FUDMA Journal of Sciences (FJS)
ISSN online: 2616-1370
ISSN print: 2645 - 2944
Vol. 10 No. 16, June, 2026, pp 541 – 550
DOI: https://doi.org/10.33003/fjs-2026-1016-5821

Oxidative Stress Biomarkers in Doxorubicin-Induced Multi-Organ Toxicity: Mechanisms, Clinical Relevance and Emerging Protective Strategies

***Isaac S. Iquot, Ifabunmi O. Osonuga, Oyedayo Akano and Soetan Olaniyi**

Department of Department of Physiology, Faculty of Basic Medical Sciences, Obafemi Awolowo College of Health Sciences, Olabisi Onabanjo University, Sagamu Campus, Sagamu, Ogun State, Nigeria.

*Corresponding authors' email: isaaciquot@gmail.com Phone: +2348058872270
ORCID: https://orcid.org/0009-0008-7036-544X

Received: 25 Aug. 2026
Accepted: 28 Aug. 2026
Published: 05 Sep. 2026

ABSTRACT
Doxorubicin is an effective anthracycline used against solid and haematological malignancies, but dose-dependent multi-organ toxicity limits its clinical use. Oxidative stress is a major mechanism underlying this injury and produces measurable changes in redox biomarkers. This review synthesises evidence on mechanisms of doxorubicin-induced oxidative stress, major biomarkers, organ-specific patterns, clinical relevance and protective strategies. PubMed/MEDLINE, targeted Google Scholar searching and backward reference-list searching were used to identify literature from January 2010 to 10 August 2026. Relevant human, animal and in-vitro studies were considered, with seminal pre-2010 studies retained selectively for mechanistic context. Doxorubicin generally increases oxidative-damage markers, particularly malondialdehyde and 8-hydroxy-2′-deoxyguanosine, while reducing superoxide dismutase, catalase, glutathione peroxidase and glutathione. Evidence is strongest for cardiotoxicity, whereas clinical validation for non-cardiac organs is limited. Dexrazoxane and liposomal doxorubicin have stronger clinical evidence for cardioprotection, while many antioxidant and nanocarrier approaches remain preclinical. Oxidative-stress biomarkers are mechanistically informative but lack sufficient standardisation and prospective validation for routine predictive use. Integrated biomarker approaches require further clinical evaluation.

Keywords: Doxorubicin; Oxidative stress; Biomarkers; Multi-organ toxicity; Reactive oxygen species; Chemotherapy

INTRODUCTION

Doxorubicin (DOX) is an anthracycline chemotherapeutic agent with broad activity against haematological malignancies and solid tumours, including breast cancer, lymphomas, leukaemias and sarcomas (Radeva & Yoncheva, 2025; Sritharan & Sivalingam, 2025). Its antineoplastic activity is principally attributed to DNA intercalation, inhibition of topoisomerase II and disruption of DNA replication and transcription. Evidence has further implicated topoisomerase IIβ in the molecular pathways underlying doxorubicin-associated cellular injury (Zhang et al., 2012). Despite advances in targeted therapy and immunotherapy, doxorubicin remains an important component of several established chemotherapy regimens because of its potent and broad-spectrum anticancer activity.

The therapeutic value of doxorubicin is, however, limited by cumulative and dose-related toxicity. Cardiotoxicity is the most extensively characterised adverse effect and may progress from subclinical myocardial injury to irreversible cardiomyopathy and heart failure (Swain et al., 2003). Beyond the cardiovascular system, experimental and clinical evidence increasingly implicates hepatic, renal, neurological and reproductive tissues, indicating that doxorubicin toxicity is a multi-organ phenomenon rather than an exclusively cardiac complication. Such toxicities may necessitate dose reduction, treatment interruption or discontinuation and can contribute to long-term morbidity among cancer survivors.

Oxidative stress represents an important pathway linking doxorubicin exposure to tissue injury. Doxorubicin undergoes redox reactions capable of generating reactive oxygen species (ROS), while mitochondrial dysfunction further amplifies oxidative imbalance. Excessive ROS generation, together with impairment of endogenous antioxidant systems, promotes lipid peroxidation, protein modification and oxidative DNA damage. Oxidative alterations have also been demonstrated following doxorubicin exposure in humans, supporting the translational relevance of redox disturbances beyond experimental models (Il'yasova et al., 2009).

These processes can be assessed using biomarkers reflecting different components of oxidative injury. Malondialdehyde (MDA) and related products indicate lipid peroxidation, whereas 8-hydroxy-2′-deoxyguanosine (8-OHdG) reflects oxidative DNA damage. Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione (GSH) provide information on enzymatic and non-enzymatic antioxidant defences. Such biomarkers are valuable for investigating mechanisms of toxicity and may potentially contribute to toxicity detection, treatment monitoring and risk stratification.

Although doxorubicin toxicity has been extensively reviewed (Radeva & Yoncheva, 2025; Sritharan & Sivalingam, 2025), existing evidence remains heavily weighted towards cardiotoxicity, frequently examined within individual organs and dominated by preclinical studies. Moreover, oxidative-stress biomarkers are inconsistently interpreted, and the extent to which experimental alterations translate into clinically useful indicators remains uncertain. This review therefore aims to critically synthesise evidence on oxidative-stress biomarkers associated with doxorubicin-induced multi-organ toxicity, their mechanistic and clinical significance, and strategies capable of mitigating oxidative injury. Specifically,

the review examines the mechanisms of doxorubicin-induced oxidative stress, characterises major oxidative-stress biomarkers and their organ-specific patterns, evaluates their clinical and translational relevance, and assesses established and emerging protective strategies.

MATERIALS AND METHODS

A structured narrative-review approach was adopted to synthesise contemporary evidence on doxorubicin-induced oxidative stress, associated biomarkers, multi-organ toxicity and protective interventions. PubMed/MEDLINE was searched and supplemented by targeted Google Scholar searches and backward reference-list searching. The final search was completed on 10 August 2026.

The principal search period was January 2010 to 10 August 2026. Seminal pre-2010 studies were retained selectively when necessary to establish foundational mechanisms or clinically important historical observations. Search concepts combined doxorubicin or Adriamycin with terms for oxidative stress and reactive oxygen species; biomarkers including MDA, 8-OHdG, SOD, CAT, GPx and glutathione; organ toxicities including cardiac, hepatic, renal, neurological and reproductive injury; and protective strategies including dexrazoxane, liposomal doxorubicin, antioxidants and nanocarriers.

