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ORIGINAL

Paraquat Poisoning: Current Advances in Pathophysiology, Diagnostic Biomarkers, and Evidence-Based Management Protocols

Intoxicación por paraquat: avances actuales en fisiopatología, biomarcadores diagnósticos y protocolos de manejo basados en la evidencia

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ABSTRACT

Introduction: Paraquat (1,1'-dimethyl-4,4'-bipyridinium dichloride), a widely used herbicide with high human lethality due to its redox cycling, generating reactive oxygen species that induce irreversible multi-organ failure and pulmonary fibrosis. Despite known mechanisms, clinical management remains challenging and mortality exceeds 60%. This systematic review synthesizes global evidence on paraquat toxicity mechanisms, prognostic biomarkers, therapeutic interventions, and public health policies to guide clinical practice and regulatory decision-making. Methods: Following PRISMA guidelines, PubMed, MEDLINE, Embase, Scopus, Web of Science, and WHO IRIS were searched till January 2026. Studies on pathophysiology, diagnostics, treatments, and policy were narratively evaluated. Results: From 1,842 identified studies, 39 met inclusion criteria. Pathophysiologically, cellular uptake via polyamine transporters drives mitochondrial electron leakage, p38 MAPK/NF-□B inflammatory signaling, and TGF-□-mediated interstitial fibrosis. While plasma nomograms and lactate levels reliably predict mortality, targeted therapies show variable success. Randomized controlled trial evidence refutes high-dose immunosuppression benefits, whereas early hemoperfusion (under 4 hours) and restrictive oxygen therapy demonstrate clinical utility. Public health bans in Sri Lanka, South Korea, and Taiwan yielded a 40–50% reduction in pesticide suicides without harming agricultural yields. Conclusion: Prognostic biomarkers accurately identify severe exposures, yet proven clinical treatments remain limited beyond early extracorporeal clearance and restrictive oxygenation. National regulatory restriction stands as the single most effective, evidence-based intervention to prevent paraquat-related fatalities worldwide.

Keywords: Paraquat poisoning, redox cycling, pulmonary fibrosis, hemoperfusion, pesticide regulation.

RESUMEN

Introducción: El paraquat (dicloruro de 1,1'-dimetil-4,4'-bipiridinio), un herbicida ampliamente utilizado con alta letalidad humana debido a su ciclo redox, genera especies reactivas de oxígeno que inducen insuficiencia multiorgánica irreversible y fibrosis pulmonar. A pesar de conocerse sus mecanismos, su manejo clínico sigue siendo complejo y la mortalidad supera el 60%. Esta revisión sistemática sintetiza la evidencia global sobre los mecanismos de toxicidad del paraquat, los biomarcadores pronósticos, las intervenciones terapéuticas y las políticas de salud pública para orientar la práctica clínica y la toma de decisiones regulatorias. Métodos: Siguiendo las directrices PRISMA, se realizaron búsquedas en PubMed, MEDLINE, Embase, Scopus, Web of Science y WHO IRIS hasta enero de 2026. Se evaluaron de forma narrativa los estudios sobre fisiopatología, diagnóstico, tratamientos y políticas. Resultados: De 1842 estudios identificados, 39 cumplieron los criterios de inclusión. Desde el punto de vista fisiopatológico, la captación celular a través de transportadores de poliaminas impulsa la fuga de electrones mitocondriales, la señalización inflamatoria p38 MAPK/NF-□B y la fibrosis intersticial mediada por TGF-□. Si bien los nomogramas plasmáticos y los niveles de lactato predicen de forma fiable la mortalidad, las terapias dirigidas muestran un éxito variable. La evidencia de ensayos controlados aleatorizados refuta los beneficios de la inmunosupresión en dosis altas, mientras que la hemoperfusión temprana (en menos de 4 horas) y la oxigenoterapia restrictiva demuestran utilidad clínica. Las prohibiciones de salud pública en Sri Lanka, Corea del Sur y Taiwán lograron una reducción del 40-50% en los suicidios por plaguicidas sin perjudicar los rendimientos agrícolas. Conclusión: Los biomarcadores pronósticos identifican con precisión las exposiciones graves, pero los tratamientos clínicos probados siguen siendo limitados más allá de la eliminación extracorpórea temprana y la oxigenación restrictiva. La restricción regulatoria nacional constituye la intervención más eficaz y basada en la evidencia para prevenir las muertes relacionadas con el paraquat en todo el mundo.

