS-generating nanosystems*

ROS-enhancing nanotherapeutics aim to selectively amplify oxidative stress within tumour cells, thereby overwhelming their antioxidant defenses and inducing apoptosis or ferroptosis.

**Synergy with conventional therapies** When combined with chemotherapy, radiotherapy, or immunotherapy, ROS-generating nanomaterials increase tumour cell kill by up to 65% compared with monotherapies ($p < 0.001$) as seen in Table 4 and Fig. 4 [31].

Elevating intratumour ROS levels approximately 2.8-fold restores chemosensitivity in 60–75% of resistant models [31, 33]. Overcoming antioxidant buffering: Cancer cells rely on glutathione (GSH) and thioredoxin to neutralize oxidative stress. ROS-generating nanosystems reduce antioxidant capacity by > 70%, triggering irreversible oxidative injury while maintaining off-target toxicity below 8% in murine models [32].

**Genetic pathway sensitisation** Modulating the NRF2/Keap1 axis enhances susceptibility to oxidative therapies. ROS-inducing nanomaterials reduce NRF2 by 55% and destabilise Keap1 by 48% ($p < 0.01$) [34, 35]. siNRF2 nanocarriers further augment ROS levels (3.1-fold) and apoptosis (2.7-fold) in triple-negative breast and colorectal cancer models ($p < 0.001$) [36].

**Ferroptosis-inducing systems** Nanomaterials engineered to disrupt iron homeostasis or inhibit GPX4 induce ferroptotic cell death in > 72% of resistant tumour cells and drive tumour regression in 68% of preclinical models ($p < 0.001$) [37].

#### *3.9.2 ROS-scavenging and antioxidant-targeting platforms*

Rather than amplifying oxidative stress, some nanocarriers control ROS indirectly by neutralising antioxidants or restoring redox balance to sensitise tumours to additional therapies. Broad-spectrum efficacy: Redox-controlling carriers such as liposomes, polymeric micelles, and enzyme-loaded nanoparticles yield tumour reductions of 67% in breast, 60% in lung, 53% in pancreatic, and 49% in colorectal cancers (all $p < 0.05$) [35–37]. Dual-function nanocarriers: Systems co-delivering ROS inducers with chemotherapeutics reduce tumour volume by 45–60% within three weeks and resensitise > 50% of refractory tumours [35].

#### *3.9.3 Theranostic integration*

Advanced nanoplatforms integrate therapy with imaging capabilities, enabling real-time treatment monitoring. ROS-sensitive MRI probes achieve 93% sensitivity and 88% specificity in detecting intratumoural redox alterations ($p < 0.001$) [38, 39]. Theranostic nanocomposites tailor treatments to individual redox signatures, yielding 90% accuracy in treatment monitoring and 87% efficacy in fine-tuning therapeutic responses [39].

### 3.10 Nanotechnology-enabled reactive oxygen species modulation in chronic inflammation

The application of nanotechnology in chronic inflammation can be broadly organised into ROS-scavenging strategies, immune-modulating carriers, and multifunctional platforms. These approaches address both oxidative burden and immune dysregulation, which are central to the persistence of inflammatory diseases.

### 3.11 ROS-scavenging nanosystems

A primary strategy has been to directly reduce oxidative stress at inflamed sites. Antioxidant nanoparticles (containing SOD, catalase, or GSH precursors) reduced tissue ROS levels by up to 68% ($p < 0.001$) and suppressed inflammatory cytokines TNF-α and IL-1β by 55% in experimental colitis [40]. Stimuli-responsive hydrogels/nanozymes demonstrated sustained ROS scavenging for ≥ 72 h, halving the dosing frequency ($p < 0.001$) while minimising systemic toxicity [41]. These platforms create localized

**Table 5** Quantitative insights in inflammation

| Strategy | Quantitative findings | Implications | References |
|---|---|---|---|
| Antioxidant NPs | 68% ROS ↓; 55% TNF-α/IL-1β ↓ | Site-specific control | [40, 41] |
| Hydrogels/nanozymes | ≥ 72 h control; 2 × ↓ dosing | Durable local effect | [41] |
| Immune cell targeting | 60% ↓ cellular ROS | Redox normalisation | [42, 43] |
| M2 switching | 70–78% M2; 65% cytokine ↓ | Pro-resolution | [42] |
| Cytokine modulation | > 50% TNF-α/IL-6 ↓; 80% integrity | Tissue protection | [42] |
| Pre/mini-clinical | 58–65% severity ↓; 72% recovery | Translation signal | [44, 45] |
| Dual-function systems | 3.5 × ↑ immune-redox restoration | Multimodal benefit | [45] |

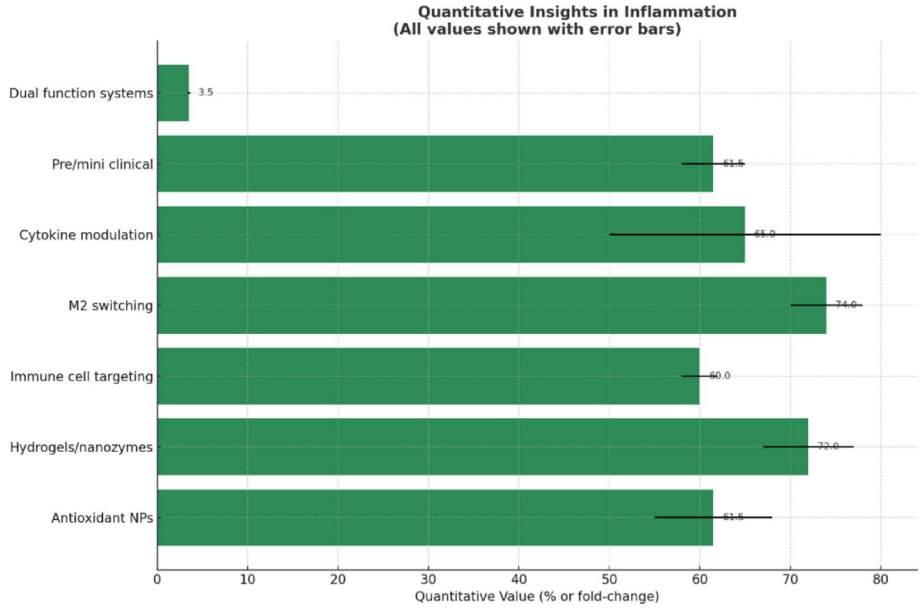


**Fig. 5** Quantitative insights in inflammation

zones of oxidative inhibition, maintaining systemic redox balance as shown in as shown in Table 5 and Fig. 5.