Eligible evidence comprised peer-reviewed primary human studies, animal experiments and mechanistically relevant in-vitro studies reporting doxorubicin-specific oxidative-stress, biomarker or organ-toxicity outcomes. Studies focused only on antitumour efficacy, reports in which doxorubicin-specific effects could not be distinguished, non-peer-reviewed material and unverifiable publications were excluded. Existing reviews were used for context and source discovery rather than as primary evidence. Broader anthracycline studies were used only to contextualise established clinical cardiac-surveillance measures. Ethical approval was not required because no new human or animal data were collected.

RESULTS AND DISCUSSION

Mechanisms of Doxorubicin-Induced Oxidative Stress

Redox Cycling and ROS Generation

The chemical structure of doxorubicin contributes directly to its capacity to disturb cellular redox homeostasis (Radeva & Yoncheva, 2025). Its quinone moiety can undergo one-electron reduction to produce a semiquinone radical, which is subsequently reoxidised in the presence of molecular oxygen. Repeated reduction–oxidation cycles generate superoxide radicals and downstream reactive species, including hydrogen peroxide and highly reactive hydroxyl radicals. When ROS generation exceeds cellular antioxidant capacity, oxidative stress develops and promotes progressive injury to lipids, proteins and nucleic acids. This oxidative pathway operates alongside other established mechanisms of doxorubicin toxicity, including topoisomerase IIβ-mediated cellular injury (Zhang et al., 2012).

Mitochondrial Dysfunction

Mitochondria are particularly important in amplifying doxorubicin-associated oxidative injury (Ichikawa et al., 2014; Zhang et al., 2012). Doxorubicin accumulates within mitochondria and interferes with electron-transport processes, facilitating electron leakage and additional ROS production. Mitochondrial oxidative stress can disrupt membrane potential, impair oxidative phosphorylation and reduce ATP availability while simultaneously damaging mitochondrial proteins, membrane lipids and mitochondrial DNA. Experimental evidence demonstrates that disruption of mitochondrial homeostasis is closely associated with doxorubicin cardiotoxicity (Ichikawa et al., 2014; Zhang et al., 2012). This mechanism is particularly important in highly energy-dependent tissues such as the myocardium, where persistent mitochondrial dysfunction can compromise cellular contractility and survival.

Iron-Mediated Oxidative Injury

Iron homeostasis provides an additional link between doxorubicin exposure and oxidative damage (Ichikawa et al., 2014). Doxorubicin can disturb intracellular iron regulation and promote accumulation of redox-active iron, particularly within mitochondria. This environment facilitates free-radical reactions and amplifies lipid and macromolecular oxidation. Experimental studies have demonstrated that mitochondrial iron accumulation contributes directly to doxorubicin-induced cardiac injury, providing mechanistic support for interventions that influence iron-dependent pathways (Ichikawa et al., 2014).

Oxidative Damage and Cellular Consequences

Persistent ROS accumulation initiates interconnected forms of cellular damage (Fang et al., 2019; Radeva & Yoncheva, 2025). Lipid peroxidation compromises membrane integrity and produces reactive products such as MDA and 4-hydroxynonenal, while oxidative DNA lesions include increased formation of 8-OHdG. Oxidation of proteins may alter enzyme activity and cellular signalling, whereas depletion or impaired activity of SOD, CAT, GPx and GSH further weakens antioxidant defence. Oxidative stress also interacts with mitochondrial dysfunction and inflammatory signalling, creating self-reinforcing pathways of cellular injury. Downstream responses include apoptosis and other regulated cell-death pathways. Importantly, experimental evidence has identified ferroptosis, an iron-dependent form of cell death characterised by excessive lipid peroxidation, as a contributor to doxorubicin-associated cardiomyopathy (Fang et al., 2019). Collectively, these mechanisms explain why altered oxidative-stress biomarkers occur across multiple organs following doxorubicin exposure and provide the biological foundation for their use in toxicity assessment.

The integrated mechanistic pathway is summarised in Figure 1.

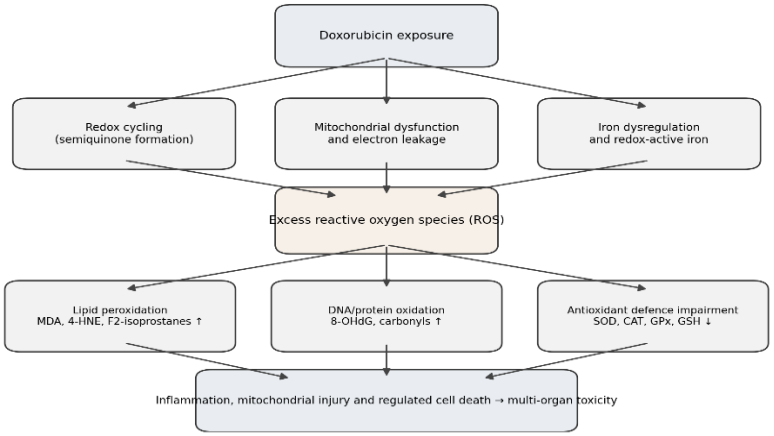

Figure 1: Mechanistic pathway linking doxorubicin exposure, reactive oxygen species generation, oxidative-stress biomarker alterations and multi-organ toxicity

Major Oxidative-Stress Biomarkers in Doxorubicin Toxicity

Oxidative-stress biomarkers used in doxorubicin research reflect different stages of redox disturbance, ranging from oxidative damage to endogenous antioxidant responses (Radeva & Yoncheva, 2025; Sritharan & Sivalingam, 2025). Their interpretation therefore requires consideration of the biological process measured, tissue or specimen analysed and analytical method employed.

Lipid-Peroxidation Biomarkers

Malondialdehyde (MDA) is among the most frequently assessed markers of doxorubicin-induced oxidative injury (Kumral et al., 2015; Kwatra et al., 2016; Tulubas et al., 2015). It is generated during peroxidation of polyunsaturated membrane lipids and is commonly elevated in cardiac, hepatic, renal and reproductive tissues following doxorubicin exposure (Kumral et al., 2015; Kwatra et al., 2016; Tulubas et al., 2015). Increased MDA generally accompanies histological injury and depletion of antioxidant defences, making it a useful indicator of oxidative membrane damage. However, MDA lacks organ specificity, and findings obtained from tissue cannot be directly extrapolated to circulating concentrations. Human evidence is also inconsistent; an acute clinical study found no significant change in plasma MDA following doxorubicin administration, whereas another study of patients receiving doxorubicin-containing chemotherapy reported increased serum MDA after three treatment cycles (Il'yasova et al., 2009; Taherkhani et al., 2017). Methodological variability is another concern because the widely used thiobarbituric acid reactive substances (TBARS) assay has limited analytical specificity and can detect compounds other than MDA (Diaz De Leon & Borges, 2020).

