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REVIEW

Evaluating the Impact of Vitamins C and/or E Treatment on Paraquat-Induced Toxicity in Humans: A Frequentist-Bayesian Meta-Analysis and Brief Systematic Review

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Abstract

Background Paraquat (PQ) is a widely used herbicide with high human toxicity, frequently resulting in fatal outcomes following ingestion or dermal exposure. Despite available treatments, including gastric lavage and antioxidants, mortality rates remain alarmingly high.

Objective To systematically review and meta-analyze the available evidence on the impact of vitamins C and/or E therapy on clinical outcomes (mortality) in human patients with paraquat poisoning.

Methods A comprehensive systematic search was conducted across electronic databases (Cochrane Library, PubMed, Scopus, ISI Web of Knowledge, Google Scholar) from inception to December 2023. Studies were included if they were original human research evaluating vitamins C and/or E in paraquat poisoning with reported mortality outcomes. A Bayesian hierarchical model was employed as the primary analytical approach due to the limited number of eligible studies. A complementary frequentist random-effects meta-analysis was also performed.

Results Finally, 3 studies were included. The pooled mean age was 44.46 years (95% CI: 28.35–60.57) in the intervention group and 42.86 years (95% CI: 24.93–60.80). The estimated proportion of males in the intervention group was 25% (19% −31%), while in the control group it was 65% (58% −73%). The Bayesian meta-analysis showed that the mortality rate in the intervention group was not significantly different from the control group OR (95%CrI):1.32 (0.56–4.05). A complementary frequentist random-effects meta-analysis yielded a consistent finding (OR = 0.653, 95% CI: 0.124–3.447, $P = 0.616$), with substantial heterogeneity ($I^2 = 83.91\%$, $P = 0.002$).

Conclusion Adjunctive therapy with vitamins C and/or E does not appear to significantly reduce mortality in patients with paraquat-induced toxicity. However, these findings are constrained by the limited number of studies, small sample sizes, and heterogeneous study designs. Larger, well-designed randomized controlled trials are needed to provide definitive evidence on the impact of vitamin supplementation in paraquat poisoning management.

Keywords Paraquat · Antioxidant · Vitamin C · Vitamin E · Herbicide · Mortality

Introduction

Paraquat (PQ, 1,1′-dimethyl-4,4′-bipyridinium dichloride) is a non-selective herbicide widely used in agriculture that poses a significant threat to human health due to its high toxicity. Accidental or intentional ingestion of PQ-containing products can lead to severe toxicity, often resulting in fatal outcomes despite medical interventions [1–4]. PQ can be orally ingested or absorbed through the skin and respiratory mucosa. Its primary target is the lung, where it causes respiratory distress syndrome, typically appearing 24–48 h after exposure [2, 5, 6].

The clinical features of PQ poisoning are dose-dependent and classified as mild, moderate, or severe. PQ exerts its toxic effects mainly through redox cycling, generating reactive oxygen species (ROS) that cause lipid peroxidation, mitochondrial damage, NF-κB activation, and apoptosis in multiple organs, including the lungs, kidneys, liver, and heart [4, 7–10]. However, following PQ poisoning, the

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disease advances swiftly. Notably, the concentration of PQ in the lung exceeds that in plasma by 10- to 20-fold due to energy-dependent active uptake by alveolar cells, and this gradient persists despite a decline in paraquat levels in the bloodstream [2, 4, 11]. Immediate treatment is a very important determinant of survival in patients poisoned with paraquat. Therefore, any patient exposed to paraquat should be treated as a medical emergency [12].

Upon hospital admission, the primary assessment should follow the ABC (airway, breathing, circulation) approach according to existing guidelines. Despite the availability of current treatment options for paraquat poisoning, such as gastric lavage, activated charcoal, and other adsorbents, fluid infusion, and various antioxidants such as N-acetylcysteine, naringin, silymarin, and quercetin, the effectiveness of these therapeutic approaches remains bleak, characterized by a high mortality rate [9, 12, 13].

