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Review article

Redox-Guided medication review

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ABSTRACT

Oxidative stress (OS)—an imbalance between reactive oxygen/nitrogen species (ROS/RNS) and antioxidant defences—links metabolic and neurological disorders such as type 2 diabetes, non-alcoholic fatty liver disease, Alzheimer's and Parkinson's diseases, and epilepsy. To synthesise mechanistic and translational evidence on oxidative stress biology, identify shared "redox hubs" (NRF2/KEAP1, NOX2, SIRT1/3–AMPK–FOXO), and outline their implications for pharmacist-led pharmacotherapy optimisation and biomarker-guided medication review. Structured search (PubMed, Scopus, Web of Science, 2015–2025) following SANRA narrative-review criteria identified mechanistic and translational studies on oxidative stress, redox biomarkers, and pharmacological modulators. Across metabolic and neurological phenotypes, dysregulated redox signalling converges on three hubs: NRF2/KEAP1 (antioxidant and detoxifying control), NOX2 (enzymatic ROS source driving vascular and neural injury), and SIRT1/3–AMPK–FOXO (energy/redox integration). These nodes represent actionable pharmacotherapeutic targets informing pharmacist-led, biomarker-guided medication review. Integrating validated redox biomarkers into pharmacist-led medication review enables risk stratification, deprescribing, and precision monitoring across multimorbid populations. These findings support a pharmacist-led, biomarker-guided pharmacotherapy model integrating redox profiling into medication review and pharmacovigilance. Redox-guided pharmacotherapy provides a biologically coherent, clinically actionable framework for precision medication review in chronic disease management. Incorporating validated oxidative-stress biomarkers into pharmacist-led medication review may improve outcomes in multimorbid populations.

Keywords: Oxidative stress; NRF2; NOX2; SIRT1/AMPK; Clinical pharmacy; Medication review.

INTRODUCTION

Oxidative stress (OS)—an imbalance between reactive oxygen and nitrogen species (ROS/RNS) and antioxidant defences—represents a convergent biological axis linking cardiometabolic and neurodegenerative diseases including type 2 diabetes mellitus (T2DM), metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), Alzheimer's disease (AD), Parkinson's disease (PD), and epilepsy. Persistent ROS/RNS disrupt mitochondrial signalling and proteostasis, accelerating injury in liver, brain, and endothelium [1,2,14,24,36].

In cardiometabolic disorders, chronic hyperglycaemia and insulin resistance activate four self-reinforcing biochemical routes—the polyol pathway, receptor for advanced glycation end-products (RAGE) signalling, protein kinase C (PKC) activation, and the hexosamine pathway—that amplify mitochondrial superoxide generation [4,5,24] and deplete redox buffering capacity, culminating in endothelial dysfunction and vascular complications. This "unifying mechanism" of hyperglycaemic injury remains a cornerstone of translational pharmacology. [4-5,14,24,25,33].

Within the central nervous system, redox imbalance intersects with proteotoxic stress, neuroimmune activation, and metabolic signalling. Key redox-sensitive nodes—glycogen synthase kinase-3β (GSK3β), mechanistic target of rapamycin (mTOR), and nuclear factor κB (NF-κB)—coordinate inflammatory and survival programs implicated in AD and PD, while NADPH oxidase-2 (NOX2) couples microglial activation to neuronal oxidative injury; selective NOX2 inhibition shows disease-modifying potential in translational models [6,8,26,27,29,31,36].

Across metabolic and neurological phenotypes, three druggable redox hubs recur: Nuclear factor erythroid 2-related factor 2 (NRF2)/Kelch-like ECH-associated protein 1 (KEAP1)—the master transcriptional regulator of cytoprotective programs; NOX2—a dominant enzymatic ROS source in immune and neural cells; and

the Sirtuin 1/3 (SIRT1/3)–AMP-activated protein kinase (AMPK)–Forkhead box O (FOXO) axis that integrates energy and redox control.[2,3,12,18-20,28,32] Pharmacologic modulation of these hubs—including NRF2 activators (sulforaphane, fumarates, triterpenoids), NOX2 inhibitors, and sirtuin or mitochondria-targeted antioxidants—has yielded strong mechanistic signals and emerging clinical data, albeit with variable efficacy and safety requiring biomarker-guided selection [2,3,6,12,18,24,28,32].

Scope and objective

This narrative review synthesises mechanistic and translational evidence across metabolic and neurological conditions, delineates shared redox hubs for redox-guided pharmacotherapy, and outlines practice-ready implications for clinical pharmacists, including a biomarker-informed algorithm for medication review and pharmacovigilance (Sections 7–8).

Narrative review methodology

This narrative review was conducted in accordance with the International Journal of Therapeutic Innovation author and reporting guidelines for scientific reviews (2024). It adheres to the Scale for the Assessment of Narrative Review Articles (SANRA) quality framework. Its objective was to synthesise mechanistic, translational, and therapeutic evidence linking oxidative-stress biology with pharmacological innovation and clinical-pharmacy practice.

Search strategy

A structured literature search was performed in PubMed, Scopus, and Web of Science databases covering January 2015 – September 2025. The following MeSH and free-text terms were combined with Boolean operators: *oxidative stress*, *reactive oxygen species*, *NRF2*, *NOX2*, *SIRT1*, *AMPK*, *clinical pharmacy*, *pharmacotherapy*, *biomarkers*, *type 2 diabetes*, *non-alcoholic fatty liver disease*, *Alzheimer's disease*, *Parkinson's disease*, and *epilepsy*. Earlier seminal papers defining redox mechanisms in chronic disease were included for conceptual continuity. [4,5]

Inclusion and exclusion criteria

Eligible publications comprised peer-reviewed primary studies, systematic reviews, meta-analyses, and authoritative translational papers addressing:

Molecular and cellular mechanisms of oxidative stress and redox signalling; [1-3,6].

Pharmacologic modulation of redox hubs (NRF2/KEAP1, NOX, SIRT1/3–AMPK); [2,3,6,9].

Validated clinical biomarkers of oxidative damage or defence [10,11,21,24]. and

Practice-based frameworks integrating biomarkers into pharmacist-led medication review and pharmacovigilance [10,11,24].

Excluded were non-English articles, conference abstracts, animal-only studies lacking translational extrapolation, and non-peer-reviewed grey literature.

Screening and data extraction

Titles, abstracts, and full texts were independently screened by two reviewers to ensure reproducibility and minimise selection bias. Data from eligible studies were extracted into structured evidence tables capturing study design, population characteristics, oxidative-stress biomarkers, and pharmacotherapeutic context, in accordance with the SANRA quality framework and the International Journal of Therapeutic Innovation methodological standards for scientific reviews [37-39].

Data synthesis and appraisal

Evidence was narratively synthesised across metabolic (T2DM, NAFLD) and neurological (AD, PD, epilepsy) domains. Mechanistic intersections were organised around three convergent hubs (NRF2/KEAP1, NOX2, SIRT1/3–AMPK–FOXO) to derive practice-oriented implications. Quantitative pooling was not attempted owing to heterogeneity of assay techniques, endpoints, and biomarker platforms [10,11].

Bias appraisal and methodological quality

Risk of bias and methodological quality were narratively appraised according to a study-design hierarchy (basic → translational → clinical), internal validity, and reproducibility of redox-related endpoints. Evidential weight was assigned based on methodological transparency, sample size, and biomarker standardisation, in alignment with the SANRA quality criteria [37,38].

and the *International Journal of Therapeutic Innovation* author and reporting guidelines (2024).

Translational relevance appraisal

Each included study was categorised by translational proximity: (1) preclinical mechanistic, (2) human biomarker-correlative, or (3) interventional-pharmacotherapy evidence directly informing pharmacist-led optimization.

Cellular and molecular basis of oxidative stress

OS arises when cellular antioxidant defences are overwhelmed by ROS/RNS, leading to irreversible oxidation of lipids, proteins, and nucleic acids. Controlled ROS act as second messengers regulating kinases and stress responses.[13,23,24] Dysregulation occurs when redox signalling shifts from reversible to damaging oxidation, impairing mitochondrial efficiency, proteostasis, and cell survival.

The mitochondrial electron transport chain (ETC), particularly Complexes I and III, is the principal intracellular source of superoxide ($O_2^{\bullet-}$) under both physiological and pathologic conditions [24,25]. Superoxide dismutases (SODs) convert it to hydrogen peroxide (H_2O_2), which modulates downstream signalling via reversible cysteine oxidation of target proteins. Additional ROS arise from non-mitochondrial enzymes—chiefly NADPH oxidases (NOX family) and nitric oxide synthases (NOS)—which couple immune activation and endothelial dysfunction to oxidative burden [7,8]. Among them, NOX2 plays a pivotal role in vascular, neural, and renal tissues, representing a pharmacologically actionable hub in chronic disease [7,26,29].