Other lipid-peroxidation products may provide complementary information. Doxorubicin increases cardiac mitochondrial proteins modified by 4-hydroxynonenal (4-HNE), demonstrating oxidative modification of proteins involved in energy metabolism (Zhao et al., 2014). F2-isoprostanes may offer particular translational value because they can be quantified in urine; increases in several urinary F2-isoprostanes were observed shortly after doxorubicin-based chemotherapy in patients with breast cancer (Il'yasova et al., 2010).

Oxidative DNA-Damage Biomarkers

8-Hydroxy-2′-deoxyguanosine (8-OHdG) is formed through oxidative modification of guanine and is widely used as an indicator of oxidative DNA injury (Belhan et al., 2020; Radeva & Yoncheva, 2025). Doxorubicin-associated increases have been demonstrated in testicular tissue, supporting its mechanistic relevance to genotoxic injury (Belhan et al., 2020). Measurement in tissue provides evidence of local DNA oxidation, whereas blood or urine could potentially permit less invasive monitoring. Nevertheless, evidence that 8-OHdG independently predicts clinically significant doxorubicin toxicity remains insufficient.

Enzymatic Antioxidant Biomarkers

Superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) constitute major enzymatic antioxidant defences (Igbashio et al., 2025; Kumral et al., 2015; Kwatra et al., 2016). SOD converts superoxide to hydrogen peroxide, which is subsequently detoxified principally by CAT and GPx. Experimental doxorubicin exposure frequently reduces their activities in heart, liver, kidney and reproductive tissues (Kumral et al., 2015; Kwatra et al., 2016; Renu & Gopalakrishnan, 2019; Tulubas et al., 2015). Such reductions indicate compromised capacity to neutralise ROS but may vary with dose, exposure duration, tissue and sampling time.

Non-Enzymatic Antioxidant Biomarkers

Reduced glutathione (GSH) is an important intracellular redox buffer and substrate for GPx (Kumral et al., 2015; Tulubas et al., 2015). Doxorubicin commonly depletes tissue GSH, while changes in oxidised glutathione (GSSG) and the GSH/GSSG ratio can provide additional information about cellular redox status (Kumral et al., 2015; Tulubas et al., 2015). However, circulating glutathione responses may differ from tissue responses, emphasising the importance of specimen selection.

Other and Emerging Markers

Protein carbonyls, 3-nitrotyrosine, total antioxidant status and redox-sensitive molecular pathways can complement conventional biomarkers (Kumral et al., 2015; Radeva & Yoncheva, 2025). Protein carbonyl accumulation has been demonstrated following multi-organ doxorubicin exposure (Kumral et al., 2015), while total antioxidant status has been examined clinically (Taherkhani et al., 2017). Their wider

application remains constrained by assay heterogeneity, limited standardisation and comparatively sparse prospective clinical validation.

Table 1 summarises the principal oxidative-stress biomarkers discussed in this review and highlights their interpretive limitations.

Table 1: Major Oxidative-Stress Biomarkers Associated With Doxorubicin Toxicity

Biomarker	Biomarker class	Biological significance	Typical alteration	Common specimen/tissue	Major limitation
MDA	Lipid peroxidation	Oxidative membrane damage	Increase	Heart, liver, kidney, tissue/plasma/serum	Limited specificity; assay variability
TBARS	Indirect lipid-peroxidation assay	Estimates thiobarbituric-acid-reactive products	Often increase	Tissue/plasma/serum	Not specific for MDA
4-HNE	Lipid peroxidation/protein adduct	Reactive lipid-derived damage	Increase	Cardiac/mitochondrial tissue	Limited routine clinical measurement
F2-isoprostanes	Lipid peroxidation	In-vivo lipid oxidation	Increase	Urine/plasma	Limited DOX-specific clinical validation
8-OHdG	Oxidative DNA damage	Oxidative modification of guanine	Increase	Tissue, blood, urine	Not organ-specific
SOD	Enzymatic antioxidant	Detoxifies superoxide	Generally decrease	Tissue/blood	Activity affected by tissue and timing
CAT	Enzymatic antioxidant	Detoxifies hydrogen peroxide	Generally decrease	Tissue/blood	Variable experimental responses
GPx	Enzymatic antioxidant	Reduces peroxides	Generally decrease	Tissue/blood	Dependent on glutathione availability
GSH/GSSG	Non-enzymatic antioxidant	Cellular redox buffering	GSH and GSH/GSSG ratio generally decrease	Tissue, erythrocytes	Circulating and tissue responses may differ
Protein carbonyls	Protein oxidation	Irreversible oxidative protein modification	Increase	Tissue/plasma	Limited specificity
Total antioxidant status	Global antioxidant capacity	Composite antioxidant defence	Often decrease	Serum/plasma	Does not identify individual pathways

Abbreviations: MDA, malondialdehyde; TBARS, thiobarbituric acid reactive substances; 4-HNE, 4-hydroxynonenal; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; GSH, reduced glutathione; GSSG, oxidised glutathione; DOX, doxorubicin.

Organ-Specific Patterns of Oxidative Stress

Although a common redox mechanism contributes to doxorubicin toxicity, the magnitude, biomarkers and pathological consequences of oxidative injury differ among organs.

Cardiac Toxicity

The heart remains the most extensively investigated target of doxorubicin toxicity (Ichikawa et al., 2014; Zhang et al., 2012). Cardiomyocytes have high mitochondrial density and substantial energy requirements, making mitochondrial dysfunction particularly consequential. Doxorubicin promotes mitochondrial ROS generation, lipid peroxidation and oxidative modification of mitochondrial proteins, while impaired antioxidant defences further amplify injury (Ichikawa et al., 2014; Zhang et al., 2012; Zhao et al., 2014). Experimental models consistently demonstrate increased cardiac MDA together with reductions in GSH, SOD, CAT and GPx activities (Kumral et al., 2015; Kwatra et al., 2016). Doxorubicin also increases 4-HNE-modified mitochondrial proteins, linking lipid peroxidation directly with disruption of energy metabolism (Zhao et al., 2014).

Persistent oxidative damage contributes to cardiomyocyte death, structural myocardial injury and progressive impairment of ventricular function. Importantly, oxidative-stress biomarkers should be distinguished from clinically established indicators of myocardial injury and dysfunction. Cardiac troponins and natriuretic peptides measure myocardial injury or haemodynamic stress rather than oxidative stress itself, while echocardiographic global longitudinal strain (GLS) identifies subclinical functional deterioration. Contemporary clinical studies demonstrate measurable changes in these cardiac parameters during anthracycline treatment, although their predictive performance varies between populations (Kumar et al., 2025; Polomski et al., 2026). Thus, oxidative markers currently provide mechanistic information that may complement, rather than replace, established cardiac surveillance methods.