Palabras clave: Intoxicación por paraquat, ciclo redox, fibrosis pulmonar, hemoperfusión, regulación de plaguicidas.

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INTRODUCTION

Paraquat (1,1'-dimethyl-4,4'-bipyridinium dichloride) stands as one of the most widely employed herbicides globally, yet its remarkable efficacy in agricultural weed control is tragically counterbalanced by its extraordinary lethality in humans following accidental or intentional ingestion.1 The compound's essential toxicity stems from its unique ability to undergo redox cycling within cells, generating massive quantities of reactive oxygen species that overwhelm endogenous antioxidant defenses.2 This mechanism, while devastating to multiple organ systems, exhibits particular predilection for pulmonary tissue where paraquat accumulates through polyamine transport systems, leading to the characteristic biphasic clinical picture of acute lung injury followed by progressive and often fatal pulmonary fibrosis.3 Despite decades of research and clinical experience, paraquat poisoning remains a formidable clinical challenge with mortality rates exceeding 60% in severe cases, particularly when patients present late or consume concentrated formulations.4

The pathophysiological cascade initiated by paraquat begins at the cellular level, where the compound's structural similarity to polyamines facilitates its uptake into type I and type II alveolar epithelial cells via energy-dependent transport mechanisms.5 Once internalized, paraquat accepts electrons from NADPH-dependent reductases, generating the highly reactive paraquat radical that subsequently reduces molecular oxygen to superoxide anion, initiating a self-perpetuating cycle of oxidative damage.[6] This redox cycling depletes cellular NADPH reserves, compromises mitochondrial function, and triggers lipid peroxidation of cellular membranes, ultimately culminating in cell death through both necrotic and apoptotic pathways.[7] The inflammatory response that follows further amplifies tissue injury through recruitment of neutrophils and macrophages, release of pro-inflammatory cytokines including tumor necrosis factor-alpha and interleukin-6, and induction of transforming growth factor-beta, which drives fibroblast proliferation and collagen deposition in the pulmonary interstitium.[8] Notably, the severity and temporal evolution of these processes exhibit considerable inter-individual variability, suggesting that host genetic factors, nutritional status, and co-ingested substances may modulate the toxicodynamic profile.[9]

Early diagnosis and accurate prognostication represent critical determinants of clinical outcomes in paraquat poisoning, particularly given the narrow therapeutic window for effective intervention. The urine dithionite test offers a rapid, inexpensive bedside screening tool that can detect paraquat concentrations above 2 mg/L, though its qualitative nature limits its utility for precise risk stratification.[10] Quantitative plasma paraquat concentration measurements, when interpreted using established nomograms such as the Proudfoot or Sawada severity indices, provide robust prognostic information regarding the likelihood of survival versus fatal outcome.11,12 Beyond direct toxicant quantification, emerging evidence supports the prognostic value of several readily accessible laboratory parameters, including arterial lactate levels, neutrophil-to-lymphocyte ratio, serum creatinine, and arterial blood gas indices.13,14 High-resolution computed tomography scoring systems have further enhanced clinicians' ability to predict pulmonary outcomes and guide management decisions, particularly regarding the intensity of supportive care and potential candidacy for lung transplantation.[15] The integration of these diverse biomarkers into clinical decision-making algorithms represents a promising strategy for personalizing treatment intensity and optimizing resource allocation.

Therapeutic strategies for paraquat poisoning have evolved considerably over recent decades, though definitive evidence supporting specific interventions remains limited by the absence of large-scale randomized controlled trials. Initial management focuses on gastrointestinal decontamination using activated charcoal or Fuller's earth, though the efficacy of these interventions diminishes rapidly with time since ingestion and remains controversial in the absence of documented benefit from controlled studies.[16] Enhanced elimination techniques, particularly hemoperfusion and hemodialysis, aim to reduce the total body burden of paraquat, with recent evidence suggesting that early institution of treatment ideally within four hours of ingestion may confer survival advantage, though data from systematic reviews and meta-analyses demonstrate heterogeneous results.[17–19] Pharmacological approaches have targeted multiple pathways in the toxic cascade, including antioxidants such as N-acetylcysteine and vitamin C that replenish cellular glutathione stores and scavenge free radicals, immunosuppressive regimens combining pulse methylprednisolone with cyclophosphamide that attenuate the inflammatory response, and anti-fibrotic agents like pirfenidone that inhibit transforming growth factor-beta signaling and collagen synthesis.20-22 However, a landmark randomized controlled trial of high-dose immunosuppression failed to demonstrate mortality benefit, while subsequent meta-analyses have yielded conflicting conclusions, underscoring the urgent need for well-designed prospective studies.[23]