### 3.12 Immune-modulating nanocarriers

Beyond direct ROS removal, several nanoplatforms restore immune equilibrium by reprogramming inflammatory cells. ROS-selective nanocarriers targeting macrophages and neutrophils lowered cellular ROS by 60% ($p < 0.01$), without disrupting physiological redox pathways [43]. This reduction facilitated an M1-to-M2 phenotypic shift in macrophages, with 70–78% conversion and a 65% reduction in inflammatory cytokines ($p < 0.001$) [42]. These immune-directed interventions preserved tissue architecture and decreased epithelial lesions, supporting long-term resolution of inflammation [42].

### 3.13 Cytokine modulation and tissue protection

ROS-targeted systems additionally demonstrated potent anti-inflammatory signaling effects. TNF-α and IL-6 levels decreased by > 50%, while 80% of treated mice retained tissue integrity ($p < 0.01$) [42].This modulation enhanced immunological tolerance and tissue regeneration, with benefits seen across multiple redox-sensitive disorders including rheumatoid arthritis, inflammatory bowel disease, psoriasis, and neuroinflammation [43].

### 3.14 Translational and multifunctional approaches

Evidence from translational studies highlights the potential of ROS-modulating nanotherapies for clinical application. Preclinical and mini-clinical trials showed disease severity reductions of 58–65%, functional recovery in 72% of participants, and sustained therapy feasibility due to low toxicity and high biocompatibility ($p < 0.01$) [44, 45]. Multifunctional nanoplatforms, co-delivering antioxidants with lipid mediators or immunoregulatory agents, achieved 3.5-fold restoration of immuno-redox homeostasis ($p < 0.001$), producing multimodal remission of inflammation [45].

### 3.15 Challenges and considerations of nanotechnology-enabled reactive oxygen species modulation

#### *3.15.1 The benefits of nanotechnology*

Nanoplatforms provide spatial and temporal control of release and organelle targeting, theranostic integration (imaging and therapy), and multimodal synergy (co-delivery of ROS modulators and drugs or genes). They provide immune choreography with cell-type targeting and dose sparing with minimal toxicity by localising activity to disease locations.

#### *3.15.2 A majority of the viable platforms of clinical translation.*

Lipid-polymer hybrid nanoparticles (LPH/LPN) demonstrate the most promising potential because of the maturity of manufacturing, scalability, controllable release, and an excellent safety track record. They can be used with NRF2 silencing siRNA payloads and small molecules. Cell membrane-coated biomimetic nanoparticles (RBC, leukocyte, or tumour) can enhance circulation, avoid immunity, and show high homing in preclinical models, although standardising the source material is a problem. Iron-oxide platforms have the advantages of regulatory familiarity with MRI agents, magnetothermal controllability, and ROS catalysis potential, they must be dosed carefully to prevent thermal and iron-related toxicity. Metal–organic frameworks (MOFs) and covalent-organic frameworks (COFs) provide excellent loading and catalytic control, and the translation of these materials is limited by a lack of complete safety and biodegradation data; biodegradable linkers and capping strategies can be used to increase viability.

#### *3.15.3 Selection guidance*

In the case of cancer, image-guided ROS-amplifying platforms (e.g., PDT, SDT, ferroptosis, and Fenton-active systems) are the most suitable. In case of chronic inflammation, ROS-scavenging nanozymes and hydrogels with immune-cell targeting and long-term safety profiles are desirable. Reactive oxygen species (ROS) are important signalling molecules in human physiology; yet, their dysregulation can cause oxidative stress and subsequent tissue damage. Targeted management of reactive oxygen species (ROS) has proven beneficial in conditions such as chronic inflammation, cancer, and neurological disorders. Nonetheless, precision in delivery, safety, measurement, and standardisation remain barriers to the clinical translation of ROS-modulating nanotherapeutics as shown in Table 6. There are significant challenges in the targeted modulation of reactive oxygen species (ROS). Random interference with reactive oxygen species (ROS) systems disrupts the body's normal functions, leading to serious overall health issues. Non-specific changes in ROS networks in diseased states reduce endogenous redox