Hepatic Toxicity

The liver is exposed to substantial doxorubicin and metabolite burden and is vulnerable to mitochondrial dysfunction and oxidative membrane injury (Kumral et al., 2015; Tulubas et al., 2015). Experimental studies demonstrate increased hepatic MDA and protein carbonyls together with depletion of GSH and alterations in SOD, CAT and GPx (Kumral et al., 2015; Tulubas et al., 2015). Oxidative injury may accompany histopathological abnormalities and increases in conventional hepatic injury indices such as alanine and aspartate aminotransferases. However, most biomarker evidence for doxorubicin hepatotoxicity remains derived from animal models rather than longitudinal studies in treated patients.

Renal Toxicity

Doxorubicin-associated renal injury involves oxidative damage to renal tissues, mitochondrial disturbance and interaction between redox and inflammatory pathways (Kumral et al., 2015; Tulubas et al., 2015). Rat studies demonstrate increased renal MDA accompanied by reductions in GSH, SOD and GPx after doxorubicin exposure (Kumral et al., 2015; Tulubas et al., 2015). These changes may coexist with increased serum urea or creatinine and histological renal injury. However, clinical evidence establishing MDA, GSH or antioxidant-enzyme activities as predictive markers of doxorubicin nephrotoxicity remains limited.

Neurotoxicity

Oxidative stress has also been implicated in doxorubicin-associated neurological effects. In rats, repeated doxorubicin exposure produced cognitive and memory impairments alongside brain lipid peroxidation, altered nitric oxide metabolism, inflammatory changes and disturbances in glutathione-related redox parameters (Cardoso et al., 2020). Other experimental models demonstrate elevated MDA and reduced antioxidant activity in brain tissue. These findings support interaction among oxidative stress, mitochondrial dysfunction and neuroinflammatory signalling. Nevertheless, direct translation to human neurotoxicity remains uncertain, particularly because systemic inflammatory and treatment-related mechanisms may contribute to chemotherapy-associated cognitive impairment.

Reproductive Toxicity

Reproductive tissues are another important target, particularly because oxidative injury to germ cells may have long-term implications for cancer survivors of reproductive age (Aslan et al., 2025; Belhan et al., 2020; Renu & Gopalakrishnan, 2019). In male rats, doxorubicin increased testicular MDA while reducing GSH and SOD and altering antioxidant signalling, accompanied by apoptosis and impaired reproductive parameters (Renu & Gopalakrishnan, 2019). Oxidative DNA damage demonstrated by 8-OHdG staining has also been observed in doxorubicin-exposed testes (Belhan et al., 2020). Female reproductive injury is similarly associated with oxidative imbalance; recent experimental evidence demonstrates reduced ovarian GSH and antioxidant status together with increased oxidant status and follicular damage following doxorubicin exposure (Aslan et al., 2025). Human validation of these oxidative biomarkers for fertility-risk prediction remains inadequate.

Other Organs

Oxidative injury has additionally been reported in pulmonary and gastrointestinal tissues, although these organs are considerably less represented than the heart, liver and kidneys (Sritharan & Sivalingam, 2025). Current evidence remains predominantly experimental and does not yet support organ-specific clinical biomarker thresholds.

Table 2 compares organ-specific biomarker patterns and the relative strength of the current evidence, while Figure 2 provides a visual overview of the multi-organ distribution.

Table 2: Organ-Specific Patterns of Oxidative-Stress Biomarkers in Doxorubicin Toxicity

Organ	Major toxicity	Common oxidative findings	Typical direction	Major consequence	Evidence base
Heart	Cardiotoxicity	MDA, 4-HNE, GSH, SOD, CAT, GPx	Damage markers increase; antioxidants decrease	Cardiomyocyte injury, ventricular dysfunction, cardiomyopathy	Strong preclinical; substantial clinical toxicity evidence
Liver	Hepatotoxicity	MDA, protein carbonyls, GSH, SOD, CAT, GPx	Damage markers increase; antioxidant defence decreases	Hepatocellular and mitochondrial injury	Moderate-strong preclinical; limited clinical biomarker evidence
Kidney	Nephrotoxicity	MDA, GSH, SOD, GPx	MDA increases; antioxidants decrease	Tubular/renal dysfunction	Predominantly preclinical
Brain	Neurotoxicity	TBARS/MDA, NO, GSH/GSSG, SOD, CAT, GPx	Variable redox imbalance	Neuroinflammation, cognitive impairment	Predominantly preclinical
Testes	Gonadotoxicity	MDA, 8-OHdG, GSH, SOD, CAT, GPx	Oxidative damage increases; defence generally decreases	Germ-cell injury, impaired sperm function	Preclinical
Ovary	Gonadotoxicity	GSH, total oxidant/antioxidant status	Oxidant status increases; antioxidant status decreases	Follicular injury and ovarian dysfunction	Preclinical
Lung/other tissues	Organ-specific injury	Lipid peroxidation and antioxidant enzymes	Variable	Tissue injury	Limited experimental evidence

Abbreviations: MDA, malondialdehyde; 4-HNE, 4-hydroxynonenal; GSH, reduced glutathione; GSSG, oxidised glutathione; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; TBARS, thiobarbituric acid reactive substances; NO, nitric oxide; 8-OHdG, 8-hydroxy-2'-deoxyguanosine.

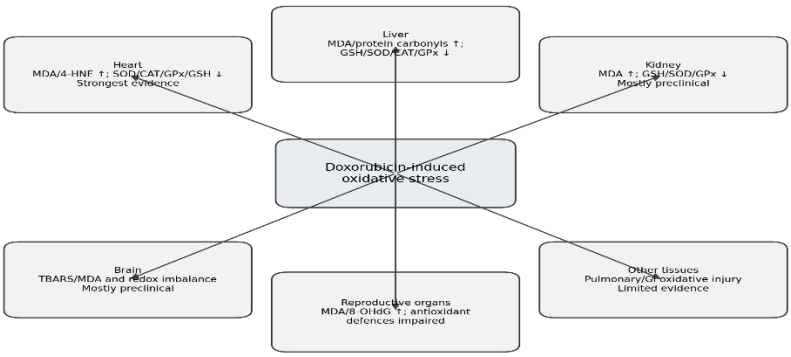

Figure 2: Multi-organ distribution of major oxidative-stress biomarker alterations associated with doxorubicin exposure

Clinical and Translational Relevance

From Experimental Marker to Clinical Biomarker

A reproducible alteration in an experimental model does not automatically establish clinical biomarker utility (Il'yasova et al., 2009; Il'yasova et al., 2010). Translation requires that a candidate marker can be measured reliably in accessible specimens, changes consistently in relation to doxorubicin exposure, correlates with clinically meaningful organ injury and demonstrates acceptable sensitivity, specificity and temporal performance. Prospective validation is particularly important when a biomarker is proposed for prediction rather than merely demonstration of established oxidative damage.