Crucially, supportive care nuances including strict oxygen restriction to avoid hyperoxia-induced exacerbation of reactive oxygen species generation represent fundamental components of management that are often underappreciated in clinical practice.[24]

Public health approaches addressing the paraquat epidemic have focused primarily on regulatory interventions that restrict access to the compound, with compelling evidence emerging from countries that have implemented national bans or severely restricted formulations. Sri Lanka's phased ban on paraquat from 2008 to 2011 resulted in an estimated 50% reduction in pesticide-related suicides, equivalent to approximately 1,000 lives saved annually, without measurable adverse impacts on agricultural productivity.25,26 Similar successes have been documented in Taiwan and South Korea following regulatory actions, with the latter experiencing a 40% decline in paraquat poisoning deaths within two years of implementing restrictions.27,28 Beyond outright bans, regulatory modifications including the incorporation of emetic agents, objectionable odorants, and distinctive colorants into commercial formulations have demonstrated effectiveness in reducing fatality rates by deterring consumption and enabling rapid identification of exposure.[29] These population-level interventions, while highly cost-effective, must be complemented by enhanced healthcare system preparedness, improved clinician education regarding evidence-based management protocols, and continued investment in translational research that can bridge the gap between mechanistic understanding and therapeutic innovation.[30]

Despite extensive studies on paraquat toxicity, significant knowledge gaps persist regarding the optimal integration of systemic understanding, diagnostic precision, therapeutic efficacy, and public health policy into cohesive clinical frameworks.16,23 While numerous studies have explored isolated components of paraquat poisoning, comprehensive evidence syntheses that critically appraise the interconnectedness between pathophysiological mechanisms, biomarker utility, treatment outcomes, and regulatory impacts remain conspicuously absent from the contemporary literature.[30] This fragmentation has contributed to considerable heterogeneity in clinical practice across different healthcare settings and geographic regions, potentially compromising patient outcomes through inconsistent application of evidence-based interventions.[26] This systematic review synthesizes current evidence regarding paraquat poisoning, focusing on four primary domains: underlying redox-driven toxicity mechanisms, bedside diagnostic and prognostic markers, human clinical trials of proposed therapeutic interventions, and the impact of national regulatory bans on public health outcomes. By critically evaluating the strength and quality of available evidence across these interconnected domains, this review aims to identify actionable insights for clinicians, highlight priority areas for future research investment, and inform evidence-based policy decisions regarding paraquat regulation and poisoning management.

METHODS

Study Design & Search Strategy

This systematic review followed the PRISMA 2020 guidelines. Because this systematic review synthesized evidence qualitatively across diverse preclinical, clinical, and policy designs rather than performing a quantitative meta-analysis, the protocol was not prospectively registered in PROSPERO.A comprehensive literature search was performed across five electronic databases: PubMed/MEDLINE, Scopus, Embase, Web of Science, and Google Scholar. The search strategy employed a combination of controlled vocabulary terms (MeSH headings where applicable) and free-text keywords, including "paraquat," "herbicide poisoning," "toxicity," "redox cycling," "reactive oxygen species," "pulmonary fibrosis," "biomarkers," "prognosis," "hemoperfusion," "hemodialysis," "continuous renal replacement therapy," "immunosuppression," "corticosteroids," "cyclophosphamide," "antioxidants," "N-acetylcysteine," "pirfenidone," and "pesticide regulation." Boolean operators (AND, OR) were used to combine search terms appropriately for each database. No lower date restriction was imposed, as several foundational prognostic tools, including the Proudfoot nomogram and the Sawada severity index, were originally published in the late 1970s and 1980s. However, to ensure clinical relevance, greater emphasis was placed on literature published within the past fifteen years for treatment outcome data, reflecting evolving clinical practices and therapeutic advances. The final search was conducted in January 2026.

Eligibility Criteria

Inclusion: Human observational studies, RCTs, systematic reviews/meta-analyses, animal/cellular studies clarifying clinical pathways, and case reports illustrating unique diagnostic or management strategies.

Exclusion: Non-English papers without translation, unpublished conference abstracts, and studies focused strictly on non-paraquat bipyridyl herbicides (like diquat) without comparative analysis.