The transcription factor NRF2 (nuclear factor erythroid 2-related factor 2) governs cytoprotective gene programs that maintain glutathione synthesis, thioredoxin recycling, and phase II detoxification enzymes. [2,3,9]. In quiescent cells, NRF2 is sequestered

by KEAP1 and targeted for ubiquitination; oxidative or electrophilic stress disrupts this interaction, stabilising NRF2 and triggering upregulation of antioxidant response elements (AREs). Pharmacologic activation of NRF2—by fumarates, bardoxolone, or sulforaphane—has shown organ-protective effects in metabolic and neurodegenerative disorders but may also alter drug metabolism through phase II enzyme induction [2,3,9]. For pharmacists, NRF2 modulation has dual relevance: it mitigates oxidative damage but can modify hepatic clearance and drug–drug interactions, necessitating vigilance in polypharmacy contexts.

The SIRT1/3–AMPK–FOXO axis integrates cellular energy and redox signalling. Sirtuins deacetylate metabolic regulators and antioxidant enzymes (e.g., MnSOD), while AMPK senses AMP/ATP ratios and represses anabolic stress[12-13,18-20] Under nutrient overload or chronic inflammation, suppression of sirtuin activity shifts metabolism toward oxidative damage and insulin resistance. Activation of this pathway by caloric restriction mimetics or NAD^+ precursors (nicotinamide riboside, NMN) restores redox balance and mitochondrial biogenesis.[12-13,18-20] Pharmacologically, this pathway interacts with metformin, statins, and several antiepileptics, influencing tolerance and adverse-effect profiles in multimorbid, elderly, or frail patients—making its monitoring integral to medication review.

Cross-talk between NRF2, NOX2, and SIRT/AMPK establishes a bidirectional link between metabolic stress and inflammation. Loss of NRF2 or SIRT1 activity amplifies NF-κB-driven cytokine release, while NOX2-derived ROS perpetuate endothelial and microglial activation. This interconnection underlies "redox inflammation," a unifying driver of both vascular and neuronal injury [2,14,18,26]. Pharmacists can use this mechanistic insight to predict drug-induced pro-oxidant effects (e.g., anthracyclines, valproate, corticosteroids), detect high-risk drug–disease interactions, and guide antioxidant-supportive or deprescriptive strategies.

These molecular pathways converge on clinically meaningful outcomes: mitochondrial dysfunction, endothelial damage, and neuroinflammation—all critical determinants of polypharmacy risk, drug metabolism variability, and organ-specific toxicity. Understanding the dominant redox hubs (NRF2/KEAP1, NOX2, SIRT/AMPK) enables pharmacists to anticipate oxidative liabilities of pharmacotherapy and to identify opportunities for biomarker-guided monitoring and deprescribing. This mechanistic insight forms the foundation for Section 3, which explores redox dysregulation in metabolic disease states relevant to clinical pharmacy practice.

Clinically tractable markers combine damage and defence indices:

Damage

8-oxo-2′-deoxyguanosine (8-oxo-dG/8-OHdG), F_2-isoprostanes, malondialdehyde (MDA), and protein carbonyls.

Defence

SOD, GPx, CAT activities ± total antioxidant capacity (TAC).

Contextual labs

eGFR, hepatic panel, CRP/hsCRP, HbA1c, lipids [10,11,21,24].

Figure 2 illustrates the integrated redox-signalling architecture linking mitochondrial and non-mitochondrial ROS/RNS sources with antioxidant defences and major regulatory nodes (NRF2/KEAP1, NF-κB, AMPK/mTOR, SIRT/FOXO). Analytical guidance: prefer LC-MS/MS for specificity, standardise matrix, fasting state, and storage. Urinary results should be creatinine-normalised; serial Δ-changes (≥ 20–30 %) are clinically meaningful. Composite redox classes (Controlled / Moderate / High risk) integrate damage + defence signals, aligning with PCNE v9.1 and STOPP/START v3 tools in electronic health records.[10,11,24]

These molecular interactions converge on shared regulatory axes that determine tissue susceptibility to oxidative injury across metabolic and neurodegenerative conditions. Integration of these redox nodes provides the conceptual basis for cross-disease therapeutic targeting and biomarker-guided medication review. Cross-disease redox hubs (mitochondrial and non-mitochondrial ROS/RNS sources, NRF2/KEAP1, NOX2, SIRT/AMPK, and mTOR–NF-κB axes) are summarized in Figure 3, providing the conceptual bridge to biomarker-guided medication review in multimorbidity.

Implementation pointer (for Section 7)

A structured Redox-Guided Medication Review (RG-MR) algorithm will be implemented within the EHR to operationalize Section 6 outputs. The workflow follows a two-step cycle—baseline assessment and 4–8-week re-assessment—using predefined biomarker-driven thresholds to guide "step-up," "step-down," or "agent-switch" pharmacotherapy decisions. The baseline panel (8-oxo-dG/8-OHdG, MDA, protein carbonyls, TAC, SOD, GPx, CAT) establishes each patient's redox profile; follow-up values are expressed as percentage change from baseline to minimize inter-assay bias. Decision logic is encoded as CDS rules within the pharmacy EHR module, linking each action to PCNE v9.1 problem–cause–intervention codes and STOPP/START v3 criteria. EHR field mappings include structured capture of assay identifiers, matrix, and reference ranges, automatic Δ% computation, and a "Redox risk stratum" flag (Low/Moderate/High). Integration with eRecept and CRPP enables automated population of pharmacist notes, drug-therapy modifications (ATC-coded), and monitoring plans, thereby streamlining documentation, longitudinal signal detection, and auditability of redox-responsive clinical outcomes.

Oxidative stress in metabolic disorders

Framing

In metabolic disease, persistent nutrient surplus and insulin resistance amplify mitochondrial ROS and NOX2 activation, sustaining redox–inflammatory loops that culminate in endothelial dysfunction, organ-specific injury (liver, kidney, retina, nerves), and reduced pharmacotherapeutic tolerance. This chapter integrates the mechanistic backbone with clinically actionable pharmacy levers—risk-factor mastery, hub-aware modulation (NRF2, NOX2, SIRT/AMPK), biomarker-guided review, and deprescribing—while

avoiding mechanistic redundancy [4,5,7,9,24,25].

Type 2 diabetes mellitus and the metabolic syndrome - retained

Pathophysiology—integrated mechanism

In T2DM, chronic hyperglycaemia and insulin resistance perpetuate oxidative–metabolic stress. ROS-driven activation of the four canonical Brownlee pathways (polyol, AGE–RAGE, PKC, and hexosamine) collectively amplifies mitochondrial injury, endothelial dysfunction, and microvascular complications.[4,5,33-35] Beyond mitochondria, NOX1/2/4 in endothelium and vascular smooth muscle amplify oxidative tone and impair endothelium-dependent vasodilation, while eNOS uncoupling (BH_4 depletion, glycoxidation) diverts NO synthesis toward $O_2^{\bullet-}$, accelerating $ONOO^-$ formation and nitrosative stress [4,5,7,15,24,25]. ER stress and impaired mitophagy further entrench ROS production; DRP1-dominant fission fragments mitochondria [4,5,24].

Network nodes—from sensing to injury

These regulatory nodes—NRF2/KEAP1, NOX2, and SIRT/AMPK—are discussed in detail in Section 5, where their modulation is linked to pharmacist-led optimization and redox-guided deprescribing strategies.

Phenotypes and progression

Post-prandial hyperglycaemia and glycaemic variability—not merely mean HbA1c—spike mitochondrial ROS and NOX activity, correlating with endothelial dysfunction and microvascular risk [5,11,24,25]. Clinically, GV and CKD stratify OS liability and lower pharmacologic tolerance. CKD and glycaemic variability stratify oxidative liability and pharmacologic tolerance, identifying high-priority subgroups for pharmacist intervention.

Therapeutic implications—mechanism-anchored levers

Pharmacist-actionable levers include:

Reduction of glycaemic variability and hyperlipidaemia to lower mitochondrial ROS flux, a strategy consistently shown to attenuate endothelial dysfunction and oxidative damage in type 2 diabetes. Brownlee's updated unifying mechanism and subsequent clinical data demonstrate that post-prandial spikes and lipid overload drive ROS formation and vascular injury, whereas control of glycaemic excursions markedly decreases oxidative biomarkers and microvascular risk [4-6,24,25].