This distinction is apparent for MDA. Experimental studies consistently demonstrate tissue elevations following doxorubicin exposure (Kumral et al., 2015; Kwatra et al., 2016; Tulubas et al., 2015), yet clinical findings are inconsistent. In 23 patients with breast cancer, acute doxorubicin-based treatment produced no significant plasma MDA response, whereas antioxidant-related changes were detectable (Il'yasova et al., 2009). Conversely, a study of 60 women receiving doxorubicin/cyclophosphamide chemotherapy reported increased serum MDA and reduced total antioxidant status after three cycles (Taherkhani et al., 2017). Such differences indicate that specimen type, sampling time, treatment regimen and patient characteristics materially influence biomarker behaviour.

Clinical Monitoring Potential

Less-invasive oxidative markers remain attractive because blood or urine sampling could facilitate repeated monitoring (Il'yasova et al., 2009; Il'yasova et al., 2010). Urinary F2-isoprostanes increased rapidly after doxorubicin-based chemotherapy in a small clinical study and returned towards baseline within 24 hours, illustrating both their responsiveness and the importance of sampling time (Il'yasova et al., 2010). Circulating MDA, glutathione indices, antioxidant-enzyme activities and 8-OHdG also warrant investigation, but evidence remains insufficient to support routine toxicity prediction.

Cardiac surveillance provides an important benchmark. Troponins, natriuretic peptides, left ventricular ejection fraction and GLS have considerably greater clinical integration than oxidative markers. Even these measures show population-dependent performance: in a prospective lymphoma cohort, interim GLS predicted subsequent cardiotoxicity while troponin T and pro-BNP did not (Kumar et al., 2025), whereas a 2026 sarcoma cohort found associations between cardiac troponin T, NT-proBNP and subsequent outcomes (Polomski et al., 2026). Oxidative biomarkers must therefore demonstrate incremental value beyond existing surveillance tools before routine adoption.

Translational Limitations

Major barriers include non-standardised assays, differences in biological specimens and collection timing, small clinical samples and absence of validated thresholds (Radeva & Yoncheva, 2025; Sritharan & Sivalingam, 2025). Cancer itself can alter systemic oxidative status, while multidrug chemotherapy, diet, comorbidities and lifestyle introduce additional confounding. Furthermore, biomarkers such as MDA and 8-OHdG indicate oxidative injury but are not specific to doxorubicin or a particular organ. At present, most oxidative-stress biomarkers therefore have stronger value for mechanistic research and experimental treatment evaluation than for routine clinical decision-making. Future prospective studies should determine whether combinations of oxidative markers with established biochemical and imaging measures improve early toxicity prediction.

Table 3 contrasts selected oxidative-stress biomarker findings with established comparator cardiac-surveillance measures used during doxorubicin-containing therapy.

Table 3: Clinical Evidence for Oxidative-Stress Biomarkers and Comparator Cardiac-Surveillance Measures during Doxorubicin-Containing Therapy

Study	Population	Biomarker/assessment	Main finding	Translational implication
Il'yasova et al. (2009)	23 breast cancer patients	Plasma MDA, protein carbonyls, erythrocyte GSH, tocopherols	Plasma MDA unchanged acutely; antioxidant-related changes detected	MDA may have limited sensitivity in acute blood sampling
Il'yasova et al. (2010)	23 breast cancer patients	Urinary F2-isoprostanes	Several F2-isoprostanes increased at 1 h and approached baseline by 24 h	Demonstrates responsiveness but strong timing dependence
Taherkhani et al. (2017)	60 breast cancer patients	Serum MDA, total antioxidant status	MDA increased and antioxidant status decreased after three AC cycles	Supports treatment-associated systemic oxidative change; regimen not DOX alone

Study	Population	Biomarker/assessment	Main finding	Translational implication
Kumar et al. (2025)	40 lymphoma patients completing follow-up	Troponin T, pro-BNP, GLS	Interim GLS predicted later cardiotoxicity; cardiac biomarkers did not in this cohort	Imaging had stronger predictive evidence in this population
Polomski et al. (2026)	44 sarcoma patients	cTnT, NT-proBNP, LVEF, GLS	Cardiac biomarkers rose during treatment; cTnT associated with cardiotoxicity	Comparator anthracycline evidence; performance varies by population and timing

Abbreviations: MDA, malondialdehyde; GSH, reduced glutathione; AC, doxorubicin plus cyclophosphamide; pro-BNP, pro-brain natriuretic peptide; GLS, global longitudinal strain; cTnT, cardiac troponin T; NT-proBNP, N-terminal pro-brain natriuretic peptide; LVEF, left ventricular ejection fraction; DOX, doxorubicin.

Established and Emerging Protective Strategies

Dexrazoxane

Dexrazoxane has the strongest clinical evidence among pharmacological strategies specifically developed to limit anthracycline cardiotoxicity (Marty et al., 2006). Its protective effect is not adequately explained by simple free-radical scavenging. Experimental work indicates that dexrazoxane acts through mechanisms beyond direct antioxidant activity, including modulation of topoisomerase IIβ-associated DNA injury and iron-dependent pathways (Lyu et al., 2007). In a randomised phase III study of previously anthracycline-treated women with advanced or metastatic breast cancer, dexrazoxane significantly reduced cardiac events and congestive heart failure without reducing tumour response (Marty et al., 2006). Experimental evidence also links cardioprotection to reduced mitochondrial iron accumulation (Ichikawa et al., 2014). These findings place dexrazoxane on a stronger clinical footing than most antioxidant supplements evaluated for doxorubicin toxicity.

Liposomal Doxorubicin Formulations

Liposomal formulations modify doxorubicin pharmacokinetics and tissue distribution rather than directly neutralising ROS (Harris et al., 2002; O'Brien et al., 2004). Encapsulation limits exposure of healthy tissues to free drugs while facilitating tumour delivery. In a phase III trial involving 509 women with metastatic breast cancer, pegylated liposomal doxorubicin produced comparable progression-free survival but significantly lower cardiotoxicity than conventional doxorubicin (O'Brien et al., 2004). Similar cardioprotective findings have been reported with non-pegylated liposomal formulations (Harris et al., 2002). Reduced cardiac drug exposure would be expected to decrease downstream mitochondrial ROS generation and oxidative injury, although clinical trials have generally evaluated cardiac outcomes rather than oxidative biomarkers directly.