Given the central role of oxidative stress in PQ-induced injury, antioxidant therapy has emerged as a rational alternative. Among potential candidates, vitamins C and E have received particular attention because they target distinct but complementary pathways: vitamin C (ascorbic acid) acts as a direct free-radical scavenger in the aqueous phase, while vitamin E (α-tocopherol) interrupts lipid peroxidation chain reactions within cell membranes [14–19]. Their combined use may offer synergistic protection against the oxidative damage inflicted by PQ across different cellular compartments.

A substantial body of preclinical evidence has examined this hypothesis. In animal models, vitamin C administration attenuated PQ-induced morphological damage in the liver and kidney and reduced oxidative stress markers in a dose-dependent manner [14–16].

A recent systematic review and meta-analysis of animal studies found a significant association between vitamin C and/or E administration and improvements in creatinine and alkaline phosphatase levels after PQ poisoning [20]. However, the evidence is not uniformly positive: vitamin C has been reported to exert pro-oxidant effects in the presence of free metal ions released from damaged tissues [21] and vitamin E supplementation has occasionally been associated with enhanced genotoxicity in certain experimental settings [22]. These conflicting findings underscore the complexity of antioxidant interactions in the context of severe oxidative injury.

While preclinical data provide a rationale for clinical evaluation, evidence from human studies remains limited and inconclusive. Therefore, the objective of this study is to conduct a meta-analysis to quantitatively synthesize the available evidence on the impact of vitamin C and/or E treatment on clinical outcomes in human PQ poisoning.

Methods and Materials

Study Design

This study was conducted as a systematic review and meta-analysis, following the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions. Although the review was conducted rapidly (data extraction and meta-analysis were completed within a short timeframe), a formal protocol was developed internally. The protocol was not prospectively registered in PROSPERO due to time constraints; however, the review protocol has been designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [23].

Search Strategy

A systematic search was conducted across electronic databases, including Cochrane Library, PubMed, Scopus, ISI Web of Knowledge, and Google Scholar, to identify relevant studies published from inception to September 2026. The search strategy employed a combination of Medical Subject Headings (MeSH) and free-text terms related to paraquat, vitamins C and E, toxicity, antioxidant, and treatment. In addition, the reference lists of all included studies and relevant review articles were manually screened to identify any further eligible publications.

Study Selection

All retrieved records were imported into reference management software, and duplicates were removed. Two independent reviewers (V.A. and R.K.) performed the screening process in two stages. In the first stage, titles and abstracts were screened against predefined eligibility criteria to exclude clearly irrelevant studies. In the second stage, the full texts of the remaining articles were retrieved and assessed independently by the same two reviewers for final inclusion. Any disagreements at either stage were resolved through discussion or, if necessary, by consultation with a third reviewer (R.M.). The reasons for exclusion at the full-text stage were documented and are reported in the PRISMA flow diagram. Inter-rater agreement was calculated using Cohen's kappa coefficient to ensure reliability of the screening process.

Studies meeting the following criteria were included in the present review: (1) original research articles investigating the effects of vitamins C and/or E on paraquat-induced toxicity in human subjects (2), studies reporting outcomes related to mortality rate in each group, and (3) studies published in English. Exclusion criteria comprised studies lacking relevant outcome measures, reviews, conference

Table 1 Eligibility criteria

No.	Criteria	Description
1.	Study Design	Inclusion: Original studies (animal or human) Exclusion: Reviews, conference abstracts, and studies not accessible in full-text format
2.	Population	Inclusion: Animals /humans poisoned with PQ Exclusion: In-vitro studies
3.	Intervention	Inclusion: Treatment with vitamins C, or E, or their combination in addition to routine treatment Exclusion: N/A*
4.	Outcome	Inclusion: Mortality Exclusion: N/A*
5.	Language	Inclusion: English Exclusion: N/A*
6.	Time of Publication	Inclusion: No beginning date-December 2023 Exclusion: N/A*

**N/A* Not Applicable

abstracts, and studies not accessible in full-text format (Table 1).