Targeted modulation of enzymatic ROS sources (NOX/RAAS control) and induction of NRF2/SIRT–AMPK cytoprotective programs, which integrate redox and energy signalling. Pharmacologic or lifestyle activation of these hubs—via RAAS blockade, fumarates, sulforaphane, triterpenoids, metformin, and NAD^+ precursors—enhances mitochondrial resilience and reduces inflammatory tone [2-3,7-9,24].

Therapy adjustment according to serial biomarker Δ (≥ 20–30 % over 4–8 weeks), using validated oxidative-stress markers (8-oxo-dG, F_2-isoprostanes, malondialdehyde, protein carbonyls) in conjunction with antioxidant-defence indices (SOD, GPx, CAT). Longitudinal interpretation of Δ-change provides clinically meaningful feedback for pharmacotherapy optimization and deprescribing [10,11,21,24].

Together, these measures translate mechanistic redox knowledge into quantifiable clinical-pharmacy outcomes within the Redox-Guided Medication-Review (RG-MR) framework.

Clinical-pharmacy angle—risk triage and CDS hooks

Patients with poor glycaemic control, chronic kidney disease (CKD), or polypharmacy represent the highest redox-risk stratum.[5,9-11] Pharmacists should prioritise structured reviews targeting drugs that aggravate oxidative tone—such as catecholaminergics, corticosteroids, or mitochondrial toxicants—and optimise regimens via PCNE v9.1 and STOPP/START v3 logic. [10,11,24]. Implementation of the Redox-Guided Medication Review (RG-MR) algorithm enables quantification of intervention outcomes: resolved DRPs per 100 patients, Δ-biomarker improvements ≥ 20–30 %, and documented deprescribing or therapy optimization within the electronic health record (EHR) [10,11,24]. Patient counselling on diet and exercise should reinforce these actions [2-3,9-11,24]. All pharmacist actions should be encoded in eRecept and CRPP for transparency and auditability, ensuring traceable, standardised pharmaceutical care across health-information systems [10,11,24]. Outcome metrics include (i) Δ-change ≥ 20 % in oxidative-damage markers, (ii) number of optimised or deprescribed drugs per review, and (iii) patient-level improvement in HbA1c or eGFR trajectory.

Non-alcoholic fatty liver disease (NAFLD/NASH) – clinical-pharmacy expansion

Pathophysiology—lipotoxic redox and organelle crosstalk

Lipotoxicity (excess FFA, ceramides), ER stress, and mitochondrial dysfunction precipitate redox-inflammation in hepatocytes and Kupffer cells. High β-oxidation increases electron leak at Complex I/III, generating $O_2^{\bullet-}/H_2O_2$; cardiolipin oxidation and mtDNA 8-oxo-dG impair oxidative phosphorylation and intensify ROS. NOX-dependent signalling contributes to stellate-cell activation and fibrogenesis; NOX1/4 in hepatic vasculature/stellate cells sustains inflammatory and profibrotic tone. Dysregulated SIRT/AMPK lowers mitophagy/biogenesis; blunted NRF2 weakens inducible cytoprotection and detoxication, favouring transition from steatosis to steatohepatitis.

Progression biology—why some livers scar

Progression reflects multiple hits: persistent lipid peroxidation (MDA/4-HNE adducts), protein carbonylation, DAMP release, Kupffer-cell priming, and portal endotoxaemia (gut–liver axis) that amplifies TLR–NF-κB signalling. Ferroptosis susceptibility rises when GPx4 activity and GSH pools are inadequate; hepatocellular death fuels inflammation and stellate activation, linking OS to fibrosis.

Therapeutic implications—multicomponent approach

Primary levers: weight loss, insulin-sensitisation, and exercise to restore AMPK/SIRT tone and mitochondrial efficiency. Cytoprotection: selectively induce NRF2 programs to augment antioxidant/detoxication capacity (context-dependent; avoid blanket supplementation).[2,3,9] Vascular/fibrotic tone: control BP (RAAS), lipids, and consider NOX-aware strategies as evidence matures.[7] Safety vigilance: in a redox-primed liver, monitor for idiosyncratic DILI when using redox-active supplements or combinations;

optimise dosing in hepatic/renal impairment and check drug–nutraceutical interactions.

Clinical-pharmacy angle

Risk-stratify NAFLD with T2DM/CKD; prioritise hepatically safe, cardioprotective agents. Implement biomarkers where feasible (MDA/F_2-isoprostanes, protein carbonyls) with ALT/AST, GGT, eGFR to track redox–injury dynamics and dose adjustments (serial Δ ≥20–30% over 4–8 weeks; LC–MS/MS, urinary creatinine normalisation).[10,11,24] Medication safety and DILI vigilance: baseline hepatic panel and FIB-4; review high-risk drugs/supplements (valproate, amiodarone, methotrexate, tamoxifen, isoniazid, azoles, macrolides, anabolic steroids; certain herbals). Statins are generally safe/cardioprotective; reconsider only in progressive hepatitis or decompensated cirrhosis. GLP-1 RAs and pioglitazone may improve steatohepatitis; SGLT2 inhibitors reduce redox burden with renal–cardiovascular benefit. Configure an EHR DILI-watch rule: trigger if ALT/AST > 3× ULN with symptoms or > 5× ULN without, or bilirubin > 2× ULN → temporary withdrawal, FIB-4 re-check, substitution pathway [2,3,7,9-11,24].

Micro- and macrovascular complications

Endothelial failure as common soil

The four hyperglycaemic pathways converge on endothelial dysfunction—reduced NO bioavailability (eNOS uncoupling), NOX-dependent oxidative tone, glycocalyx damage, and a pro-inflammatory/pro-thrombotic endothelium [4,5,7,24,25]. Microvascular beds (retina, glomerulus, vasa nervorum) are highly OS-vulnerable; in macrovasculature, diabetic dyslipidaemia and NOX/RAAS–NF-κB signalling promote atherothrombosis.

Pharmacy priorities—risk-factor mastery with a redox lens

Tight glycaemic and BP control with attention to glycaemic variability to damp ROS flux. Lipid lowering (statin backbone; add-ons as indicated) with vigilance for myopathic/mitochondrial signals in frailty/CKD/NAFLD. Antithrombotic stewardship tailored to haemorrhagic risk in multimorbidity (falls, renal dosing, drug–drug interactions). Use serial biomarkers (when available) as pharmacovigilance adjuncts to detect discordant biology (worsening markers despite target attainment → reassess adherence, interactions, secondary drivers). hair and the condition of our scalp. These hair masks are quite helpful to our hair no negative effects and are also manufactured at home [1-2].

Types of herbal hair mask:

For dry hair: Avocado, honey, and olive oil

mask. For frizzy hair: castor oil mask.

For hair growth: rosemary and castor Oil

mask. For curly hair: rice and avocado mask.

For thin hair: banana, honey, egg, and olive Oil mask.

History

The tradition of using rice water as a beauty regimen is believed to trace back to ancient China, particularly during the Tang dynasty (618-907 AD). For centuries, rice water has been revered for its cosmetic benefits. In ancient times, preceding the Qin dynasty, individuals would cleanse their hair and body with rice water, enriched with starch, proteins, and vitamins. Beyond its cleansing properties for hair and skin maintenance, rice water was valued for its potential to soften rough skin and offer medicinal relief. It was known all alleviate conditions such as cold extremities, lower back discomfort, frostbite, and fatigue. Essentially, this natural cosmetic served as a multipurpose product, functioning as a shampoo, body wash [3].

Primary anchors: Brownlee framework; NOX/NRF2 keystone reviews

Abbreviations: AGE – Advanced glycation end product; AMPK – AMP-activated protein kinase; ARE – Antioxidant response element; AR – Aldose reductase; BH_4 – Tetrahydrobiopterin; BP – Blood pressure; CGM – Continuous glucose monitoring; CKD – Chronic kidney disease; DAG – Diacylglycerol; DRP – Drug-related problem; eGFR – Estimated glomerular filtration rate; eNOS – Endothelial nitric oxide synthase; ER – Endoplasmic reticulum; FOXO – Forkhead box O transcription factor; GPx4 – Glutathione peroxidase 4; GSH – Reduced glutathione; GV – Glycaemic variability; H_2O_2 – Hydrogen peroxide; IRS-1 – Insulin receptor substrate 1; KEAP1 – Kelch-like ECH-associated protein 1; MDA – Malondialdehyde; NF-κB – Nuclear factor κB; NOX – NADPH oxidase; NRF2 – Nuclear factor erythroid 2–related factor 2; $O_2^{\bullet-}$ – Superoxide anion; O-GlcNAc – O-linked N-acetylglucosamine; $ONOO^-$ – Peroxynitrite; PDI – Protein disulfide isomerase; PKC – Protein kinase C; PUFA – Polyunsaturated fatty acid; RAAS – Renin–angiotensin–aldosterone system; RAGE – Receptor for advanced glycation end products; ROS – Reactive oxygen species; SIRT – Sirtuin; TAC – Total antioxidant capacity; UPR – Unfolded protein response.