Nanocarrier and Targeted Delivery Systems

Nanoparticles, polymeric carriers and stimulus-responsive delivery systems seek to restrict doxorubicin exposure in non-target tissues while maintaining or enhancing tumour accumulation (Kim et al., 2024). Such platforms may be engineered for pH-, enzyme- or receptor-responsive release. A 2024 tumour-targeted, hydrogen-peroxide-responsive polymeric prodrug nanoparticle system improved tumour delivery while mitigating doxorubicin-associated hepatic and cardiac toxicity in animal models (Kim et al., 2024). Their potential advantage is therefore upstream prevention of oxidative injury rather than correction after ROS generation. However, evidence for many advanced nanocarriers remains preclinical, and translation requires evaluation of pharmacokinetics, long-term safety, manufacturing reproducibility and antitumour efficacy.

Antioxidant and Redox-Modulating Therapies

Several antioxidant and redox-modulating agents have been investigated with variable results (Abdeahad et al., 2025; Radeva & Yoncheva, 2025). Experimental studies commonly report reductions in MDA or other lipid-peroxidation products and restoration of GSH, SOD, CAT or GPx. More recently, MitoQ reduced mitochondrial ROS, DNA damage and cellular senescence in doxorubicin-treated human endothelial cells (Abdeahad et al., 2025). Nevertheless, clinical evidence remains insufficient for routine recommendation of most antioxidant agents. Any adjunctive antioxidant strategy must also demonstrate that organ protection does not compromise antitumour activity.

Phytochemicals and Natural Compounds

Curcumin and resveratrol illustrate both the promise and limitations of natural compounds (Arafa et al., 2014; Benzer et al., 2018). In rat models, curcumin reduced lipid peroxidation, oxidative DNA damage and glutathione depletion while improving SOD, CAT and GPx activities (Benzer et al., 2018). Resveratrol has likewise attenuated lipid peroxidation and cardiac injury experimentally (Arafa et al., 2014). These effects are mechanistically encouraging, but heterogeneous dosing, limited bioavailability and a predominance of preclinical studies prevent direct clinical extrapolation.

Non-Pharmacological Approaches

Exercise may enhance endogenous antioxidant capacity and mitochondrial resilience (Chicco et al., 2006). Preclinical exercise training reduced doxorubicin-induced cardiac lipid peroxidation and functional impairment (Chicco et al., 2006). Human studies are still needed to establish whether such effects translate into reproducible oxidative-biomarker or organ-protection benefits during chemotherapy.

The major protective strategies, their proposed effects on oxidative injury and the maturity of their evidence base are summarised in Table 4 and Figure 3.

Table 4: Protective Strategies Targeting Oxidative Stress in Doxorubicin-Induced Toxicity

Intervention	Proposed mechanism	Target organ/model	Biomarker effect	Toxicity outcome	Evidence level	Major limitation
Dexrazoxane	Modulates Top2β-associated and iron-dependent injury	Heart; humans and experimental models	Reduced downstream oxidative injury	Reduced cardiotoxicity and heart failure	Strong clinical evidence	Evidence primarily cardiac
Pegylated/non-pegylated liposomal DOX	Reduced free-drug exposure to healthy tissues	Heart; human trials	Indirect reduction in oxidative exposure	Lower cardiotoxicity	Randomised clinical evidence	Oxidative biomarkers rarely primary endpoints
Advanced nanocarriers	Targeted or controlled DOX delivery	Multiple experimental models	Potential reduction in ROS and oxidative damage	Reduced off-target toxicity	Predominantly preclinical	Translation, manufacturing and safety challenges
MitoQ/redox modulators	Reduction of mitochondrial ROS	Cells/experimental models	Reduced mtROS and DNA damage	Reduced cellular injury	Preclinical	Limited clinical validation
Curcumin	Antioxidant and anti-inflammatory activity	Heart; rat models	Reduced lipid/DNA oxidation; improved antioxidant enzymes	Reduced cardiac injury	Preclinical	Bioavailability and dosing
Resveratrol	Redox and mitochondrial modulation	Heart; rat models	Reduced lipid peroxidation; improved antioxidant defence	Reduced cardiac injury	Preclinical	Lack of robust clinical trials
Exercise	Improved antioxidant and mitochondrial adaptation	Heart; animal models	Reduced lipid peroxidation	Improved cardiac function	Preclinical	Human biomarker evidence limited

Abbreviations: DOX, doxorubicin; Top2β, topoisomerase II beta; ROS, reactive oxygen species; mtROS, mitochondrial reactive oxygen species.

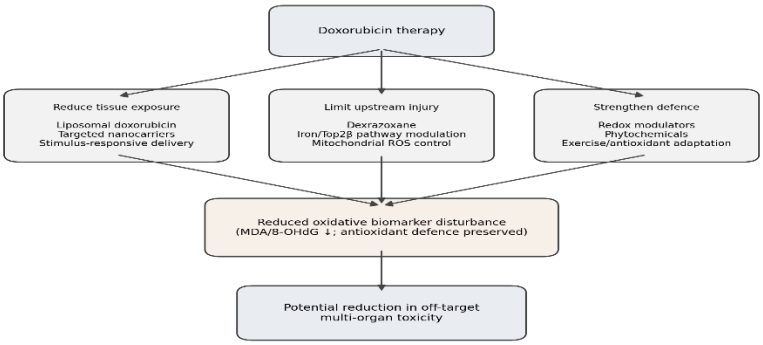

Figure 3: Protective intervention points in doxorubicin-induced oxidative injury, including reduced tissue exposure, modulation of ROS-generating pathways and enhancement of antioxidant defences

Current Evidence Gaps and Future Directions

Despite extensive investigation of doxorubicin-induced oxidative stress, several limitations restrict clinical translation (Radeva & Yoncheva, 2025; Sritharan & Sivalingam, 2025). First, much of the biomarker evidence is derived from cell and animal models. These studies are valuable mechanistically but do not reproduce the complexity of cancer, multidrug chemotherapy, comorbidity and interindividual variability in patients. Second, cardiotoxicity dominates the literature, whereas hepatic, renal, neurological and reproductive toxicities remain comparatively under-characterised, particularly in longitudinal clinical cohorts.