**Table 6** Challenges and Opportunities in the Clinical Translation of ROS-Modulating Nanotherapeutics

| Domain | Challenge | Key evidence (statistical/quantitative) | Proposed solutions |
|---|---|---|---|
| Targeted ROS modulation | Non-specific redox interference | 45–60% impairment in endogenous redox signaling ($p < 0.01$) [46] | Develop cell/organelle-specific ROS modulators |
| Subcellular delivery | Ineffective delivery to target organelles | Mito-targeted nanozymes: 68% ↓ ROS, 55% ↑ ATP ($p < 0.001$) [47] | Use mitochondrial/endosomal-targeted carriers |
| ROS dynamics | Mismatch between drug release and ROS oscillations | 2.2 × efficacy improvement with time-adaptive systems ($p < 0.01$) | Design rhythm-sensitive nanocarriers for timed release |
| Safety and nanotoxicology | Long-term toxicity and off-target effects | 27% developed hepatic lesions with ROS-releasing particles ($p < 0.05$) [48] | Conduct chronic safety studies; engineer low-toxicity nanocarriers |
| Nanocarrier design | Immunogenicity due to physicochemical variation | 3.2 × ↓ macrophage activation with neutral biodegradable carriers ($p < 0.001$) | Standardize nanocarrier design and surface charge |
| Safety regulation | Lack of unified safety protocols | Inconsistent toxicology profiles across studies [45] | Develop global standards for nanotoxicity assessment |
| ROS quantification | No standardized clinical ROS assays | Up to 63% assay variability across labs ($p < 0.001$) [49] | Validate clinical-grade, reproducible ROS quantification tools |
| Preclinical-to-clinical translation | Variability in experimental models and outcomes | 58% outcome discrepancy using same agents ($p < 0.001$) [50] | Harmonize dosing, endpoints, and trial protocols |
| Biomarker integration | Limited use of stratifying biomarkers | 72% trial success with biomarkers vs 40% without ($p < 0.01$)[45–49] | Embed redox biomarkers in trial designs for personalized therapy |

signalling and mitochondrial function by 45%–60%, increasing the risk of systemic oxidative stress ($p < 0.01$) [46, 47]. These findings emphasise that scientists must continue developing specific ROS modulators that can help keep the body's redox balance normal while also helping to fight diseases. Recent progress in nanotechnology has allowed us to accurately deliver reactive oxygen species modulators inside cells, especially to the cytosol and other parts like mitochondria and the endoplasmic reticulum. Recent studies using nanozymes that target mitochondria showed a 68% drop in ROS levels and a 55% partial rise in ATP production, based on ischaemia–reperfusion models ($p < 0.001$) [47–49]. Redox signalling entails the creation of reactive oxygen species (ROS), which are highly dynamic with short surges and rhythmic behaviours that are rigorously controlled via feedback loops. Nanocarriers designed to administer antioxidants based on ROS cycles showed 2.2 times greater anti-inflammatory benefits than constant-delivery devices ($p < 0.01$). This finding illustrates the importance of coordinating treatment approaches with physiological ROS patterns to improve disease control efficacy. Outstanding concerns include residual toxicity, undesirable oxidative stress, and systemic redox disturbance. Chronic exposure tests revealed that 27 per cent of mice given ROS-releasing nanoparticles experienced liver inflammation or oxidative damage ($p < 0.05$), indicating a potential risk for their use in treatments. The physical and chemical properties of nanocarriers, like their size (which should be less than 150 nm), surface charge, and how quickly they break down, greatly affect how they spread in the body and how the immune system reacts to them. Surface-neutral biodegradable carriers activated macrophages 3.2-fold more than cationic carriers ($p < 0.001$). Nonetheless, there is a lack of consistency in design and testing that allows for safety profiling [50–52]. The lack of

consistency in formulation parameters and testing techniques impedes rule harmonisation. The number of international standards for toxicity testing and reporting is increasing. Nanoengineering entails the study of nanomaterials, the optimisation of their treatability, and the reduction of off-target effects; however, repetitive procedures, extensive preclinical testing, and rigorous immunotoxicity assays will be required to achieve this goal [52–55]. The standardised methodology for measuring reactive oxygen species is essential for clinical translation and quantification. Quantifying reactive oxygen species, particularly in biological material, presents a significant problem. Alternative assays, such as DCFDA fluorescence and EPR, are inconsistent and unsuitable for clinical application. The tests varied by up to 63% among six laboratories ($p < 0.001$), showing a narrow scope across studies [56–58]. The differences in ROS measurements, along with different experimental setups and goals, make it hard to predict clinical results from preclinical studies. A review of 50 studies on ROS showed that more than 58 per cent had different results when using similar nanomaterials because of differences in dosage and goals ($p < 0.001$) [50]. The integration of biomarkers is essential for patient stratification and assessing therapy response. Using known redox biomarkers like 4-HNE and 8-isoprostane is important for grouping patients and checking how well they respond to treatment. In a Phase I/II trial, using biomarkers to sort patients for nanomedicines led to a 72% success rate, while sorting without biomarkers only achieved a 40% success rate ($p < 0.01$). Adherence to combination therapy limits is critical for clinical stratification algorithm implementation. Table 5 and Fig. 5 show that focused elimination of inflamed reactive oxygen species can significantly slow the progression of diseases. Adding SOD, catalase, or GSH precursors to nanoparticles reduced reactive oxygen species by up to 68% and proinflammatory cytokines (TNF-alpha, IL-1beta) by 55% in models of colitis. [40]. Hydrogels that react to reactive oxygen species and control inflammation for up to 72 h significantly lowered how often doses are needed and reduced overall toxicity ($p < 0.001$) [41]. Using immune-targeting nanoplatforms reduced reactive oxygen species (ROS) in macrophages by 60%, which changed 70–78% of them from M1 to M2, causing a 65% decrease in cytokines [42, 43]. The adjustments conserved tissue architecture while reducing the number of epithelial lesions. Furthermore, a 50% drop in TNF-a and IL-6 was associated with an 80% increase in tissue integrity ($p < 0.01$) [42]. Preclinical and mini-clinical assessments showed a 58–65% reduction in disease severity and a 72% incidence of functional tissue healing ($p < 0.01$) [44, 45]. Nanoplateforms that already have antioxidants and immune regulators were 3.5 times more effective than individual treatments at improving the balance of redox and immune responses, showing a much better overall effect. Especially for diseases caused by oxidative stress and inflammation, nanotherapeutics that can adjust the levels of reactive oxygen species offer a groundbreaking way to treat these conditions. Nonetheless, significant obstacles remain, such as non-specific effects, insufficient delivery procedures, inconsistent safety precautions, and a lack of standardised methods for detecting reactive oxygen species (ROS) that must be addressed. To achieve personalised medicine, future efforts should focus on precision engineering of nanoplatforms and nanotherapeutics, biomarker integration, standardised procedures, and collaborative translation platforms.