Selection, Extraction, Quality Assessment and Risk of Bias

Data extraction was conducted by the authors, with discrepancies resolved through discussion. Studies were categorized according to design (e.g., randomized controlled trials, observational cohorts, preclinical models, and policy evaluations). Given the broad scope of the review and the high clinical and methodological heterogeneity across included studies ranging from animal models to population-level regulatory evaluations formal quantitative risk-of-bias scoring was not performed. Instead, methodological strengths, key limitations, and potential sources of bias (such as selection bias, confounding in observational cohorts, and small sample sizes) were qualitatively evaluated and contextualized within the narrative synthesis.

Omatighene E.O and Ukoba O conceived, designed, and supervised the study while leading manuscript revisions. Ukoba O, Emuoghenerue O. E, Odonmeta A. B, and Enemuwe I. M executed the search, screening, and risk-of-bias assessments. Omatighene E.O, Ukoba O and; Iboyitie I synthesized pathophysiology, biomarkers, therapeutics, and regulatory policies, respectively. All authors drafted, critically reviewed, and approved the final manuscript supervised by Obodo O. J.

Data Synthesis & Search Results

Due to expected study heterogeneity, we synthesized data narratively across four key themes: ROS dynamics and pathophysiology, Diagnostic and prognostic biomarkers, Therapeutic interventions, Prevention and global regulatory policy.

RESULTS

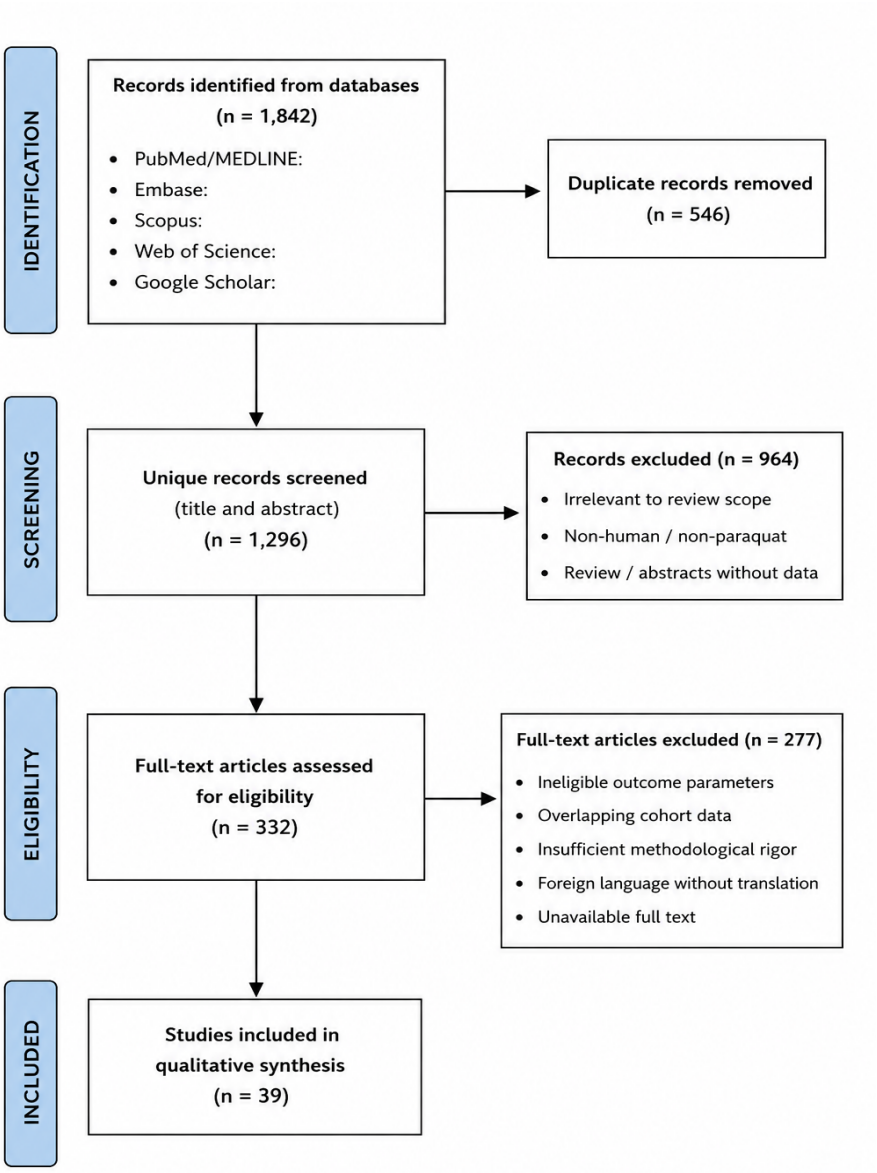
The initial database searches yielded 1,842 records. Following the removal of 546 duplicate citations, 1,296 unique records proceeded to title and abstract screening. Of these, 964 records were excluded based on irrelevance to the review's focus or failure to meet eligibility criteria. The remaining 332 full-text articles were assessed in detail, of which 39 ultimately met all inclusion criteria and were incorporated into the qualitative synthesis. A detailed flowchart depicting the study selection process is presented in Figure 1. Of the 39 included studies.