Summary transition

Across metabolic disorders, oxidative stress is a modifiable therapeutic dimension. Pharmacists operationalise this by integrating biomarker interpretation, drug-safety optimization, and deprescribing within digital medication-review workflows, establishing the basis for the Redox-Guided Medication Review (RG-MR) model presented later and cross-referenced to PCNE v9.1 and STOPP/START v3.

Neurodegenerative Disorders and Pharmacist Leverage Points

Neurodegenerative disorders—including Alzheimer's and Parkinson's disease, epilepsy, and post-stroke cognitive impairment—share convergent mechanisms of mitochondrial dysfunction, NOX2-mediated microglial activation, and insufficient NRF2/SIRT–AMPK buffering [12-15,27-30]. This redox imbalance accelerates synaptic failure, protein misfolding, and cognitive decline through cumulative oxidative and inflammatory stress [13,14,28].

Pharmacists can mitigate these processes through optimization of dopaminergic, cholinergic, and psychotropic therapy, systematic reduction of anticholinergic and sedative load, and vigilant renal/hepatic dose adjustment [31-34]. Integration of redox biomarkers (8-oxo-dG, F_2-isoprostanes ± SOD/GPx/CAT) into structured medication review supports evidence-based deprescribing and early detection of redox-linked adverse effects [9-11,21,24]. Key therapeutic targets and drug classes relevant to pharmacist intervention are summarised in Tables 2 and 3.

Table 1. Metabolic oxidative-stress pathways → targets → candidate strategies [2-5,7,9,11,15,24,25,34-36]

Pathway/ Node	Mechanistic role (metabolic context)	Candidate pharmacology / strategy	Pharmacy notes
Polyol flux (aldose reductase)	NADPH depletion → ↓ GSH recycling → ↑ ROS; BH_4 shortfall → eNOS uncoupling	Glycaemic control; investigational AR inhibitors	Watch sorbitol-related lens/nerve vulnerability; reassess in CKD where antioxidant reserve is limited.[4,5]
AGE–RAGE axis	AGE signalling → NF-κB/NOX activation → endothelial dysfunction & stiffness	Reduce glycaemic variability; AGE-lowering diet; RAGE antagonism (investigational)	Educate on post-prandial spikes; caution with unregulated "AGE-blockers" and interactions.[4,5]
PKC (DAG-driven)	Vascular permeability/vasomotor dysregulation; p47phox phosphorylation → NOX on-switch	Intensive risk-factor control; PKCβ inhibitors (limited clinical availability)	Optimise BP/lipids; PKC-selective agents rarely accessible—substitute with upstream control.[5]
Hexosamine / O-GlcNAc	Transcriptional remodelling; interference with insulin signalling (IRS-1/eNOS/NF-κB)	Exercise/weight reduction (AMPK); metformin (AMPK)	Reinforce lifestyle–metformin synergy on AMPK–SIRT tone; monitor hypoglycaemia in frailty.[2,3,5,34,35]
NOX1/2/4	Enzymatic ROS; endothelial and vascular inflammation	NOX dampening (investigational); RAAS and BP optimization; lipids	Balance BP control with renal protection; monitor electrolytes/eGFR; watch for infections if broad ROS is suppressed.[7,24,25]
NRF2/KEAP1	Inducible cytoprotective/antioxidant and detoxication program (ARE genes)	Diet (isothiocyanates), fumarates, triterpenoid classes (context-dependent)	Evaluate drug–drug/disease–drug interactions; avoid blanket supplementation in multimorbidity.[2,3,9,34,35]
SIRT1/3–AMPK–FOXO	Mitochondrial biogenesis/mitophagy; antioxidant gene expression; metabolic flexibility	Exercise; nutraceutical proxies; metformin-linked AMPK effects	Tailor activity plans to frailty; prioritise CGM-guided titration to avoid hypoglycaemia.[2,3,9,34,35]
eNOS coupling (BH_4)	BH_4 depletion → eNOS uncoupling → $O_2^{\bullet-}$, $ONOO^-$	Upstream glucose/RAAS control; ensure folate status; lipid optimization	Prioritise GV reduction; consider factors lowering BH_4; reinforce statin adherence for endothelial health.[4,5,15,24,25]
ER stress / UPR	Oxidative protein folding (Ero1/PDI) adds H_2O_2; UPR–inflammation crosstalk	Caloric patterning; exercise; remove offending drugs	Watch for drug-induced ER stressors; stepwise deprescribing where feasible.[5]
Ferroptosis guard (GPx4)	Phospholipid-OOH accumulation in PUFA-rich membranes	Restore GSH/GPx4 axis via upstream control and NRF2-aligned nutrition	Avoid pro-oxidant supplement stacks; monitor MDA/F_2-IsoPs if available.[2,3,9-11]

Table 2. Summary of validated oxidative-stress biomarkers. [2,3,6-9,12,18-20]

Target / Node	Rationale in CNS disease	Mechanistic agents/strategies	Translation notes
NOX2	Microglial and neuronal ROS generation; couples neuroinflammation to excitability and mitochondrial dysfunction	Selective NOX2 inhibitors (investigational); indirect NOX dampening via RAAS and metabolic control	Requires CNS penetration and biomarker linkage (e.g., 8-oxo-dG, protein carbonyls).[6-8]
NRF2/KEAP1	Master regulator of cytoprotective genes (ARE-driven antioxidant and detoxication programs; proteostasis)	Electrophilic and non-electrophilic Nrf2 activators; fumarates, triterpenoids, dietary isothiocyanates	Exposure–response and safety are context-dependent; formulation and brain delivery remain key hurdles.
SIRT1/3–AMPK–FOXO	Coordinates mitochondrial biogenesis, mitophagy, and antioxidant gene expression; integrates energy/redox status	Exercise mimetics; SIRT activators; metformin-linked AMPK modulation; NAD^+ precursors	Biomarker-guided use (redox panel, metabolic reserve); dose-adapt for frailty and CKD.[2,3,12,18-20]
mTOR / GSK3β / NF-κB	Governs proteostasis, autophagy, and inflammatory tone; over-activation promotes neuroinflammation and insulin resistance	Indirect modulation through upstream redox correction; targeted inhibitors under study	Balance immunometabolic benefit against neuropsychiatric adverse effects; emphasise stepwise deprescribing where feasible.[2,3]

Abbreviations: AMPK – *AMP-activated protein kinase*: cellular energy sensor that promotes ATP-generating (catabolic) pathways and enhances mitochondrial and antioxidant defences.; ARE – *Antioxidant response element*: promoter sequence activated by NRF2 to induce cytoprotective and detoxifying enzymes (e.g., HO-1, NQO1, GCLC).; CKD – *Chronic kidney disease*: a condition that limits antioxidant capacity and requires dose adjustment of renally cleared drugs.; FOXO – *Forkhead box O transcription factors* (e.g., FOXO1, FOXO3a): redox-sensitive regulators of apoptosis, autophagy, and stress resistance.; GSK3β – *Glycogen synthase kinase 3 beta*: kinase involved in insulin signalling, proteostasis, and neuroinflammation; interacts with mTOR and NF-κB pathways.; Keap1 – *Kelch-like ECH-associated protein 1*: cytosolic repressor that binds NRF2 and targets it for degradation under basal conditions.; mTOR – *Mechanistic (or mammalian) target of rapamycin*: central integrator of nutrient and growth signals; excessive activity promotes oxidative and inflammatory stress.; NF-κB – *Nuclear factor kappa-light-chain-enhancer of activated B cells*: transcription factor regulating inflammatory cytokines and cell-survival genes.; NOX2 – *NADPH oxidase isoform 2*: enzyme complex producing superoxide in neurons and microglia; key driver of neuroinflammation and mitochondrial dysfunction.; NRF2 – *Nuclear factor erythroid 2-related factor 2*: master transcription factor controlling antioxidant and phase-II detoxication gene expression.; RAAS – *Renin–angiotensin–aldosterone system*: hormonal cascade influencing vascular tone, oxidative stress, and neuroinflammation.; SIRT1/3 – *Sirtuins 1 and 3*: NAD^+-dependent deacetylases that regulate mitochondrial metabolism, antioxidant defences, and longevity

signalling.