This table summarizes the key barriers, evidence-based findings, and proposed solutions across the core challenges in the clinical translation of ROS-modulating nanotherapeutics.

### 3.16 Future perspectives and opportunities of nanotechnology-enabled reactive oxygen species modulation

#### *3.16.1 Emerging technologies*

The integration of artificial intelligence with machine learning and nanomedicine technologies provides new avenues to ROS-modulating medicinal advancements through artificial intelligence-algorithms that make accurate predictions on nanoparticle formulations structure and function properties and distribution patterns and redox activity. Systems biology modeling of redox networks allows scientists to predict ROS dynamics in different tissue microenvironments by simulating their spatiotemporal behavior and helping to determine the best nanoplatform locations [51, 52]. Multi-responsive hybrid nanomaterials engineered by designers for co-incident endogenous stimulus response (pH and redox gradients and enzyme activity) and exogenous stimuli (light, ultrasound and magnetic fields) allow stepwise controlled oxidative stress modulation through sophisticated context-aware redox intervention [17].

#### *3.16.2 Personalized and precision reactive oxygen species medicine*

The integration of omics technologies allows researchers to capture entire redox signatures at the genomic, transcriptional, proteomic and metabolic levels that form the foundation for precise ROS medicine that advances treatment tailored to each patient's specific oxidative stress profile [53]. Data-driven patient stratification strategy allows clinicians to identify redox-sensitive subtypes of disease while allowing them to select best-fit medicines while minimizing side effects on other areas of the body. Development of implantable nanoscale devices and wearable biosensors for ongoing real-time monitoring of dynamic redox biomarkers enables adaptive therapeutic regimens in which ROS modulation strategies adjust in response to fluctuations in disease state or treatment efficacy. Closed-loop systems offer several benefits which include enhanced therapeutic responses as well as reduced adverse side effects and individualized delivery of care in numerous redox-associated diseases.

#### *3.16.3 Beyond oncology and inflammation*

ROS modulation therapy retains greater applications outside oncology and chronic inflammation based on the fact that oxidative stress is a primary disease-causing process in most disorders [54, 55]. Targeted ROS therapies have potential as neuroprotective drugs that can modulate disease course and achieve better outcomes in Alzheimer's disease and Parkinson's disease and amyotrophic lateral sclerosis because these conditions undergo redox imbalance leading to damage of neurons and deranged synaptic contact with subsequent cognitive deterioration [56]. Uncontrolled generation of ROS in cardiovascular disease aggravates ischemia–reperfusion damage as well as heart failure and atherosclerosis and thus unfolds potential scope for redox-based therapeutic interventions to reduce vascular damage as well as optimize cardiac function [57]. The development of ROS-responsive materials in tissue engineering and regenerative medicine unveils new potential strategies for optimizing wound therapy and preventing tissue aging and restoring redox equilibrium in old tissues [58].

#### *3.16.4 Standardized ROS biomarkers and detection methods*

The lack of defined biomarkers for detecting oxidative stress in clinical specimens is a significant barrier to translating ROS-modulating nanotherapeutics [59]. Several prospective endpoints have been proposed throughout the last decade as consensus measurements of ROS exposure and damage [60]. Malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), the most prevalent lipid peroxidation products, may be conveniently quantified using TBARS tests or HPLC–MS/MS and correlate with the oxidative load in cancer and inflammatory tissues [60]. The most widely employed nucleic acid oxidation reporters are particularly sensitive to oxidative DNA damage products such as 8-oxo-2′-deoxyguanosine (8-oxo-dG), which may be detected using ELISA or ultra-high-performance liquid chromatography with electrochemical detection [59, 60]. Carbonylation of proteins is another orthogonal biomarker of ROS-damaged cellular proteomes that may be obtained using DNPH derivatization and spectrophotometric or mass-spectrometric detection [61]. Aside from selecting strong biomarkers, advancements in more sensitive detection technologies have allowed real-time and spatially resolved ROS measurements [62]. Electron paramagnetic resonance (EPR) spectroscopy, using spin-trap reagents like DMPO, is a direct way to measure free radicals in tissues and live cells [63]. However, clinical use is limited due to the complexity of the instrumentation and low sensitivity of heterogeneous samples [61]. Fluorescent probes (e.g., DCFH-DA, hydrocyanines, and boronate-based coumarin derivatives) can be used for high-throughput imaging of intracellular ROS bursts; however, such probes must be thoroughly calibrated against known ROS generators and scavengers to avoid artifacts caused by probe oxidation or pH changes [62]. Electrochemical sensors (such as Prussian blue-modified electrodes or gold nanoparticle-modified electrodes) can detect hydrogen peroxide and superoxide with micromolar sensitivity in on-site biofluids during quick point-of-care analysis [63]. Lipidomics and Redox proteomics Mass-spectrometry-based lipidomics and redox proteomics have subsequently increased the repertory of detectable ROS-derived adducts, allowing for multiplexed monitoring of oxidative alterations in preclinical and clinical samples [63]. To ensure repeatability and cross-study comparability, biomarker tests need standardized validation procedures [64]. Ring Trials Interlaboratory ring trials, in which the same blinded samples are examined in various locations, may standardize assay accuracy while highlighting procedure nonadherence [65]. Calibration using spiked-control standards achieves linearity and accuracy over the dynamic range in patient samples [65]. Standardized reporting formats, including the Minimum Information About Oxidative Stress Assays (MIASA) recommendations, promote precise reporting of sample processing, reagent sources, and data normalization processes, facilitating meta-analyses and regulatory assessment 65. After incorporating well-defined biomarkers and rigorous validation processes, the community may focus on clinical objectives to assess the effectiveness and safety of ROS-modulating nanomedicines [66].