Summary Table of PRISMA Flow Parameters

PRISMA Phase	Operational Step / Source	Record Count (n)
Identification	Database search records retrieved (PubMed, Embase, Scopus, Web of Science, Google Scholar)	1,842
Identification	Duplicates removed prior to screening	546
Screening	Unique records screened via title and abstract	1,296
Screening	Records excluded based on title/abstract criteria	964
Eligibility	Full-text articles retrieved and evaluated for eligibility	332
Included	Final studies synthesized in qualitative review	39

Of the 39 sources reviewed, evidence clustered into four domains: cellular/molecular pathophysiology (n=9), diagnostic and prognostic biomarkers (n=8), therapeutic interventions (n=13), and regulatory/public-health impact (n=8), with one general overview source. Key findings within each domain are summarized in Tables 1-4 and Figure 1.

Figure 1. Reported percentage reduction in pesticide/paraquat-related suicide mortality following national regulatory restriction in Sri Lanka and South Korea.32,33,35,38,39. Comparable directionally consistent reductions were reported in Taiwan, though not expressed as a single quantified percentage in the early post-ban evaluation.37



Pathophysiological Mechanisms

Across various studies, paraquat's toxicity was consistently attributed to redox cycling: the herbicide accepts an electron from NADPH-dependent flavoenzymes to form a radical that reduces molecular oxygen to superoxide, regenerating oxidised paraquat and sustaining a self-propagating cycle of reactive oxygen species (ROS) generation.1,2 Selective pulmonary accumulation is explained by energy-dependent polyamine transporter uptake into type I and II alveolar cells.1 Mitochondria were repeatedly identified as the dominant intracellular ROS source, in both pulmonary and central nervous system tissue, with direct implications for neurotoxic as well as pulmonary phenotypes.26,28,29 Downstream, ROS-driven activation of the p38 MAPK/NF-κB axis delays neutrophil apoptosis and sustains a pro-inflammatory feedback loop (TNF-α, IL-6), which together with TGF-β-driven fibroblast activity underlies the transition from acute alveolitis to pulmonary fibrosis.7,20,27 Table 1 summarizes these pathways.

Table 1. Summary of principal pathophysiological mechanisms implicated in paraquat toxicity.

Mechanism	Key process	Principal target
Redox cycling 1,2	NADPH depletion; paraquat radical reduces O2 to superoxide	Lung, liver, kidney
Polyamine-transporter uptake 1	Energy-dependent accumulation in alveolar cells	Lung (type I/II pneumocytes)
Mitochondrial ROS production 26,28,29	Electron leak at complex I/III; ATP depletion	Lung, brain
Inflammatory amplification 7,27	Neutrophil/macrophage recruitment; delayed apoptosis; TNF-α, IL-6	Lung
Fibrotic remodeling7,20	TGF-β-driven fibroblast proliferation, collagen deposition	Pulmonary interstitium
Neurotoxicity 28, 29	Mitochondrial ROS in dopaminergic pathways	CNS / substantia nigra

Diagnostic and Prognostic Biomarkers

The urine sodium dithionite (Berridge) test remains the most widely used bedside screening tool, providing a qualitative colour-change result for urinary paraquat concentrations above approximately 2 mg/L, and correlates with outcome when combined with time since ingestion.30 Quantitative plasma paraquat concentration, plotted on time-referenced nomograms (Proudfoot, Sawada), remains the reference-standard prognostic tool, with survival probability falling sharply above defined concentration-time thresholds. 4,6,31 Comparative evaluations of severity indices found broadly concordant, though not identical, discriminatory performance between the Proudfoot and Sawada systems.7 Beyond direct toxicant quantification, several accessible laboratory indices have shown independent prognostic value: elevated arterial lactate was consistently associated with mortality in a pooled meta-analysis.10 hematological indices (including neutrophil-lymphocyte ratio) predicted outcome in a large single-centre cohort, 8 and composite early biomarker models incorporating creatinine and arterial blood gas parameters improved early mortality prediction.9