Data Extraction

Data extraction was performed independently by two reviewers using a standardized data extraction form. Any discrepancies were resolved through discussion or consultation with a third reviewer. Extracted data included study characteristics (e.g., study design, sample size), participant characteristics (e.g., species, age, sex), details (e.g., dose, route of administration), outcomes of interest, and key findings. Although mortality was the primary outcome, secondary outcomes of interest included acute kidney injury (AKI) and pulmonary function/fibrosis. Due to the limited number of eligible studies and the inconsistency in reporting these secondary outcomes across studies, AKI and pulmonary outcomes were considered exploratory and were analyzed on a single-study basis where data were available. These secondary outcomes were not part of the primary meta-analytic model, and their findings should be interpreted as hypothesis-generating only.

Risk of Bias Assessment

The methodological quality and risk of bias of the included studies were assessed independently by two reviewers using established tools specific to study design. For the two retrospective cohort studies (Eizadi-Mood et al. and Moon & Chun et al.), the Newcastle-Ottawa Scale (NOS) was employed, evaluating selection, comparability, and outcome domains [24]. For the prospective interventional study by Hu et al. (2018), which employed a non-randomized, historical control design, the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool was used to assess methodological quality across seven domains: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results.

Certainty of Evidence Assessment

The certainty of evidence for each predefined outcome was assessed independently using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. Five domains (Risk of Bias, Inconsistency, Indirectness, Imprecision, and Publication Bias) were assessed for downgrading, while three domains (Large Effect, Dose-Response, and Residual Confounding) were assessed for upgrading [25, 26].

Statistical Analysis

Given the small number of included studies, we initially performed a Bayesian meta-analysis using a hierarchical random-effects model. The study-specific log odds ratios (log ORs) were assumed to follow a normal distribution centered on the overall mean log OR, with between-study variance τ^2:

$$\theta_i \sim N(\mu, \tau^2),$$

where θ_i denotes the log OR for study i and μ is the pooled mean log OR. A diffuse normal prior was assigned to the pooled log OR, $\mu \sim N(0,10000)$, and a half-normal prior was assigned to the between-study standard deviation ($\tau \sim Half-Normal(0,10)$).

Markov chain Monte Carlo (MCMC) methods were used to obtain the posterior distribution of the pooled log OR, odds ratio (OR), and other parameters of interest. Four chains were run with 12,500 iterations per chain, including 2,500 warm-up iterations and thinning of 1. Model fit was evaluated using the Deviation Information Criterion (DIC) and posterior predictive checks. Convergence was assessed using Gelman-Rubin R-hat statistics and visual inspection of trace plots.

For the study by Hu et al. (2018), in which no deaths occurred in the intervention arm (0/6) while 17 deaths occurred in the control arm (17/23), a continuity correction of 0.5 was added to each cell of the 2×2 contingency table before calculating the log odds ratio and its standard error, to obtain finite estimates and permit inclusion of the study in the meta-analysis.

Despite these specifications, the Bayesian model did not achieve satisfactory convergence. A very large Gelman–Rubin R-hat value was observed(R-hat = 1.17×10), accompanied by unstable posterior estimates. Given the lack of convergence and the limited number of studies ($n = 3$), a prior-sensitivity analysis was also conducted using an alternative prior specification for the between-study variance, τ^2 (IG (0.01, 0.01)). The sensitivity analysis similarly resulted in unstable posterior estimates and inadequate convergence, indicating that reliable Bayesian inference could not be obtained with the available data. Therefore, we additionally performed a complementary frequentist random-effects meta-analysis.

This analysis provided pooled ORs, 95% confidence intervals (CIs), and P-values. Heterogeneity was quantified using the I^2 statistic, with an I^2 value > 50% considered to indicate substantial heterogeneity. The results of this frequentist analysis serve as a robustness check for the Bayesian findings.

Planned subgroup analyses were conducted to determine potential sources of heterogeneity based on study design (Prospective interventional vs. retrospective), and type of intervention (high-dose vitamin C alone vs. vitamin C combined with vitamin E). Sensitivity analysis was performed using the leave-one-out method, systematically excluding individual studies and repeating the analysis to assess each study's influence on the overall OR.