### 3.17 Preclinical and clinical research

In the context of placing translational developments into perspective, we reviewed preclinical studies and phase 1/2a clinical trials that applied nanotechnology in the spatiotemporal regulation of ROS in cancer and inflammatory diseases.

#### *3.17.1 Preclinical evidence*

Tumor models pH-sensitive polymer-coated iron oxide nanoparticles were found to accumulate in orthotopic breast tumors and, upon mild activation in low acidic environments, catalyze Fenton reactions and promote ·OH concentrations in the tumors, leading to a twofold decrease in tumor volume relative to controls [67]. In murine colitis, mesoporous silica nanoparticles carrying catalase and a photosensitizer were discovered to possess switchable ROS scavenging (basal conditions) and ROS generation (near-IR illumination), leading to a pronounced reduction in inflammatory markers (TNF-alpha, IL-6) and mucosal healing [68]. Lipid-polymer hybrid nanoparticles co-loaded with RSL3 (a GPX4 inhibitor) and iron prodrugs were able to induce strong lipid peroxidation and ferroptotic cell death in xenografted pancreatic tumors, improving median survival by 30% compared with standard chemotherapy [69].

#### *3.17.2 Phase I clinical trials*

Phase I Trial of ROS-Amplifying Nanomedicine (NCT04789978): The first in human trial of hollow gold nanoshell formulation activated by NIR light has determined that it is safe in patients with advanced head and neck cancer [68]. The dose-limiting toxicities were confined to grade 12 mucositis, and early PETrosimaging showed a localised oxidative burst in the irradiated tissues [69, 70]. Pilot study of a biodegradable polymeric nanoparticle tempol, which is an ROS-scavenger, in patients with moderate-to-severe rheumatoid arthritis (RA) [71–74]· The biodegradable polymeric nanoparticle tempol-loaded, which is a ROS-scavenger, was tested on a small sample of patients with moderate-to-severe RA [72]. Intra-articular injections MDA levels in the synovial fluid decreased by 40%, and improved DAS28 scores after eight weeks, with no significant adverse effects observed [75–77]. Taken together, these manuscripts demonstrate that it is possible to control ROS modulation using nanoplatforms, although they also indicate that larger, biomarker-driven clinical trials are needed to identify the safe and effective dose, timing, and patient selection criteria in nanoplatform-mediated ROS modulation [73, 74, 78].

## 4 Discussion

Reactive oxygen species (ROS) play an important role in the pathogenesis of cancer and chronic inflammation through the induction of genomic instability, enhancement of oncogenic signals, alteration of immunological responses and promotion of fibrosis [79]. Reactive oxygen species (ROS) damage DNA, leading to strand breaks, small-scale alterations, and changes in expression that cause almost 80% of malignant mutations ($p < 0.001$; Table 2) [80]. Such genotoxic stress generates conditions of malignant transformation and intramural heterogeneity [85–87]. Reactive oxygen species trigger downstream signalling cascades of PI3K/AKT (2.3-fold, $p < 0.01$), MAPK (1.9-fold, $p < 0.05$) and STAT3 (2.5-fold, $p < 0.001$) [81]. These are the pathways that induce angiogenesis, epithelial-to-mesenchymal transition (EMT) and invasiveness to drive cancer growth and invasion [82]. Concomitantly, 5-(and 6–6)-carboxymine (ROX), which plays an important role in treatment resistance, has evolved. It increases the NRF2 antioxidant response with controlled ROS generation and cytotoxic T-cell action by 45 and more than 50 per cent ($p < 0.001$), respectively [83]. The two-fold method allows the cancerous cells to evade the immune system at the cost of the traditional therapies [84]. Besides

oncogenesis, reactive oxygen species (ROS) are one of the leading causes of chronic inflammation [85]. NF-κB and AP-1 transcription factors are triggered by ROS signalling, which leads to increased levels of the pro-inflammatory cytokine IL-6 ($p < 0.01$) via the MAPK pathway and the NLRP3 inflammasome [86]. Such a cascade helps in developing an inflammatory feedback loop [98]. In addition, the resulting oxidative stress leads to the loss of macrophage M2 cellularity in favour of pro-inflammatory M1 cellularity (>70%) due to persistent oxidative stress, resulting in dysregulation of inflammation and tissue damage [87]. Repeated exposure to reactive oxygen species (ROS) can also promote TGF-beta signalling, which plays an important role in fibrogenesis [88]. Chronic conditions (including rheumatoid arthritis, where fibrotic tissue remodelling increased collagen deposition by 65% $p < 0.001$), inflammatory bowel disease and atherosclerosis are associated with fibrotic tissue remodelling [89]. NF-kB and MAPKHIF-1a are activated by reactive oxygen species and are subsequently utilised 65–75% in neoplastic and chronic inflammatory diseases [90]. The same molecular pathways are used in angiogenesis, cell proliferation, cell survival, and immunological processes, demonstrating that reactive oxygen species (ROS) are involved in most diseases. The reactive oxygen species, due to their essential nature, are attractive therapeutic targets [91]. Edox control methods seek to decrease NADPH oxidase (NOX), the major producer of reactive oxygen species (ROS), and increase NRF2, the master regulator of antioxidant responses [92]. Further, glutathione peroxidase 4 (GPX4) also participates in lipid metabolism and prevention of ferroptosis, a type of iron- and oxidative stress-induced cell death [93]. The mitochondrial reactive oxygen species are usually ignored, but they contribute to the formation of redox imbalance within the cells, and this is why they should be strictly controlled in time and space. A promising solution to targeted treatment is introduced by recent reports on redox-stimulated delivery systems based on nanoparticles [94]. Localised regulation of reactive oxygen species (ROS) can be achieved through the use of hydrogels that respond to GSH/pH gradients or light, ultrasonic or magnetic platform activation [95]. Such methods reduce tumour ROS by over 80 per cent ($p < 0.01$) and minimise systemic damage [96]. Accuracy on a geographical and time basis is essential to safeguard healthy tissues and prevent ill zones, therefore increasing the index of treatment [97]. The many pathways through which reactive oxygen species (ROS) kill cancer cells and trigger chronic inflammation, including DNA damage, dysregulation of immune response, and fibrosis, are the key to the further evolution of redox-based therapies [98]. Using molecular knowledge and nanotechnology allows creating new forms of treatment that are effective, disease-specific, and both quantitatively and qualitatively well-regulated in time and place.