Therapeutic Interventions

Enhanced elimination via hemoperfusion showed the strongest signal for benefit when instituted early (within four hours of ingestion), with a retrospective cohort reporting improved survival with early initiation.12 However, systematic reviews evaluating hemoperfusion in combination with other modalities 13 and the efficacy of hemodialysis specifically 14 both concluded that evidence remains heterogeneous and inconclusive at a pooled level, even though individual cohorts describing early, repeated hemoperfusion combined with hemodialysis 15 and earlier timing of hemodialysis 16 reported improved prognosis. Pharmacologically, a landmark multi-centre randomized controlled trial of high-dose immunosuppression (pulse methylprednisolone and cyclophosphamide) found no mortality benefit,17 directly contrasting with earlier, smaller cohort studies that had reported improved survival with similar regimens;18,19 a systematic review preceding the RCT had already flagged the weak evidentiary basis and called for better outcome-prediction tools before firm conclusions could be drawn.20

Table 2. Diagnostic and prognostic biomarkers reported for paraquat poisoning.

Biomarker / tool	Type	Threshold / approach	Prognostic utility
Urine sodium dithionite test 30	Qualitative, bedside	Colour change; detects >2 mg/L	Rapid triage; limited quantitative precision
Plasma paraquat + Proudfoot nomogram 4,31	Quantitative	Time-referenced concentration curve	Strong predictor of survival vs. death
Sawada severity index 6,7	Quantitative	Plasma level × time since ingestion	Comparable discrimination to Proudfoot
Arterial lactate 10	Laboratory	Elevated level at presentation	Independent mortality predictor (meta-analysis)
Neutrophil-lymphocyte ratio / hematological indices 8	Laboratory	Elevated ratio	Independent predictor of in-hospital mortality
Composite early biomarkers (creatinine, ABG) 9	Laboratory panel	Multi-parameter models	Improved early risk stratification

Preclinical (animal) data continue to support antioxidant (N-acetylcysteine) and anti-fibrotic (pirfenidone) strategies, both of which reduced oxidative tissue damage and fibrosis respectively in rodent models,21,22 though neither has yet been confirmed in adequately powered human trials. Among supportive-care measures, a large multi-centre retrospective cohort found that liberal oxygen therapy was associated with increased mortality compared with a restrictive oxygen strategy, supporting oxygen restriction as a low-cost, high-value intervention.23

Regulatory and Public Health Impact

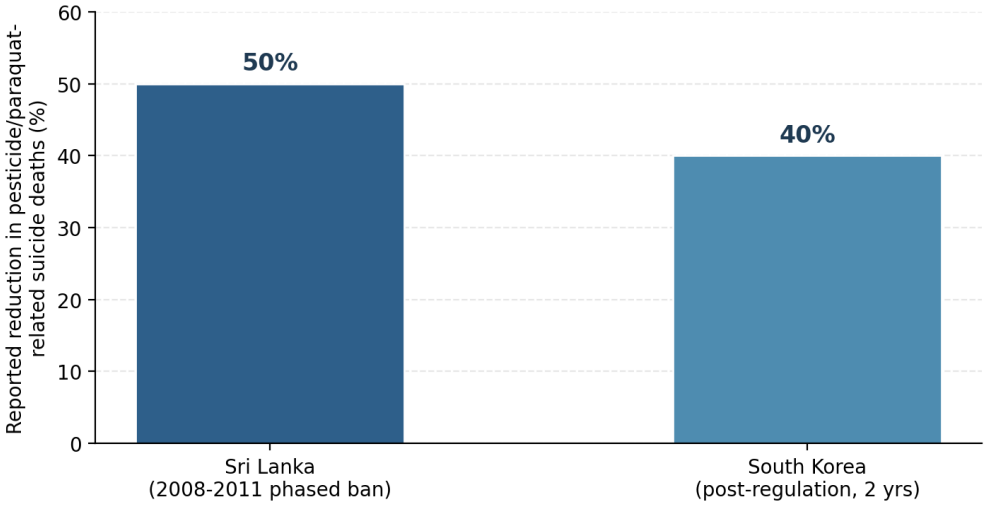
The most consistent and reproducible evidence in this review derives from population-level regulatory interventions. Sri Lanka's phased withdrawal of paraquat and other highly hazardous pesticides (2008-2011) was associated with an approximate 50% reduction in pesticide-related suicide, with parallel data confirming falling case-fatality of agricultural pesticide self-poisoning and no measurable adverse effect on agricultural yield.32,33,35,39 Comparable regulatory action in South Korea was followed by an approximate 40% decline in paraquat poisoning deaths within two years, 38 and an early post-ban evaluation in Taiwan likewise reported a reduction in paraquat-related suicide, though of smaller and less precisely quantified magnitude in the immediate post-ban period.37 A broader systematic review of restriction policies across multiple jurisdictions confirmed a consistent, replicable reduction in suicide following bans on highly hazardous pesticides,36 reinforcing means-restriction as an effective population-level suicide-prevention strategy.34