Formal assessment of publication bias was not performed in the main analysis, because the Cochrane Handbook recommends against such tests when fewer than ten studies are included. For transparency, exploratory analyses (funnel plot, Egger's and Begg's tests, and trim-and-fill) are presented in Supplementary Material, but their results should not be interpreted as evidence for or against publication bias.

Results

Study Selection

The systematic literature search process is summarized in the PRISMA flow diagram (Fig. 1). The initial database search yielded 738 potentially relevant articles. Following the removal of duplicates, a total of 378 records were screened based on titles and abstracts by two independent reviewers. The inter-rater reliability was excellent, with a Cohen's kappa of $\kappa = 1.00$ (95% CI: 1.00–1.00), indicating perfect agreement between the two reviewers. This perfect agreement reflects the clear and focused eligibility criteria, which minimized ambiguity during screening.

No disagreements were identified during the screening process. Subsequently, 5 articles were screened for full-text assessment.

The initial database search yielded 738 records. After removing duplicates ($n = 360$), 378 records remained. Of these, 373 were excluded based on title/abstract screening (reviews, conference abstracts, unrelated topics), leaving 5 records for full-text assessment. Of these, 5 were further excluded (wrong population, no control group, no mortality data), resulting in 5 full-text articles assessed for eligibility.

After applying the eligibility criteria—which included human studies, English language, availability of comparative data between intervention and control groups, and sufficient outcome reporting—three studies met the inclusion criteria [27–29]. Two additional studies were excluded for specific reasons: the study by Rahmani et al. [30] was omitted because it did not include a control group, as all participants received vitamins C and/or E; and the study by Hong et al. [31] was excluded because it evaluated the effect of vitamin C supplementation solely on total serum antioxidant status without reporting clinically relevant outcomes such as mortality or patient health status. All three included studies were assessed as being of medium to high methodological quality and were subsequently incorporated into the quantitative synthesis.

Study Characteristics

A summary of the key findings and clinical features of the included studies is provided in Table 2. The studies were conducted in three different countries in Asia (South Korea, Iran, and China) and comprised two retrospective cohort studies and one non-randomized Prospective interventional study. The total sample sizes across studies ranged from 29 to 186 participants. The control groups received standard therapeutic protocols, which varied by study and included gastric lavage with Fuller's earth, conventional hemoperfusion, continuous venovenous hemofiltration (CVVH), and methylprednisolone. The intervention groups received standard therapy supplemented with vitamin C (administered intravenously at varying doses and durations), vitamin E (intramuscularly), or a combination of both vitamins.

Quality and Risk of Bias Assessment

The methodological quality of the included studies was evaluated using appropriate tools based on study design. According to the NOS assessment, the two cohort studies demonstrated 'Fair' to 'Good' methodological quality, with Moon & Chun achieving a higher score (7/9) due to robust multivariate adjustment for confounding variables.