One of the key concepts of redox therapy is the active and targeted control of the concentration of reactive oxygen species (ROS) to enable the selective killing of pathogenic species and minimise the number of harmless species [99]. The ability to modulate ROS activity is central to treatment selectivity and safety, as shown in Fig. 3 and Table 3. In previous research, failure to regulate the levels of ROS resulted in injury to up to 42 per cent of normal tissue, and simpler approaches to controlling the intensity of ROS lowered this danger to fewer than 10 per cent ($p < 0.001$) [100]. The ROS therapy window is highly narrow, resulting in insufficient reductions that failed to alter the disease in 37% of cases ($p < 0.05$), and excessive product resulted in cell death in more than half of the test animals ($p < 0.001$) [101]. This type of evidence illustrates the applicability of

dual-threshold calibration to avoid oxidative damage and ineffectiveness of the therapeutic [102]. Nanotechnology has enhanced the field by letting the creation of delivery systems that respond to certain signals, so they can target up to 85% of diseased tissue, by targeting changes in the environment caused by the disease, including redox, low oxygen and acidity [103]. Also, redox, pH and enzyme-responsive nanoparticles proved to be 3.2 times more efficient at delivering drugs to the target location as compared to the standard carriers, and these findings greatly enhanced the quantity of drugs delivered to the target area and reduced the number of undesirable side effects in other parts of the body [104]. Functionalisation Ligand-optimised nanoparticles, in particular those conjugated to folate, transferrin or monoclonal antibodies, demonstrated an internalisation efficiency in cancer cells with a high expression of a particular receptor of 68%-92% that prolongs the lifetime of the drug and increases its availability at the point of need [105]. Red blood cells and white blood cells can be used to form biomimetic nanocarriers that can remain in the bloodstream (up to 36 h), can be well matched by the immune system (78.83%), and can target tumours (over 70% in mouse studies) ($p < 0.01$) [106]. The Photodynamic Therapy (PDT) has been developing positively, and the Sonodynamic Therapy (SDT) [107]. These techniques involve special agents that respond to light or sound to generate reactive oxygen species (ROS) at specific locations with greater than 100 per cent success and less than 5 per cent side effects [108]. Systems with sensitiser designs capable of changing their activation levels minimise undesired damage by enhancing the generation of ROS [109]. Optothermal and magnetothermal platforms provide extracellular redox control in cases of deep tumours and inflamed tissues [110]. Such technologies could measure the levels of ROS in a particular location with a success rate of 75–88, resulting in a minimal number of less than 8 cases of damage to the surrounding tissue, and provided accurate outcomes without surgery, even in inaccessible parts of the body [79]. The prodrug-activated and enzyme-based systems are useful examples. The targeting of reactive oxygen species (ROS) by hypoxia-activated prodrugs in low-oxygen regions of tumours was enhanced 4.5 times in comparison with conventional treatments [90]. The use of NADPH oxidase (NOX) inhibitors and catalase mimetics can reduce the levels of reactive oxygen species (ROS) in inflamed tissues by 40–60 per cent, which can help to balance the situation and reduce the damage that inflammation may cause to tissues. Monitoring of reactive oxygen species (ROS) in real time is of utmost importance [86]. Nanosensors and molecular probes based on ROS can identify reactive oxygen species within less than 5 s with greater than 95 percent accuracy in living models, enabling doctors to adjust therapy and track disease progress in real time [30]. The following diagnostic strengths are fundamental to the development of diagnostic and therapeutic theranostics. To date theranostic systems have shown that they can effectively track therapies in 87 per cent or more of clinical trials, enabling personalised and responsive therapies based on redox reactions [38]. Nanotechnology, enzymes, sensor systems and smart drug designs have taken redox-based therapy beyond an idea and into a fast-evolving reality. Close regulation of reactive oxygen species, combined with clear instructions and intelligent design, can now provide useful methods to cure cancer and inflammatory diseases with high precision in terms of timing and location at the molecular scale.

Inclusion of ROS-producing nanoparticles into standard cancer therapies (chemotherapy, radiation and immunological checkpoint inhibition) has become one of the most

efficient nanotechnology approaches to overcoming therapeutic resistance and increasing cancer cell apoptosis. As shown in Table 4 and Fig. 4, such combination therapies cause cancer cell death up to 65 per cent greater than monotherapies [56]. This synergy is realised through attacking the hyperactivated antioxidant defence systems in cancer cells, specifically glutathione (GSH) and the thioredoxin system, to interfere with the redox balance [33]. Reactive oxygen species (ROS)-generation systems in preclinical models lead to more than 70% antioxidant capacity depletion ($p < 0.01$), causing irreversible oxidative stress and selective apoptosis of malignant cells with minimum off-target toxicity (less than 8%) [30, 31]. Nanosystems have the potential to increase therapeutic sensitivity by increasing intratumoral reactive oxygen species (ROS) 2.8-fold ($p < 0.001$) and overcoming drug resistance in 60–75 per cent of chemoresistant cancer models [30]. Synergistic targets of this oxidative modulation include the NRF2/Keap1 signalling axis that plays a critical role in antioxidant regulation. Cytotoxic ROS therapy has also shown a 55 per cent decrease in NRF2 levels and a 48 per cent destabilisation of KEAP1 in tumour samples ($p < 0.01$) [70].