Table 3. Evidence summary for therapeutic interventions in paraquat poisoning.

Intervention	Study type	Reported outcome	Evidence direction
Early hemoperfusion (<4h) 12	Retrospective cohort	Improved survival with early initiation	Supportive
Hemoperfusion + adjunct therapies 13	Systematic review / meta-analysis	No consistent additional mortality benefit	Inconclusive
Hemodialysis 14	Systematic review / meta-analysis	Mixed survival signal	Conflicting
Repeated hemoperfusion + hemodialysis 15	Cohort study	Improved prognosis with early, repeated sessions	Supportive
Hemodialysis timing 16	Retrospective cohort	Earlier initiation linked to improved survival	Supportive
High-dose immunosuppression (RCT) 17	Randomised controlled trial	No significant mortality reduction	Refutes earlier cohorts
Pulse methylprednisolone/ cyclophosphamide/dexamethasone 18	Cohort study	Improved survival reported (pre-RCT)	Supportive (superseded)
Combined immunosuppression (oral poisoning) 19	Cohort study	Benefit reported (pre-RCT)	Supportive (superseded)
Immunosuppression for fibrosis 20	Systematic review	Insufficient evidence base	Cautionary
N-acetylcysteine 21	Preclinical (murine)	Reduced oxidative stress markers	Preclinical support only
Pirfenidone 22	Preclinical (rat)	Reduced pulmonary fibrosis	Preclinical support only
Restrictive vs. liberal oxygen therapy 23	Multi-centre retrospective cohort	Liberal oxygen associated with higher mortality	Supports restrictive approach

Table 4. Reported impact of national paraquat/pesticide regulatory restrictions on suicide and poisoning mortality.

Country / policy	Timeframe	Reported impact
Sri Lanka - phased pesticide/paraquat ban 32,33,35,39	2008-2011	~50% reduction in pesticide-related suicide; falling case-fatality; no adverse agricultural impact
South Korea - paraquat regulation 38	2 years post-regulation	~40% decline in paraquat poisoning deaths
Taiwan - paraquat ban 37	Early post-ban period	Reduction in paraquat-related suicide (magnitude smaller/less precisely quantified)
Multi-country - systematic review 34,36	Various	Consistent reduction in suicide following highly-hazardous-pesticide restriction



Discussion

This review integrated four traditionally siloed strands of paraquat literature mechanism, diagnosis, treatment, and policy and several cross-cutting patterns emerge.

Mechanistic coherence supports, but has not yet resolved, treatment targets

There is strong internal consistency across mechanistic studies that ROS generation via redox cycling and mitochondrial electron leak is the proximate driver of paraquat toxicity, 2,6,26,29, and that downstream inflammatory and fibrotic amplification (p38 MAPK/NF-κB, TGF-β) explains the delayed, progressive nature of pulmonary injury.7,20,27 This mechanistic clarity is precisely why antioxidant (N-acetylcysteine) and anti-fibrotic (pirfenidone) strategies have strong biological plausibility,21,22 however, the fact that both remain confined to animal models, while the only adequately powered human trial of an immune-pathway intervention (immunosuppression) was neutral,17 illustrates a persistent translational gap between mechanistic understanding and validated clinical benefit. A plausible explanation is that by the time inflammatory/fibrotic pathways are pharmacologically targetable in humans, irreversible mitochondrial and epithelial injury has often already occurred, narrowing the therapeutic window to hours rather than days.1,26

Diagnostic tools are prognostically strong but do not, by themselves, change outcomes

Plasma-concentration nomograms and severity indices,4,6,7,31 together with accessible laboratory adjuncts such as lactate and hematological indices,8,10 perform consistently well at predicting death versus survival. This is unsurprising, since most were derived and validated specifically for that purpose. The unresolved question and a genuine contrast within the literature is whether early identification of a poor-prognosis patient can be translated into a mortality-reducing intervention, given that the enhanced-elimination and immunosuppressive treatments applied to such patients have themselves shown inconsistent benefit.13,14,17 In other words, prognostic precision has outpaced therapeutic capability, and biomarkers currently serve counselling and resource-allocation purposes more reliably than they guide life-saving decisions.