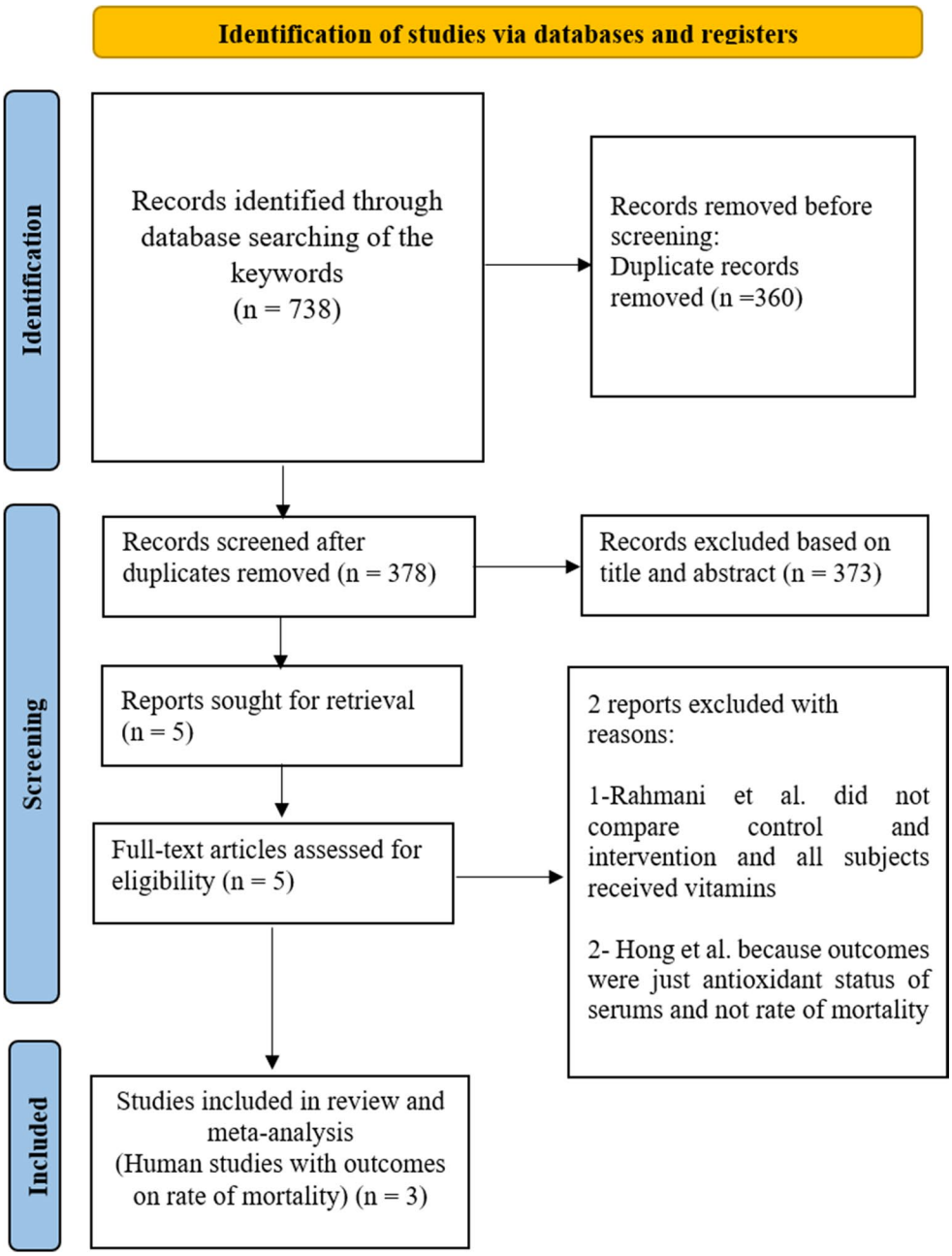


Fig. 1 Flowchart of study selection

The single interventional study (Hu et al.) was graded as having a 'Serious' overall risk of bias per ROBINS-I criteria. Critically, the confounding domain was rated as serious due to the use of a historical control group (patients enrolled from 2011 to 2013 versus 2013–2017), which introduces temporal biases including potential changes in standard critical care protocols over time, alongside the absence of any multivariate adjustment for prognostic factors. The selection of participants domain was also rated as serious because the allocation to the intervention group was non-random and non-contemporaneous, with an extremely small sample size ($n = 6$) that raises substantial concerns about selection bias and lack of generalizability (Table 3). Due to the limited number of eligible studies, no study was excluded on the basis of quality assessment.

Certainty of Evidence Assessment

Based on the GRADE assessment, the certainty of evidence for the primary outcome (Mortality) is Very Low (Table 4). This is primarily driven by the extreme statistical heterogeneity and the reliance on retrospective, non-randomized historical controls.