Third, biomarker measurement lacks standardisation. Studies differ in specimen type, assay method, sampling time, reporting units and analytical cut-offs, limiting comparability and preventing establishment of clinically meaningful thresholds. Fourth, prospective evidence is insufficient to determine whether oxidative-stress biomarkers rise before measurable organ dysfunction, predict persistent toxicity or improve risk stratification beyond established biochemical and imaging markers.

Future studies should therefore prioritise adequately powered longitudinal cohorts with predefined sampling schedules, standardised assays and clinically relevant endpoints. Multi-marker approaches are also likely to be more informative than reliance on a single oxidative marker. Integration of oxidative-stress indices with inflammatory mediators, organ-injury biomarkers, imaging findings and emerging genomic, proteomic and metabolomic signatures may better capture the complex biology of doxorubicin toxicity. Such approaches should be externally validated before incorporation into routine clinical monitoring.

CONCLUSION

Oxidative stress is an important mechanistic component of doxorubicin-induced multi-organ toxicity. Across

experimental models, doxorubicin consistently increases markers of oxidative damage, including MDA and 8-OHdG, while impairing antioxidant defences represented by SOD, CAT, GPx and GSH. Evidence is strongest for cardiac injury, whereas hepatic, renal, neurological and reproductive biomarker profiles remain supported predominantly by preclinical studies. These biomarkers are therefore valuable for mechanistic investigation and evaluation of protective interventions, but their clinical predictive utility is unequal and generally insufficiently validated. Dexrazoxane and liposomal doxorubicin have stronger clinical evidence for reducing cardiotoxicity, whereas nanocarriers, redox-modulating agents and phytochemicals remain promising but largely experimental. Future research should standardise biomarker measurement, establish clinically meaningful thresholds and determine whether integrated multi-marker strategies improve toxicity prediction beyond existing clinical surveillance methods. Prospective clinical validation remains essential before routine implementation.

REFERENCES

Abdeahad, H., Moreno, D. G., Bloom, S. I., Norman, L., Lesniewski, L. A., & Donato, A. J. (2025). MitoQ reduces senescence burden in doxorubicin-treated endothelial cells by reducing mitochondrial ROS and DNA damage. *American Journal of Physiology-Heart and Circulatory Physiology, 329*(5), H1154–H1161. https://doi.org/10.1152/ajpheart.00568.2025

Arafa, M. H., Mohammad, N. S., Atteia, H. H., & Abd-Elaziz, H. R. (2014). Protective effect of resveratrol against doxorubicin-induced cardiac toxicity and fibrosis in male experimental rats. *Journal of Physiology and Biochemistry, 70*(3), 701–711. https://doi.org/10.1007/s13105-014-0339-y

Aslan, İ. Ö., Öz, M., Erdal, H., Karaboğa, İ., & Doğan, M. (2025). Protective effect of N-acetylcysteine in doxorubicin-induced primary ovarian failure in female rats. *Turkish Journal of Obstetrics and Gynecology, 22*(3), 266–274. https://doi.org/10.4274/tjod.galenos.2025.71654

Belhan, S., Özkaraca, M., Özdek, U., & Kömüroğlu, A. U. (2020). Protective role of chrysin on doxorubicin-induced oxidative stress and DNA damage in rat testes. *Andrologia, 52*(9), e13747. https://doi.org/10.1111/and.13747

Benzer, F., Kandemir, F. M., Ozkaraca, M., Kucukler, S., & Caglayan, C. (2018). Curcumin ameliorates doxorubicin-induced cardiotoxicity by abrogation of inflammation, apoptosis, oxidative DNA damage, and protein oxidation in rats. *Journal of Biochemical and Molecular Toxicology, 32*(2), e22030. https://doi.org/10.1002/jbt.22030

Cardoso, C. V., de Barros, M. P., Bachi, A. L. L., Bernardi, M. M., Kirsten, T. B., Martins, M. F. M., Rocha, P. R. D., Rodrigues, P. S., & Bondan, E. F. (2020). Chemobrain in rats: Behavioral, morphological, oxidative and inflammatory effects of doxorubicin administration. *Behavioural Brain Research, 378*, 112233. https://doi.org/10.1016/j.bbr.2019.112233

Chicco, A. J., Schneider, C. M., & Hayward, R. (2006). Exercise training attenuates acute doxorubicin-induced cardiac dysfunction. *Journal of Cardiovascular Pharmacology, 47*(2), 182–189. https://doi.org/10.1097/01.fjc.0000199682.43448.2d

Diaz De Leon, J. A., & Borges, C. R. (2020). Evaluation of oxidative stress in biological samples using the thiobarbituric acid reactive substances assay. *Journal of Visualized Experiments*, (159), e61122. https://doi.org/10.3791/61122

Fang, X., Wang, H., Han, D., Xie, E., Yang, X., Wei, J., Gu, S., Gao, F., Zhu, N., Yin, X., Cheng, Q., Zhang, P., Dai, W., Chen, J., Yang, F., Yang, H.-T., Linkermann, A., Gu, W., Min, J., & Wang, F. (2019). Ferroptosis as a target for protection against cardiomyopathy. *Proceedings of the National Academy of Sciences of the United States of America, 116*(7), 2672–2680. https://doi.org/10.1073/pnas.1821022116

Harris, L., Batist, G., Belt, R., Rovira, D., Navari, R., Azarnia, N., Welles, L., Winer, E., & TLC D-99 Study Group. (2002). Liposome-encapsulated doxorubicin compared with conventional doxorubicin in a randomized multicenter trial as first-line therapy of metastatic breast carcinoma. *Cancer, 94*(1), 25–36. https://doi.org/10.1002/cncr.10201

Igbashio, M. D., Eluehike, N., & Oriakhi, K. (2025). Liver function and biomarkers of oxidative stress levels in streptozotocin-induced diabetic rats treated with leaves extract of Carica papaya. *FUDMA Journal of Sciences, 9*(5), 222–231. https://doi.org/10.33003/fjs-2025-0905-3665

Ichikawa, Y., Ghanefar, M., Bayeva, M., Wu, R., Khechaduri, A., Naga Prasad, S. V., Mutharasan, R. K., Naik, T. J., & Ardehali, H. (2014). Cardiotoxicity of doxorubicin is mediated through mitochondrial iron accumulation. *The Journal of Clinical Investigation, 124*(2), 617–630. https://doi.org/10.1172/JCI72931

Il'yasova, D., Mixon, G., Wang, F., Marcom, P. K., Marks, J., Spasojevich, I., Craft, N., Arredondo, F., & DiGiulio, R. (2009). Markers of oxidative status in a clinical model of oxidative assault: A pilot study in human blood following doxorubicin administration. *Biomarkers, 14*(5), 321–325. https://doi.org/10.1080/13547500902946757