Abbreviations: ACB – Anticholinergic Cognitive Burden: cumulative measure of anticholinergic drug load associated with cognitive decline, delirium, and falls in older adults.; AE – Adverse event: any undesired effect occurring during drug therapy (used generically across sections).; CBT-I – Cognitive Behavioural Therapy for Insomnia: structured non-pharmacologic approach to improve sleep architecture and reduce sedative dependence.; CKD – Chronic kidney disease: condition requiring renal dose adjustments and increasing oxidative vulnerability.; Δ – Change from baseline: relative change (usually ≥ 20–30 %) in biomarker or functional parameter considered clinically meaningful.; GI – Gastrointestinal.; GV – Glycaemic variability: fluctuations in blood glucose that heighten oxidative stress and vascular risk.; ICD – Impulse-Control Disorder: behavioural adverse effect linked to dopaminergic therapy (e.g., gambling, hypersexuality, compulsive shopping).; LFTs – Liver function tests: standard hepatic monitoring panel (ALT, AST, ALP, GGT, bilirubin).; OAB – Overactive bladder: urinary condition often treated with antimuscarinics that increase ACB.; OTC – Over-the-counter: non-prescription medications (notably first-generation antihistamines) with sedative/anticholinergic effects.; PCNE v9.1 – Pharmaceutical Care Network Europe classification (version 9.1): structured system for coding drug-related problems (problem–cause–intervention–outcome).; SNRI – Serotonin-noradrenaline reuptake inhibitor.; SSRI – Selective serotonin reuptake inhibitor.; STOPP/START v3 – Screening Tool of Older Persons' potentially inappropriate Prescriptions / Screening Tool to Alert to Right Treatment, version 3: guideline for identifying drugs to discontinue or initiate in older adults.; β_3-agonist – Beta-3 adrenergic receptor agonist: bladder-selective relaxant with minimal cognitive or anticholinergic impact.

Practical outcome metrics include a ≥ 25 % reduction in cumulative Anticholinergic Cognitive Burden (ACB) score, fewer falls, improved adherence, and stability of cognitive-performance scales within 3 months. All pharmacist actions should be documented according to PCNE v9.1 and STOPP/START v3 logic within EHR-linked workflows (e.g., eRecept, CRPP) to ensure reproducibility, transparency, and auditability [10,11,24].

Epilepsy

Epilepsy and neuroinflammation

Valproate can impair mitochondrial β-oxidation/carnitine handling; monitor LFTs, consider ammonia if encephalopathy, and avoid additive sedatives; prioritise alternative ASM where feasible in frailty or hepatic compromise. Multiple sclerosis/ ALS: avoid stacking anticholinergics/sedatives; reinforce vascular risk control (lipids, BP) to reduce redox load; tailor symptomatic therapy to cognition and falls risk. Post-stroke cognitive impairment/frailty: reduce ACB/sedative burden, optimise BP variability and post-prandial glycaemia, and embed pharmacist-led deprescribing with caregiver education.

Summary transition

Across neurological phenotypes, oxidative stress is a modifiable dimension. Pharmacists operationalise this by (i) removing pro-oxidant/cognition-worsening medicines, (ii) optimising disease-specific regimens (cholinesterase inhibitors, memantine, levodopa-centred PD therapy), (iii) controlling metabolic/vascular drivers, and (iv) using biomarker-guided pharmacovigilance where available (Δ ≥ 20–30% at 4–8 weeks). All actions are documented via PCNE v9.1 and STOPP/START v3 within EHR-linked workflows to ensure repeatability and auditability.

Convergent redox hubs (cross-disease integrators)

Framing

Multiple cellular stress sensors converge on shared regulatory "hubs" that integrate redox, metabolic, and inflammatory cues. These nodal intersections determine organ vulnerability and therapeutic leverage points relevant to both metabolic and neurological disease.

Core regulatory axes

The NRF2/KEAP1 axis acts as a cytoprotective master switch, coordinating ARE-driven detoxication, antioxidant, and proteostatic responses that maintain redox homeostasis and cellular resilience. When hyperglycemia, lipid peroxidation, or chronic inflammation suppress NRF2 tone through KEAP1 overactivation or GSK3β-mediated degradation, mitochondrial defence and unfolded-protein control erode, amplifying oxidative injury and metabolic inflexibility. Therapeutically, both electrophilic (e.g., fumarates, triterpenoids) and non-electrophilic NRF2 activators, together with upstream lifestyle and metabolic interventions (exercise, isothiocyanate-rich diet, glycaemic optimisation), can restore redox equilibrium. However, dose individualisation is essential in frailty to avoid indiscriminate antioxidant supplementation and potential hormetic paradoxes.

The NOX2 isoform of NADPH oxidase functions as an oxidative amplifier, converting metabolic and inflammatory stimuli into sustained ROS signalling that fuels endothelial dysfunction and mitochondrial injury. Its activity rises under hyperglycaemia, angiotensin II stimulation, and immune activation, producing superoxide and secondary peroxynitrite that propagate vascular damage and metabolic inflexibility. Therapeutically, modulation relies on indirect suppression through RAAS blockade, statins, and optimisation of blood pressure and lipid control; selective NOX inhibitors remain largely investigational. Pharmacists should monitor renal function, potassium balance, and infection risk when broad ROS dampening strategies are combined [6-8,24,25].

The SIRT1/3–AMPK axis acts as a metabolic and redox integrator, synchronising mitochondrial biogenesis, autophagy, and antioxidant gene expression. Caloric excess, physical inactivity, and chronic oxidative load down-regulate this signalling cascade, weakening mitophagy and insulin sensitivity while accelerating endothelial ageing. Interventions that restore AMPK tone—such as structured exercise, caloric patterning, and metformin therapy—simultaneously reinforce SIRT-dependent stress resistance and mitochondrial quality control. Emerging nutraceuticals (resveratrol, NAD^+ precursors) may provide adjunctive activation, though evidence remains translational; individualisation and safety monitoring are

warranted in frail or multimorbid populations.

The mTOR–GSK3β–NF-κB axis represents a proteostasis-inflammation triad linking anabolic signalling with autophagy control and immune activation. Under physiological conditions, mTOR balances protein synthesis and autophagic recycling, while GSK3β and NF-κB integrate metabolic and inflammatory cues. Chronic hyperactivation of this pathway sustains insulin resistance, lipotoxicity, and neuroinflammation, driving progression of metabolic and neurodegenerative disorders. Therapeutic modulation relies on upstream redox correction through AMPK, SIRT, and NRF2 activation, which indirectly restores autophagic flux and limits inflammatory amplification. Pharmacologic mTOR or GSK3β inhibitors remain largely investigational; clinical translation will require precision timing to avoid over-suppression of proteostasis and immune defence.

Pharmacotherapeutic translation

Shared consequences across organ systems

Endothelial dysfunction → micro/macrovascular complications.

Impaired mitochondrial turnover → tissue-specific fatigue and injury.

Neuroinflammation → cognitive and motor decline.

Altered drug metabolism (CYP and phase II enzymes) → variable pharmacokinetics in polypharmacy.

Pharmacist-anchored applications

Identify redox-high-risk phenotypes (age > 70 yr, CKD < 45 mL/min/1.73 m², polypharmacy ≥ 8 drugs).

Integrate damage + defence panels (8-oxo-dG, F_2-isoprostanes, protein carbonyls ± SOD/GPx/CAT).

Link biomarker Δ-changes (≥ 20–30 % over 4–8 weeks) to therapy adjustment via EHR CDS rules.

Code interventions using PCNE v9.1 (problem–cause–intervention–outcome) and STOPP/START v3 for transparency and reproducibility.

Visual schematic

Conceptual integration

Metabolic, inflammatory, and ischemic inputs converge on four principal redox hubs—NRF2/KEAP1, NOX2, SIRT/AMPK, and mTOR–GSK3β–NF-κB—that collectively determine cellular resilience or injury [2,3,7,9-11,24,33-36].

Upstream inputs: nutrient overload, chronic inflammation, or ischemia activate overlapping stress circuits that amplify mitochondrial and enzymatic ROS production [2,3,9,24].

Regulatory responses: **NRF2/KEAP1** ↓ → loss of cytoprotection, reduced ARE-driven detoxication, and impaired mitochondrial quality control.

NOX2 ↑ → oxidative amplification via microglial, endothelial, and renal ROS generation.

SIRT/AMPK ↓ → energy deficit, suppressed mitophagy, and increased mitochondrial leakage.

mTOR–GSK3β–NF-κB ↑ → proteostatic stress, chronic inflammation, and insulin-resistance signalling.

Downstream outputs: endothelial dysfunction, neuroinflammation, tissue injury, and pharmacotherapy-response variability. These nodes form a unifying mechanistic scaffold that links metabolic and neurological disorders and provides actionable leverage points for pharmacist-led interventions.

Pharmacist leverage points

Integration of redox monitoring with medication review enables biomarker-based surveillance, optimisation, deprescribing, and EHR-linked feedback.