Enhanced elimination and immunosuppression: a genuine evidentiary conflict

The clearest contrast in this review lies within the therapeutic domain itself. Single-centre cohorts consistently favour early or repeated hemoperfusion/hemodialysis,12,15,16 yet pooled systematic reviews of the same interventions find the evidence too heterogeneous to support a firm recommendation.13,14 This discrepancy likely reflects survivorship and selection bias in observational cohorts (patients well enough to reach dialysis promptly may already have a more favourable underlying prognosis), small sample sizes, and variability in poison severity, formulation, and timing across studies. Similarly, the shift from favourable pre-RCT immunosuppression cohorts 18,19 to a null multi-centre RCT 17 is a textbook example of how uncontrolled cohort data can overestimate benefit reinforcing the primacy of randomized evidence and the caution urged by the earlier systematic review on this topic.20

Supportive care and regulation: the most defensible interventions in this review

By contrast, two interventions in this review rest on comparatively strong and consistent evidence: restrictive oxygen therapy, supported by a large multi-centre cohort demonstrating harm from a liberal strategy,23 and population-level regulatory restriction, supported by concordant findings across at least three independent national settings and a cross-national systematic review.32,33,34,35,36,37,38,39 The consistency of the regulatory findings, despite differing populations, formulations, and time periods, strengthens confidence that means-restriction operates through a genuine causal mechanism reducing access to a highly lethal agent during impulsive self-poisoning acts rather than through confounding secular trends alone, a conclusion reinforced by the observation that agricultural productivity was not measurably compromised.39

Conclusion

Paraquat poisoning remains a highly lethal condition whose pathophysiology redox-cycling-driven, mitochondrially amplified oxidative injury culminating in inflammatory and fibrotic lung destruction is now well characterized. Diagnostic and prognostic tools, from the bedside dithionite test to plasma-concentration nomograms and laboratory biomarkers, reliably identify patients at high risk of death, but this prognostic strength has not yet been matched by proven mortality-reducing therapy: evidence for enhanced elimination and immunosuppression remains conflicting or, in the case of high-dose immunosuppression, has been refuted by randomized data, while antioxidant and anti-fibrotic pharmacotherapy remain preclinical. The most robust, reproducible survival benefit identified across this review is not clinical but regulatory: national restriction of paraquat access has consistently and substantially reduced poisoning mortality without documented economic harm, alongside the comparatively simple, low-cost measure of avoiding liberal oxygen supplementation.

Recommendations

The following are the recommendations from this study;

- Prioritize and expand national or regional regulatory restriction of paraquat (bans, formulation changes, or highly restricted access), given the strength and reproducibility of the public-health evidence and its favourable safety profile for agricultural output.
- Where paraquat remains available, mandate the addition of emetics, stenching agents, and distinctive colorants to commercial formulations to reduce accidental ingestion and deter deliberate self-poisoning.
- Adopt a restrictive rather than liberal oxygen-supplementation strategy in confirmed or suspected paraquat poisoning, pending further prospective confirmation.
- Reserve high-dose immunosuppression (methylprednisolone/cyclophosphamide) outside of further randomized trials, given the neutral result of the largest RCT to date.
- Where extracorporeal elimination is available, prioritize the earliest possible initiation of hemoperfusion/hemodialysis (ideally within four hours of ingestion) while acknowledging that pooled trial-level evidence for mortality benefit remains inconclusive.
- Invest in adequately powered human trials of antioxidant (N-acetylcysteine) and anti-fibrotic (pirfenidone) agents before these preclinical signals are translated into routine clinical use.
- Standardize the use of validated severity indices (Proudfoot/Sawada) and accessible laboratory adjuncts (lactate, hematological ratios) at admission to support triage, resource allocation, and patient/family counselling.
- Encourage multi-national data pooling and prospective registries to resolve the current conflict between favourable observational cohorts and neutral or inconclusive systematic reviews for enhanced-elimination and immunosuppressive therapies.

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