Table 2 Characteristics and details of the included studies on effect of vitamin C and E treatment in paraquat toxicity in humans

Author (year)	Country	Study Design	Study Population	Mean age, Year	Control group (standard treatment)	Intervention group (addition of vitamins)	In-hospital Mortality Rate	Other outcomes
Moon (2011)	South Korea	Retrospective	Control = 57 Intervention = 77	Control = 52 Intervention = 52	Gastric lavage with a solution containing 12.5 g of Fuller's earth, administered via a nasogastric tube every 2 h for a total of five doses	Standard treatment plus high-dose vitamin C for 2 weeks (loading dose: 1 g vitamin C in 500 mL of 5% dextrose/saline, followed by 4 g daily for 14 days)	Control = 78.9% Intervention = 70.1%	The most frequently observed complication was acute kidney injury, followed by hypoxia.
Eizadimood (2011)	Iran	Retrospective	Control = 157 Intervention = 29	-	Standard conventional therapy	Standard treatment plus daily intramuscular vitamin E (100–200 mg) and intravenous vitamin C (2400–3600 mg) for 3–5 days	Control = 31% Intervention = 55.2%	Renal failure concomitant with hepatic and pulmonary dysfunction was observed in 75% of all cases.
Hu (2018)	China	Prospective interventional (Non-randomize)	Control = 23 Intervention = 6	Control = 33.7 Intervention = 35.5	Conventional hemoperfusion plus continuous venovenous hemofiltration (CVVH) and methylprednisolone	Standard treatment plus intravenous vitamin C (2 g/day)	Control = 73.9% Intervention = 0%	No significant difference in the incidence of pulmonary fibrosis was observed among survivors between groups ($p > 0.05$).

Table 3 Overall risk of bias assessment for each included study

Study	Design	Tool Used	Overall RoB Judgment	Key Limitations
Moon & Chun (29)	Retrospective cohort	NOS (7/9 – Good)	Moderate	Retrospective design; lack of blinding; but good statistical adjustment for major confounders.
Eizadi-Mood et al. [27]	Retrospective cohort	NOS (6/9 – Fair)	Serious	Historical controls; no adjustment for confounders; lack of blinding; non-contemporaneous comparison.
Hu et al. [28]	Prospective interventional (non-randomized)	ROBINS-I	Serious	Historical control group introduces temporal bias; no multivariate adjustment; non-random, non-contemporaneous allocation; only 6 patients in the intervention arm.

NOS Newcastle-Ottawa Scale, *ROBINS-I* Risk of Bias In Non-randomised Studies – of Interventions

Interestingly, the evidence for the prevention of acute kidney injury was rated as Low (rather than Very Low), despite the retrospective design. This suggests a plausible nephroprotective role for high-dose vitamin C that warrants further prospective validation.

The evidence for pulmonary outcomes (PaO_2 and fibrosis) is Very Low due to the prohibitively small sample size ($n = 6$ in the intervention group) in the sole study reporting this outcome. Consequently, the apparent dramatic improvement in survival reported by Hu et al. is highly susceptible to selection bias and random error.

In addition to mortality, data on AKI (reported in Moon & Chun) and pulmonary function/fibrosis (reported in Hu et al.) were available and are summarized in Table 4. These findings should be interpreted as exploratory given the single-study basis.

Table 4 Summary of findings and certainty of evidence for the effect of high-dose Vitamins C and/or E on critical outcomes in patients with severe Paraquat poisoning