These relationships are synthesized in Figure 4, which consolidates the four principal redox hubs (NRF2/KEAP1, NOX2, SIRT/AMPK, and mTOR–GSK3β–NF-κB) and maps pharmacist leverage points to EHR-linked clinical decision support.

Therapeutic strategies and drug development

Translational update

Translational progress in redox-modulating pharmacotherapy has expanded across several mechanistic domains, including NOX inhibition, NAD^+/sirtuin restoration, and NRF2 activation.

Table 3: Medication classes with pro-oxidant or cognition-worsening potential in neurodegeneration, and pharmacist actions.5,10,11,24,27-36

Class / examples	Mechanistic concern (redox/cognition)	Typical clinical signal(s)	Pharmacist action (PCNE v9.1 / STOPP–START v3)
Strong anticholinergics (oxybutynin, solifenacin; TCAs; first-gen antihistamines; benztropine, trihexyphenidyl)	↑ ACB; cholinergic antagonism worsens attention/memory; sleep disruption → inflammatory priming	Cognitive decline, delirium, falls, constipation, urinary retention	Deprescribe/substitute (β3-agonist for OAB; SSRI/SNRI for depression; 2nd-gen antihistamine). Record ACB and follow Δ after change.10,11,24
Sedative-hypnotics/ benzodiazepines/Z-drugs	Sleep architecture disruption; inactivity → ↑ redox load	Daytime somnolence, falls, paradoxical agitation	Taper**;** use CBT-I/sleep hygiene; consider melatonin. Monitor cognition/falls; revisit need.10,11,24
Dopamine agonists (pramipexole, ropinirole, rotigotine)	Autonomic dysregulation; ICDs; possible oxidative stress via sleep/behavioural disruption	Orthostasis, sleep attacks, ICDs	Dose review/switch toward levodopa-dominant regimens; screen ICDs; educate caregivers.27-30,32-36
Typical antipsychotics; high-ACB atypicals	Worsen parkinsonism; anticholinergic load; metabolic stress	Motor worsening, cognitive decline	Prefer pimavanserin or cautious quetiapine/clozapine; avoid haloperidol; minimise ACB.28-32,36
Peripheral antimuscarinics (bladder/GI)	Added ACB; constipation/retention; sleep disruption	Confusion, constipation, urinary retention	Switch to β3-agonists; non-pharm strategies; reassess falls and sleep.10,11,24
First-gen antihistamines (OTC)	Central anticholinergic effects; sedation	Confusion, imbalance	Replace with non-sedating antihistamines; caregiver counselling re OTC risks.10,11,24
Corticosteroids (chronic/high dose)	Mood/cognition effects; metabolic and oxidative stress	Agitation, insomnia, hyperglycaemia	Use lowest effective dose; avoid evening dosing; watch GV spikes; taper when possible.5,24
Valproate (selected indications)	Mitochondrial stress; carnitine depletion; hepatotoxicity	Lethargy, encephalopathy, ↑ LFTs	Consider alternatives; monitor LFT**s**, ammonia if encephalopathy; consider carnitine in risk profiles.5,11,24

Table 4: Pharmacist intervention domains.2,3,6,9,11,12,18-20,26 Pharmacist implementation: integrate redox-hub knowledge into medication reviews (PCNE v9.1) and STOPP/START v3 deprescribing logic.

Target / program	Representative agent(s)	Development status (2023–2025)	Translational and pharmacy notes
NOX1/4 inhibition	*Setanaxib (GKT137831)*	Phase 2 data in fibrotic and cholestatic liver disease6,26	First-in-class NOX inhibitor with human efficacy signals; limited CNS penetration. Suggests indirect cardiovascular/neural benefit via reduced ROS flux.
Pan-NOX inhibition	*APX-115*	Phase 2 renal and AKI studies6	Expands NOX strategy to nephrovascular domains; monitoring of eGFR and oxidative markers advised.
NOX2-selective inhibition	*GSK2795039 (preclinical)*	No confirmed human efficacy6,26	Mechanistically promising for microglial activation but limited translation; keep as research-level context.
NAD^+ augmentation → Sirtuin activation	*NR, NMN (NAD^+ precursors)*	Multiple randomised trials show increased intracellular NAD^+12,19,20	Confirms biological target engagement; pharmacist implication: monitor redox panels (8-oxo-dG, F_2-IsoPs, SOD/GPx/CAT) and glycaemic response.
SIRT1 activation (direct)	*SRT2104*	Phase 2 updates across metabolic and neurodegenerative models18	Prototype direct sirtuin activator with acceptable safety; potential synergy with AMPK and NRF2 pathways.
NRF2 activation	*Fumarates, sulforaphane, triterpenoids*	Approved/clinical use in multiple chronic disorders2,3,9	Supports cytoprotective detoxication; context-dependent dosing; pharmacovigilance for hepatic induction effects.

Table 5. Operational reference ranges and risk-stratification thresholds for oxidative-stress biomarkers.10,11,21,24 Concordant elevation of two or more oxidative-damage markers or discordance between damage and defence (e.g., elevated 8-oxo-dG + low SOD/GPx) denotes *high composite redox risk*. A longitudinal Δ-change ≥ 20–30 % within the same matrix and analytical method constitutes a clinically meaningful shift warranting therapy review.10,11,24

Biomarker	Controlled	Moderate risk	High risk	Matrix / Units	Key interpretive domain
8-oxo-2′-deoxyguanosine (8-oxo-dG)	≤ 2.0	2.1 – 4.9	≥ 5.0	Urine (nmol/mmol Cr)	DNA oxidation index
F_2-isoprostanes (8-iso-$PGF_2\alpha$)	≤ 0.30	0.31 – 0.80	≥ 0.81	Urine (ng/mg Cr)	Lipid peroxidation marker
Malondialdehyde (MDA)	≤ 1.5	1.6 – 2.5	≥ 2.6	Plasma (µmol/L)	Lipid peroxidation / secondary oxidation
Protein carbonyls	≤ 0.80	0.81 – 1.20	≥ 1.21	Serum / Plasma (nmol/mg protein)	Protein oxidation load
SOD / GPx / CAT activities	Within LLN–ULN	Mild decline (↓ < 20 %)	Marked decline (↓ ≥ 20 %)	Erythrocytes / Plasma (U/mg protein)	Enzymatic antioxidant capacity

Abbreviations: AKI – Acute kidney injury: sudden decline in renal function requiring oxidative-stress monitoring and dose adjustment.; AMPK – AMP-activated protein kinase: central metabolic and redox-sensing enzyme that promotes mitochondrial biogenesis and inhibits mTOR-driven anabolic stress.; CNS – Central nervous system: target site for neuroprotective redox modulation (relevant to NOX2, SIRT1/3, and NRF2 pathways).; eGFR – Estimated glomerular filtration rate: indicator of renal function used for redox risk stratification and dose adjustment.; F_2-IsoPs – F_2-isoprostanes: lipid-peroxidation biomarkers reflecting systemic oxidative damage.; GPx – Glutathione peroxidase: selenium-dependent antioxidant enzyme reducing hydrogen and lipid peroxides using GSH.; GSH – Glutathione: tripeptide antioxidant that maintains redox balance and detoxifies reactive species.; MDA – Malondialdehyde: secondary product of lipid peroxidation; marker of oxidative stress intensity.; NF-κB – Nuclear factor kappa-light-chain-enhancer of activated B cells: transcription factor controlling pro-inflammatory and stress-response genes. NOX – NADPH oxidase: enzyme family (NOX1/2/4) producing superoxide and hydrogen peroxide as signalling or damaging species.; NR – Nicotinamide riboside: NAD^+ precursor enhancing sirtuin activity and mitochondrial resilience.; NRF2 – Nuclear factor erythroid 2–related factor 2: master regulator of antioxidant and cytoprotective gene expression.; NMN – Nicotinamide mononucleotide: NAD^+ precursor involved in sirtuin activation and metabolic regulation.; ROS – Reactive oxygen species: collectively denotes oxidants such as superoxide, hydrogen peroxide, and hydroxyl radicals.; SIRT – Sirtuin: NAD^+-dependent deacetylases (SIRT1/3) regulating mitochondrial metabolism, inflammation, and

NOX-directed modulation—primarily targeting NOX1/2/4 isoforms—remains supported by mechanistic and early translational evidence, highlighting tissue-specific roles in vascular, renal, and neural oxidative injury. Proof-of-concept studies demonstrate biochemical signal attenuation and endothelial benefit, though indication-specific translation and long-term safety are still under investigation.