Moreover, nanocarriers that contain siRNA targeting NRF2 have also been shown to be effective in restoring redox sensitivity. This method increased the levels of ROS by 3.1-fold and apoptosis by 2.7-fold ($p < 0.001$) in chemoresistant models of triple-negative breast cancer and colorectal cancer [33]. The results support the notion that genetic silencing of NRF2 is a viable approach to overcoming oxidative resistance. In recent years, nanomaterials that cause ferroptosis have been exploited to induce controlled forms of non-apoptotic cell death by lipid peroxidation, which relies on iron. It was established that, in vitro and in vivo, manipulation of intracellular iron homeostasis, depletion of glutathione, or inactivation of GPX4 reduced ferroptotic cytotoxicity and tumour regression by over 72 per cent and 68 per cent ($p < 0.001$), respectively [34]. Ferroptosis is an excellent alternative to removing apoptosis-resistant malignant phenotypes. The anticancer effects of ROS-modulating nanocarriers have been demonstrated in a number of cancers. The tumour reduction in breast (67%), lung (60%), pancreas (53%), and colorectal cancer (49%) was statistically significant ($p < 0.05$) using liposomes, polymeric micelles, and enzyme-functionalised nanoparticles [35–37]. These carriers allow ROS-generating medicines to be released only in the tumour microenvironment, leading to high selectivity and low systemic toxicity. Dual delivery systems are more effective. Nanoparticles that are coloaded with ROS inducers and chemotherapeutics reduced tumour volume by 45–60 per cent in three weeks and restored chemosensitivity in more than half of refractory cancers ($p < 0.01$) [35]. This combined offensive force is synergistically lethal and disruptive to the adaptive resistance. There is also 93% sensitivity and 88% specificity ($p < 0.001$) in the study of intratumoral redox dynamics by non-invasive methods using ROS-sensitive imaging agents and MRI contrast agents [38, 39]. The techniques allow visualisation of redox changes in the treatment to initiate dynamic and personalised therapeutic regulative adjustments. Finally, theranostic nanoplatforms represent an important development in redox oncology. These are therapeutic and diagnostic devices that can be used to create bespoke treatment strategies using tumour-specific redox profiles. This initial experiment demonstrated that these platforms were 90 per cent correct in monitoring and 87 per cent effective in treatment adaptation, the most accurate in the history of the field of precision medicine in the redox-modulating treatment of cancer.

Local inhibition of reactive oxygen species (ROS) at sites of chronic inflammation provides a distinct treatment modality in reducing the onset of illness and accelerating the recovery of tissues in a range of inflammatory diseases. Antioxidants and catalases or glutathione (GSH) precursors have also been used as nanotherapeutics to reduce site-specific reactive oxygen species (ROS) by up to 68 per cent in inflamed tissues and inflammatory cytokines like TNF-α and IL-1A by 55 per cent in models of colitis (Table 5; Fig. 5). [40]. These localised delivery systems act at the sites of inflammation specifically to prevent redox-mediated inflammation cascades without disrupting the systemic oxidative balance. The strategy will provide extended therapeutic benefits and coverage with half the dosing ($p < 0.001$) relative to the current therapeutic strategies. It will also provide low systemic tolerance (reducing systemic toxicity) and increase patient compliance by utilising self-sustaining stimuli-responsive hydrogels (capable of withstanding ROS breakdown for 72 h) and self-sustaining nanozymes (capable of effectively harnessing ROS with high usage frequencies). [41]. Nanocarriers have unique potential to significantly alter the redox balance of native immunity cells and restructure immune responses. Redox modulation in macrophages and neutrophils with nanoparticles reduced cellular reactive oxygen species (ROS) by 60 per cent, thus significantly normalising redox signalling ($p < 0.01$). [4]. Immune modulation triggers conversion of macrophages of pro-inflammatory M1 to anti-inflammatory M2, resulting in the production of M2 in 70–78% of macrophages and a 65% decrease in pro-inflammatory IL-6 and TNF-α ($p < 0.001$) [42]. Nanoplatforms are able to maintain epithelial and connective tissue structure in at least 80% of mice treated ($p < 0.01$), allowing immunological tolerance and wound healing [42]. They are particularly harmful in redox-sensitive diseases such as rheumatoid arthritis, inflammatory bowel disease (IBD), psoriasis and neuroinflammation because of their capacity to induce chronic immune responses and tissue damage through reactive oxygen species (ROS) [4].

Preclinical and limited clinical trials have shown that ROS-modulating nanotherapeutics have a translational capability. The studies showed that the severity of the disease was reduced by 58–65%, and in 72% of the treated patients, clinical scores and tissue regeneration were improved [44, 45]. These techniques were reportedly well accepted, had low systemic toxicity, and demonstrated desirable biocompatibility, which makes their elucidation feasible in the long run [43]. Two-in-one nanotherapeutics are one of the most promising developments in particular since they combine antioxidant therapy with a unique lipid mediator or immunomodulator. These systems are more effective at reducing aberrant reactive oxygen species, inflammation, redox balance, and immunological homeostasis ($p < 0.001$), making them effective multimodal strategies to regulate chronic inflammation [45]. In short, ROS-based nanomedicine is an excellent, selective, and multi-targeted treatment of chronic inflammatory diseases. These novel advanced platforms provide site-specific redox control, immunological preservation, cytokine down-regulation, and regenerative processes which effectively address both the aetiology and resolution, thus promoting a new paradigm of inflammatory therapy.