Il'yasova, D., Spasojević, I., Wang, F., Tolun, A. A., Baše, K., Young, S. P., Marcom, P. K., Marks, J. R., Mixon, G., DiGiulio, R. T., & Millington, D. S. (2010). Urinary biomarkers of oxidative status in a clinical model of oxidative assault. *Cancer Epidemiology, Biomarkers & Prevention, 19*(6), 1506–1510. https://doi.org/10.1158/1055-9965.EPI-10-0211

Kim, N., Kwon, S., Kwon, G., Song, N., Jo, H., Kim, C., Park, S., & Lee, D. (2024). Tumor-targeted and stimulus-responsive polymeric prodrug nanoparticles to enhance the anticancer therapeutic efficacy of doxorubicin. *Journal of Controlled Release, 369*, 351–362. https://doi.org/10.1016/j.jconrel.2024.03.046

Kumral, A., Giriş, M., Soluk-Tekkeşin, M., Olgaç, V., Doğru-Abbasoğlu, S., Türkoğlu, Ü. & Uysal, M. (2015). Effect of olive leaf extract treatment on doxorubicin-induced cardiac, hepatic and renal toxicity in rats. *Pathophysiology, 22*(2), 117–123. https://doi.org/10.1016/j.pathophys.2015.04.002

Kumar, L., Vijayvergiya, R., Jain, A., Singh, C., Jain, A., Prakash, G., Khadwal, A., & Malhotra, P. (2025). Incidence, risk factors and early prediction of doxorubicin-induced cardiotoxicity by global longitudinal strain and cardiac biomarkers in Indian patients with lymphoma: A prospective

observational study. *Clinical Lymphoma, Myeloma & Leukemia*, *25*(3), e143–e150. https://doi.org/10.1016/j.clml.2024.10.008

Kwatra, M., Kumar, V., Jangra, A., Mishra, M., Ahmed, S., Ghosh, P., Vohora, D., & Khanam, R. (2016). Ameliorative effect of naringin against doxorubicin-induced acute cardiac toxicity in rats. *Pharmaceutical Biology*, *54*(4), 637–647. https://doi.org/10.3109/13880209.2015.1070879

Lyu, Y. L., Kerrigan, J. E., Lin, C. P., Azarova, A. M., Tsai, Y. C., Ban, Y., & Liu, L. F. (2007). Topoisomerase IIβ mediated DNA double-strand breaks: Implications in doxorubicin cardiotoxicity and prevention by dexrazoxane. *Cancer Research*, *67*(18), 8839–8846. https://doi.org/10.1158/0008-5472.CAN-07-1649

Marty, M., Espié, M., Llombart, A., Monnier, A., Rapoport, B. L., Stahalova, V., & Dexrazoxane Study Group. (2006). Multicenter randomized phase III study of the cardioprotective effect of dexrazoxane (Cardioxane) in advanced/metastatic breast cancer patients treated with anthracycline-based chemotherapy. *Annals of Oncology*, *17*(4), 614–622. https://doi.org/10.1093/annonc/mdj134

O'Brien, M. E. R., Wigler, N., Inbar, M., Rosso, R., Grischke, E., Santoro, A., Catane, R., Kieback, D. G., Tomczak, P., Ackland, S. P., Orlandi, F., Mellars, L., Alland, L., Tendler, C., & CAELYX Breast Cancer Study Group. (2004). Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. *Annals of Oncology*, *15*(3), 440–449. https://doi.org/10.1093/annonc/mdh097

Polomski, E. A. S., Speetjens, F. M., Jukema, J. W., Heemelaar, J. C., van de Sande, M. A. J., Gelderblom, H., & Antoni, M. L. (2026). Asymptomatic cardiotoxicity after high-dose anthracycline treatment in sarcoma patients assessed by biomarkers and echocardiography. *International Journal of Cancer*, Advance online publication. https://doi.org/10.1002/ijc.70620

Radeva, L., & Yoncheva, K. (2025). Doxorubicin toxicity and recent approaches to alleviating its adverse effects with focus on oxidative stress. *Molecules*, *30*(15), 3311. https://doi.org/10.3390/molecules30153311

Renu, K., & Gopalakrishnan, A. V. (2019). Deciphering the molecular mechanism during doxorubicin-mediated oxidative stress and apoptosis through Nrf2 and PGC-1α in a rat testicular milieu. *Reproductive Biology*, *19*(1), 22–37. https://doi.org/10.1016/j.repbio.2019.02.004

Sritharan, S., & Sivalingam, N. (2025). A recent decade update on combating doxorubicin-induced toxicities. *Archives of Toxicology*, *99*(9), 3565–3578. https://doi.org/10.1007/s00204-025-04112-1

Swain, S. M., Whaley, F. S., & Ewer, M. S. (2003). Congestive heart failure in patients treated with doxorubicin: A retrospective analysis of three trials. *Cancer*, *97*(11), 2869–2879. https://doi.org/10.1002/cncr.11407

Taherkhani, M., Mahjoub, S., Moslemi, D., & Karkhah, A. (2017). Three cycles of AC chemotherapy regimen increased oxidative stress in breast cancer patients: A clinical hint. *Caspian Journal of Internal Medicine*, *8*(4), 264–268. https://doi.org/10.22088/cjim.8.4.264

Tulubas, F., Gurel, A., Oran, M., Topcu, B., Caglar, V., & Uygur, E. (2015). The protective effects of omega-3 fatty acids on doxorubicin-induced hepatotoxicity and nephrotoxicity in rats. *Toxicology and Industrial Health*, *31*(7), 638–644. https://doi.org/10.1177/0748233713483203

Zhang, S., Liu, X., Bawa-Khalfe, T., Lu, L. S., Lyu, Y. L., Liu, L. F., & Yeh, E. T. (2012). Identification of the molecular basis of doxorubicin-induced cardiotoxicity. *Nature Medicine*, *18*(11), 1639–1642. https://doi.org/10.1038/nm.2919

Zhao, Y., Miriyala, S., Miao, L., Mitov, M., Schnell, D., Dhar, S. K., Cai, J., Klein, J. B., Sultana, R., Butterfield, D. A., Vore, M., Batinic-Haberle, I., Bondada, S., & St Clair, D. K. (2014). Redox proteomic identification of HNE-bound mitochondrial proteins in cardiac tissues reveals a systemic effect on energy metabolism after doxorubicin treatment. *Free Radical Biology and Medicine*, *72*, 55–65. https://doi.org/10.1016/j.freeradbiomed.2014.03.001