NAD^+/SIRT-axis interventions show consistent evidence of target engagement in humans, with oral nicotinamide riboside (NR) or nicotinamide mononucleotide (NMN) supplementation producing measurable increases in intracellular and extracellular-vesicle NAD^+ pools across metabolic and neurological contexts. These findings confirm the pharmacologic feasibility of restoring sirtuin cofactor availability and mitochondrial resilience, supporting further exploration in multimorbid populations [12,19,20].

NRF2 activation—via fumarates, sulforaphane, or triterpenoid derivatives—remains the most clinically validated cytoprotective strategy, enhancing antioxidant and detoxication pathways while modulating inflammatory tone and phase-II metabolism.

Collectively, these translational signals establish the three hubs—NOX, NAD^+/SIRT, and NRF2—as convergent, druggable axes for redox-targeted pharmacotherapy. Their mechanistic complementarity underpins the pharmacist-led framework for biomarker-anchored monitoring, medication review, and deprescribing detailed in subsequent sections.

longevity signalling.; SOD – Superoxide dismutase: enzyme converting superoxide radicals into hydrogen peroxide, key in antioxidant defence.

Clinical-pharmacy translation

Emerging redox-modulating therapies emphasise the pharmacist's role in biomarker-anchored pharmacovigilance and drug-therapy optimization:

Monitoring

Implement combined "damage + defence" panels (8-oxo-dG, F_2-isoprostanes/MDA; SOD/GPx/CAT ± TAC) with contextual labs (eGFR, HbA1c, lipids, CRP).

Medication review

Adjust or substitute pro-oxidant drugs (e.g., catecholaminergics, corticosteroids, mitochondrial toxicants) when biomarkers indicate high redox risk.

Dynamic reassessment

Interpret Δ-changes ≥ 20–30 % across 4–8 weeks as clinically meaningful for therapy escalation or deprescribing.

Documentation

Encode all actions using PCNE v9.1 (problem–cause–intervention–outcome) and STOPP/START v3, embedded within EHR-linked CDS modules to ensure transparency and auditability.

Biomarker-guided clinical translation

The operationalisation of pharmacist-led redox monitoring integrates quantitative biomarker assessment with structured clinical decision support (CDS). A baseline composite panel capturing oxidative-damage and antioxidant-defence indices enables dynamic risk stratification, serial reassessment, and intervention tracking within the electronic health record (EHR). Longitudinal interpretation is anchored to intra-individual change (Δ ≥ 20–30 %), regarded as clinically meaningful in redox pharmacovigilance.

Pre-analytical and analytical standards

Methodological stringency is indispensable for interpretive validity.

Specimen integrity: Matrices (urine, plasma, serum) must be explicitly documented, with urine indices normalised to creatinine (nmol/mmol Cr; ng/mg Cr). Fasting or time-standardised sampling is recommended to limit metabolic noise.

Handling and storage: Immediate cooling and −80 °C preservation are mandatory for LC–MS/MS-quantified biomarkers; repeated freeze–thaw cycles must be avoided.

Analytical fidelity: Liquid chromatography–tandem mass spectrometry (LC–MS/MS) remains the reference method for 8-oxo-2′-deoxyguanosine (8-oxo-dG) and F_2-isoprostanes; laboratories should disclose method-specific reference intervals and coefficients of variation.

Core biomarker panel and contextual laboratories

Oxidative-damage markers: urinary or plasma 8-oxo-dG/8-OHdG, F_2-isoprostanes (e.g., 8-iso-$PGF_2\alpha$), malondialdehyde (MDA), and protein carbonyls provide complementary readouts of nucleic-acid, lipid, and protein oxidation.

Antioxidant-defence markers: erythrocyte or plasma superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) activities, supplemented by total antioxidant capacity (TAC).

Contextual biochemical indices: eGFR, hepatic-function panel, C-reactive protein (CRP/hsCRP), HbA1c, and fasting lipid profile are integral for pharmacotherapeutic interpretation and dose adjustment.

Operational thresholds and longitudinal interpretation

Quantitative cut-offs represent pragmatic anchors for clinical risk stratification and pharmacovigilance. Laboratories should verify transferability according to assay precision, recovery rate, and analytical bias.

Abbreviations: CAT – Catalase; Cr – Creatinine; F_2-IsoPs – F_2-isoprostanes; GPx – Glutathione peroxidase; LLN/ULN – Lower/Upper limit of normal; MDA – Malondialdehyde; SOD – Superoxide dismutase.

Analytical caveat: Values represent operational cut-offs reported in human redox-monitoring literature; laboratories must establish matrix- and method-specific reference ranges.

Pharmacist decision algorithm (PCNE v9.1 / STOPP–START v3)

Baseline documentation – capture complete redox panel, contextual labs, and pharmacotherapy list within EHR metadata fields.[10,11,24]

Risk stratification – classify the patient's *Redox Risk Stratum* (Controlled/Moderate/ High) using operational cut-offs and serial reproducibility criteria.

Medication review – identify pro-oxidant liabilities (agents with high anticholinergic burden, chronic corticosteroids, catecholaminergics, mitochondrial toxicants) and drug–disease mismatches (e.g., renally cleared oxidative stress-prone agents in CKD).

Targeted intervention

Step-up: intensify metabolic control (glycaemic variability, lipids, BP), reinforce NRF2-aligned dietary patterns, and consider NAD^+/sirtuin restoration where evidence supports benefit.

Deprescribe/switch: replace strong anticholinergics or sedative-hypnotics with cognitively safe alternatives (e.g., β_3-agonists, non-pharmacologic sleep interventions).

Re-assessment – repeat panel at 4–8 weeks; interpret Δ ≥ 20–30 % to adjudicate efficacy, toxicity, or futility, and modify therapy accordingly.

Documentation and feedback loop – encode each action using PCNE v9.1 (problem–cause–intervention–outcome) and STOPP/START v3 criteria; activate CDS triggers for follow-up intervals and automated alerts.

Redox-guided medication-review workflow

Figure 5 summarises the pharmacist-led redox-guided workflow, linking biomarker data with therapy optimisation and follow-up. By aligning laboratory signals (8-oxo-dG, F_2-isoprostanes, MDA, protein carbonyls) with cognitive pharmacy actions (monitoring, optimisation, deprescribing, and documentation), the model operationalises precision pharmacotherapy and establishes a reproducible template for integration into digital CDS environments.

Quality and safety considerations

Interpretive caution is required when damage and defence indices diverge; trend direction and clinical phenotype should guide

decision-making rather than isolated absolute values.[10,11,24] In patients with CKD, NAFLD, or frailty, lower thresholds for intervention are appropriate, with vigilant review of drug–lab interferences and organ-function-based dosing. Evidence from NAD^+/sirtuin human trials confirms biological target engagement yet underscores the necessity of biomarker-anchored, indication-specific implementation.[9-11,24,36]

Implementation metrics

List 3 measurable outcomes: (1) Resolved DRPs/100 patients; (2) Concordance between biomarker improvement and therapy optimisation; (3) Documentation completeness in EHR ≥ 95 %.

Clinical pharmacy implications

Medication review & optimisation

Clinical pharmacists should conduct structured medication reviews integrating pharmacodynamic and pharmacokinetic principles, renal/hepatic function, and interaction screening. Redox status and oxidative-stress markers (when available) can complement traditional parameters (e.g., HbA1c, eGFR, lipid profile) to guide therapeutic optimisation, particularly in multimorbid or polypharmacy patients. Applying PCNE v9.1 and STOPP/START v3 criteria enables identification of drug-related problems (DRPs) such as therapeutic duplications, suboptimal dosing, or inappropriate continuation of pro-oxidant agents (e.g., chronic NSAID use, high-dose statins). Deprescribing and substitution with antioxidant-supportive alternatives should be systematically considered [10,11,24,37-40].

Patient counselling

Patient education should emphasise adherence to both pharmacologic and non-pharmacologic measures targeting redox balance—dietary antioxidants, physical activity, and avoidance of tobacco or alcohol excess [2,3,9-11]. Pharmacists must communicate the rationale behind medication changes, expected benefits, and monitoring parameters in accessible language. When novel biomarkers or digital tools (e.g., redox panels, clinical decision support systems) are implemented, patients should be informed about their role in personalised therapy optimization.

Safety monitoring

Continuous pharmacovigilance and biomarker-guided safety monitoring are crucial. Pharmacists should proactively monitor for drug-induced oxidative burden (e.g., from certain antipsychotics, chemotherapeutics, or antivirals) and anticipate adverse effects in vulnerable populations (elderly, renal impairment, malnourished). Integration of safety dashboards within EHRs (e.g., CRPP/eRecept) can facilitate early signal detection and follow-up documentation.[9] Collaboration with prescribers ensures timely dose adjustments or therapy discontinuation in case of cumulative toxicity.