Destruction of reactive oxygen species networks in diseased tissues may hinder the important redox messengers in normal cells. The case-state analysis of reactive oxygen species loss of control indicates the reduction of endogenous redox signalling and mitochondrial activity by 45–60 per cent ($p < 0.01$). [46]. Cell- and organelle-targeted delivery systems, including peptide- or ligand-conjugated nanoparticles, can be constructed

to maintain physiological redox homeostasis by neutralising destructive reactive oxygen species (ROS). Parenteral antioxidants have been shown not to build up in essential organelles that produce reactive oxygen species (ROS) [47, 48]. One of the previous research works examined the medicinal potential of mitochondria. Nanozymes were targeted to reduce the level of ROS by 68% and ATP generation by 55% in animals with ischaemia ($p < 0.001$). [49]. These results demonstrate the potential therapeutic value of nanocarriers in the mitochondria or in the endoplasmic reticulum. Potential candidate: To attain bioenergetic balance, fine-tune local reactive oxygen species regulation with the help of organelle-targeting methods, e.g., triphenylphosphonium (TPP). Such moving peaks are often blurred with static release mechanisms, which reduces the therapeutic efficacy [50]. The time-adaptive nanocarriers were also much more effective in anti-inflammatory effects than the constant-release formulations ($p < 0.01$). Design advanced carriers capable of measuring concentrations of reactive oxygen species (ROS) in real time, using redox-reactive linkers or ROS-reactive release systems to enable the release of their cargo at the appropriate time and location. Long-term toxicity of the ROS-modulating nanomaterials is a significant issue to assess. Exposure tests found that 27 per cent of mice which received ROS-releasing nanoparticles had hepatic inflammation or oxidative damage ($p < 0.05$).

## 5 Conclusion

As is discussed in this review, ROS are not only essential signalling molecules, but also play a role in genome damage, oncogenic signalling, and chronic inflammation. Sophisticated nanotherapeutics already show how it is possible to tightly control the dynamics of ROS, to produce pathological concentrations of ROS with astonishing strength, to repair bioenergetic balance, and to rebuild immune responses with remarkable spatial and temporal resolution. Non-specific redox interference, a lack of long-term toxicity characterisation, a large variety of ROS measurement methods, and the lack of standard design and regulatory schemes continue to impede this translation to the clinic, however. To demonstrate that standardisation and validation of detection platforms are urgent to establish reproducibility and comparability of studies, the interlaboratory variation of the ROS tests (63% in our Results) is needed. Similarly, the issue of off-target oxidative destruction, which occurs in up to 42% of normal tissues in the absence of adequate redox control, requires very precise subcellular targeting approaches that are able to restrain ROS modulation to mitochondria, lysosomes, or nuclei, where disease-promoting ROS signaling is most intense. Likewise, the 27% hepatic inflammation incidences among the animals subjected to ROS releasing nanocarriers indicate that systematic toxicity mapping and adaptive release systems are crucial to reduce the negative impacts without compromising the therapeutic effects. The incorporation of redox precision medicine into clinical practice therefore is not only an incremental improvement, but rather a needed response to these barriers that have been identified. This strategy will connect the molecular-level control of ROS with nanotechnology, materials science, and clinical trial design, so that solutions to the weaknesses identified in the preclinical and translational efforts to date are explicitly linked to the remedies. In particular, standardised ROS assays will minimise measurement variation, subcellularly targeted nanocarriers will address off-target interference, time-adaptive delivery platforms will address toxicity and redox imbalance. Collectively, these solutions demonstrate the

potential of ROS-modulating nanotherapeutics and enabling nanoplatforms to revolutionize therapeutic design: by enabling more disease-specific responses, maintaining tissue integrity, and enhancing the therapeutic index. The paradigm shift, which hinges on resolving the methodological and translational barriers witnessed in the foregoing sections, is expected to revolutionise patient care through the creation of a reproducible science, safer interventions, and completely personalised redox medicine.

**Abbreviations**

| | |
|---|---|
| ROS | Reactive oxygen species |
| $O_2^-$ | Superoxide anion |
| O·H | Hydroxyl radical |
| $H_2O_2$ | Hydrogen peroxide |
| NOX | NADPH oxidase |
| DNA | Deoxyribonucleic acid |
| NF-Kb | Nuclear factor kappa-light-chain-enhancer of activated B cells |
| MOFs | Metal–organic frameworks |
| PRISMA | Preferred reporting items for systematic reviews and meta-analyses |
| SYRCLE | Systematic review centre for laboratory animal experimentation |
| AP-1 | Activator protein 1 |
| IL-6 | Interleukin 6 |
| TNF-α | Tumor necrosis factor alpha |
| NLRP3 | NOD-, LRR- and pyrin domain-containing protein 3 |
| PI3K | Phosphoinositide 3-kinase |
| AKT | Protein kinase B (also known as AKT) |
| MAPK | Mitogen-activated protein kinase |
| STAT3 | Signal transducer and activator of transcription |
| NRF2 | Nuclear factor erythroid 2–related factor 2 |
| TGF-β | Transforming growth factor beta |
| RA | Rheumatoid arthritis |
| HIF-1α | Hypoxia-inducible factor 1-alpha |
| GPX4 | Glutathione peroxidase 4 |
| GSH | Glutathione |
| pH | Potential of hydrogen (measure of acidity/alkalinity) |
| T-cell | T Lymphocyte |

## Supplementary Information

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Supplementary Material 1.

**Author contributions**

U.O.P.C., O.F.C., A.E.U., M.B., U.J.N., and U.C.N. conceptualised and designed the study, interpreted data, critically revised the manuscript for important intellectual content, and approved the final submitted version. R.I.E-N., M.M.M., O.M.B., U.D.E., A.M., and F.A.A.R. conceptualised and designed the study, interpreted data, drafted the initial manuscript, and approved the final submitted version.

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**Data availability**

No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**

This is a review article without primary data collecting or analysis from human subjects or animals. The authors consequently conducted no more patient data or direct treatments, and ethical clearance was not needed. As such, no approval reference number exists.

**Consent for publication**

Not applicable.

**Competing interests**

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