Research and quality improvement

Future studies should evaluate the correlation between biomarker-guided pharmacist interventions and hard outcomes such as rehospitalisation rate, therapy persistence, and cost-offset. Clinical pharmacists should lead or co-develop prospective studies evaluating the clinical utility of redox-guided medication review frameworks.[37-40] Quality improvement initiatives can benchmark DRP resolution rates, adherence outcomes, or hospital readmissions before and after pharmacist-led interventions. Implementation research should explore interoperability between redox analytics, clinical decision support, and EHR systems to enable seamless pharmaceutical care and generate real-world evidence for national and international guideline refinement.

Challenges and future perspectives

Challenges and opportunities

The proposed redox-guided medication review (RG-MR) framework operationalises an additional clinical signal—oxidative-stress (OS) biology—alongside standard pharmacotherapy review (renal/hepatic function, interactions, adherence, indications). Its principal opportunity lies in targeted optimisation in multimorbidity and polypharmacy, where subtle redox-linked toxicities (endothelial dysfunction, mitochondrial stress) may amplify adverse outcomes and reduce treatment durability. Future pharmacist-led trials should prospectively evaluate the clinical and economic impact of the RG-MR framework, tracking DRP resolution, adherence, hospitalisation, and biomarker–outcome correlation. Validation across multimorbid populations will establish redox-guided pharmacotherapy as a measurable quality indicator in precision clinical pharmacy.

A second opportunity is methodological rigour: RG-MR embeds established PCNE and STOPP/START frameworks, preserving reproducibility and auditability. Using these scaffolds preserves reproducibility, comparability, and auditability across settings and populations. In geriatric care specifically, the expanded STOPP/START v3 set (133 STOPP and 57 START criteria) improves signal detection for inappropriate exposure and omission, enabling pharmacists to translate redox-relevant risk into concrete actions (dose reduction, substitution, monitoring).

The principal challenges are (i) biomarker validity and standardisation, (ii) workflow integration, and (iii) evidence translation. (i) OS biomarkers vary by assay, pre-analytics, and matrix; without harmonised cut-offs and external quality assessment, spurious positives or site-specific thresholds may drive inconsistent recommendations. Caution is warranted given recent critiques of OS markers' reliability outside controlled research, underscoring the need for method validation and context-specific interpretation [10,11,21]. (ii) Integration requires interoperable data plumbing (terminologies, LOINC mapping, EHR ingestion, decision-support surfaces) and role-based documentation within clinical systems; where national infrastructures (e.g., CRPP/eZdravje; soon EHDS-compatible primary/secondary-use rails) exist, RG-MR can be surfaced as templated CDS with audit trails, outcome dashboards, and DRP loop-closure. (iii) Translation demands prospective, pharmacist-led studies that quantify *incremental* value over current best practice: reduction of ADEs, hospitalisations, and total cost of care; improved patient-reported outcomes; and durability of disease control. Pragmatic designs with stepped-wedge or cluster randomization within hospital and ambulatory networks are feasible, particularly when coupled to real-world data access under EHDS secondary-use governance [8-10,24].

In short, RG-MR should be positioned as a contextual enhancer of the medication-review stack—not a stand-alone trigger—

prioritising validated markers, conservative thresholds, and explicit linkage to PCNE/STOPP-START actions with measurable outcomes.

SANRA alignment and limitations

This review adheres to SANRA criteria—explicit rationale, comprehensive literature search, transparent selection, critical appraisal, and justified conclusions [24,39]. Limitations include publication bias, heterogeneity of biomarker methods, and lack of RCT-level validation for several oxidative-stress indices [9-11,21].

Link to pharmacogenomics and precision medicine

RG-MR is naturally complementary to pharmacogenomics (PGx) and broader precision-medicine initiatives. CPIC publishes drug-gene guidelines with graded, implementable recommendations that convert genotype to prescribing actions (dose, drug choice).[11-13] Embedding CPIC-based PGx phenotypes (e.g., CYP2D6, CYP2C19, NAT2) alongside OS phenotypes allows bi-axis personalisation: PGx addresses *inherited* variability in exposure/response, while RG-MR addresses *acquired* redox vulnerability (inflammation, multimorbidity, frailty). In practice, combined PGx + OS dashboards can (a) pre-empt exposure-related toxicities (e.g., poor metabolisers plus pro-oxidant co-therapy), (b) set adaptive monitoring plans, and (c) guide deprescribing/re-sequencing strategies. The European Health Data Space (EHDS), adopted in February 2025 and entering into force in March 2025, establishes legal and technical rails for cross-border access and secondary use of electronic health data, creating a favourable environment for multi-site pharmacist-led learning health systems that fuse lab/PGx/clinical outcomes into iteratively improving RG-MR/PGx algorithms [8,9,24].

Limitations

Short, distinct; bullets for clarity.

Analytical heterogeneity of OS assays: pre-analytical variability, assay platforms, and lack of universally accepted clinical cut-offs limit external validity and portability across sites [10,11,21].

Attribution bias: OS abnormalities are often non-specific; causal assignment to a single medicine versus comorbidity or lifestyle factor can be uncertain without longitudinal triangulation.

Evidence maturity: high-quality, prospective trials isolating the *incremental* contribution of RG-MR over standard review are limited; most data are associative or disease-specific.

Operational burden: additional lab panels, CDS configuration, and staff training increase initial workload; benefits depend on EHR interoperability and governance readiness (e.g., EHDS implementing acts).

Generalizability: findings may not extrapolate to low-resource settings or populations with distinct exposure patterns or assay availability.

Future directions

The integration of redox-guided medication review (RG-MR) into clinical workflows represents a transitional phase between evidence generation and evidence implementation. Future research must move beyond associative biochemistry toward interventional validation—demonstrating that incorporating redox parameters into pharmacist-led medication reviews produces measurable gains in safety, quality of life, and cost-effectiveness. Pragmatic, multicenter trials embedded within EHR infrastructures (e.g., CRPP/eZdravje, EHDS primary- and secondary-use domains) can supply the real-world evidence required for policy endorsement [1415,16].

Technically, RG-MR will advance through convergence with AI-enabled decision support and federated analytics. Integrating machine-learning classifiers trained on longitudinal OS and pharmacotherapy datasets could facilitate adaptive risk stratification and automated prioritisation of high-risk medication clusters. Interoperability with EHDS-compliant architectures and controlled terminologies (LOINC, SNOMED CT, ATC) will ensure cross-border data portability and reproducible digital phenotyping for pharmacovigilance and precision therapeutics.

Strategically, progress depends on co-development among clinical pharmacists, clinical chemists, bioinformaticians, and policymakers to establish clinical-grade reference intervals, validated pre-analytical SOPs, and cost–benefit thresholds for reimbursement (e.g., ZZZS, NHS, EU HTA). Educational alignment is equally critical: postgraduate pharmacy curricula should incorporate structured modules on redox biomarkers and data interpretation, aligning with competencies defined by the European Association of Hospital Pharmacists (EAHP) and FIP Global Competency Framework.

In summary, RG-MR can evolve from a conceptual academic model into a mainstream precision-pharmacy instrument, synergising with pharmacogenomics and advancing the European Health Data Space vision of interoperable, learning health systems that strengthen medication safety and patient-centred outcomes [15,16,21].

CONCLUSION

The proposed redox-guided medication review (RG-MR) framework integrates oxidative-stress biology into clinical decision-making, reinforcing pharmacists' role in risk stratification, deprescribing, and personalised therapy optimization. By aligning biochemical insights with validated clinical-pharmacy tools (PCNE v9.1, STOPP/START v3) and interoperable digital infrastructures (CRPP, eRecept, EHDS), RG-MR offers a practical pathway to improve medication safety, therapeutic precision, and system sustainability. Prospective validation will determine its incremental impact on patient outcomes and healthcare efficiency.

Risk of bias and methodological quality were narratively appraised according to a study-design hierarchy (basic → translational → clinical), internal validity, and reproducibility of redox-related endpoints. Evidential weight was assigned based on methodological transparency, sample size, and biomarker standardisation, in alignment with the SANRA quality criteria[37,38] and the *International Journal of Therapeutic Innovation* author and reporting guidelines (2024).

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Conflicts of interest

The author declares no conflicts of interest relevant to this work.

Author contributions

The author used ChatGPT (OpenAI, GPT-5) for language-level editing only; all scientific content, analyses, figures, and tables were conceived and verified by the author. The author conceptualized the review, performed the literature search and data synthesis, created all figures and tables, and drafted and revised the manuscript.

Ethical approval

Not applicable – this narrative review is based exclusively on previously published, peer-reviewed literature and did not involve any human or animal participants, in accordance with the International Journal of Therapeutic Innovation author and ethical publishing guidelines (2024).

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