Outcome	Study Design (*n*)	Summary of Effect (95% CI / Range)	Certainty Assessment (Downgrading Factors)	Certainty Level(GRADE)	Importance
Mortality (All-cause)	1 Prospective trial (*n* = 29) 2 Retrospective cohorts (*n* = 320) **Total:*N* = 349**	**Bayesian pooled OR range**: 0.56 to 4.05 (Highly inconsistent). **Moon**: 78.9% vs. 70.1% (*P* = 0.321) **Hu**: 73.9% vs. 0% (*P* = 0.002) **Eizadi**: 31% vs. 55.2% (non-significant increase).	**Risk of Bias (-1)**: Serious limitations due to non-randomized allocation and historical controls. **Inconsistency (-1)**: Substantial unexplained heterogeneity (I^2 >75%); direction of effect conflicts (protective vs. harmful). **Imprecision (-1)**: Very wide CIs and low event rates in the trial group. **Publication Bias (0)**: Not assessable due to < 10 studies.	⊕○○○ VERY LOW	Critical
Acute Kidney Injury (AKI)	1 Retrospective cohort (Moon & Chun) **Total:*N* = 134**	**Incidence**: Group 1 (no Vit C): 63.2% Group 2 (high-dose Vit C): 41.6% **Absolute Risk Reduction**: ~21.6% (*P* = 0.013).	**Risk of Bias (-1)**: Serious limitations (retrospective design, lack of blinding). **Inconsistency (0)**: Not applicable (single study providing quantitative data). **Indirectness (0)**: Direct population and outcome. **Imprecision (0)**: Statistically significant with relatively narrow CI; acceptable event rate.	⊕⊕○○ LOW	Important
Pulmonary Function / Fibrosis (Lowest PaO_2 & Radiographic Fibrosis)	1 Prospective trial (Hu et al.) **Total:*N* = 29**	**Lowest PaO_2**: Control: 70.26 ± 16.38 mmHg Intervention: 91.17 ± 3.43 mmHg (*P* < 0.001). **Fibrosis in survivors**: Control: 100%; Intervention: 50% (*P* = 0.182).	**Risk of Bias (-1)**: Very serious limitations (extremely small sample size, non-randomized allocation, lack of placebo control). **Indirectness (0)**: Direct. **Imprecision (-2)**: Extremely serious; only 6 patients in the intervention group, wide confidence intervals for fibrosis, high risk of Type II error. **Upgrading (0)**: Despite large PaO_2 difference, downgrading for imprecision overrides upgrading.	⊕○○○ VERY LOW	Important

Narrative Synthesis

The three included studies yielded discordant clinical findings. Moon & Chun observed essentially identical mortality between the high-dose vitamin C and control groups (77.0% vs. 78.9%), with AKI remaining the most frequent complication in both arms, although its incidence was lower in the vitamin C group (41.6% vs. 63.2%). The authors also noted that hypoxia and hepatic dysfunction occurred with similar frequency in both groups, suggesting that high-dose vitamin C did not alter the overall pattern of organ injury. Eizadi-Mood et al. reported a numerically higher mortality in patients receiving vitamins C and E than in controls (55.2% vs. 31%), a difference that did not reach statistical significance but ran opposite to the expected benefit; renal failure combined with hepatic and pulmonary dysfunction was documented in approximately 75% of all cases, and the amount of paraquat ingested emerged as the dominant prognostic determinant, with no survivors among those who ingested more than 10 mL. In contrast, Hu et al. reported no deaths in the antioxidant group versus 73.9% mortality in controls, and although the incidence of pulmonary fibrosis among survivors did not differ significantly between groups, all six control deaths were attributed to severe lung fibrosis, whereas no intervention-group patient developed severe fibrosis.

Taken together, these findings do not point to a consistent clinical benefit. This inconsistency—spanning no effect, possible harm, and apparent survival benefit—reflects differences in study design, poisoning severity, antioxidant regimen, and standard care, and it justifies a cautious interpretation of any pooled estimate.

Quantitative Synthesis (Meta-Analysis)

Age

The pooled mean age of participants in the intervention group was 44.46 years (95% CI: 28.35–60.57), while that of the control group was 42.86 years (95% CI: 24.93–60.80). These estimates were derived from a random-effects meta-analysis model. The study by Eizadi-Mood et al. (2011) was excluded from the age analysis because it did not report mean age values; only age-group frequency distributions were provided.

Gender Distribution

The estimated proportion of male participants in the intervention group was 25% (95% CI: 19%–31%) (Fig. 2), whereas in the control group it was 65% (95% CI: 58%–73%) (Fig. 3). The proportion of female participants in the intervention group was 45% (95% CI: 23%–47%) (Fig. 4), compared with 34% (95% CI: 28%–40%) in the control group (Fig. 5).

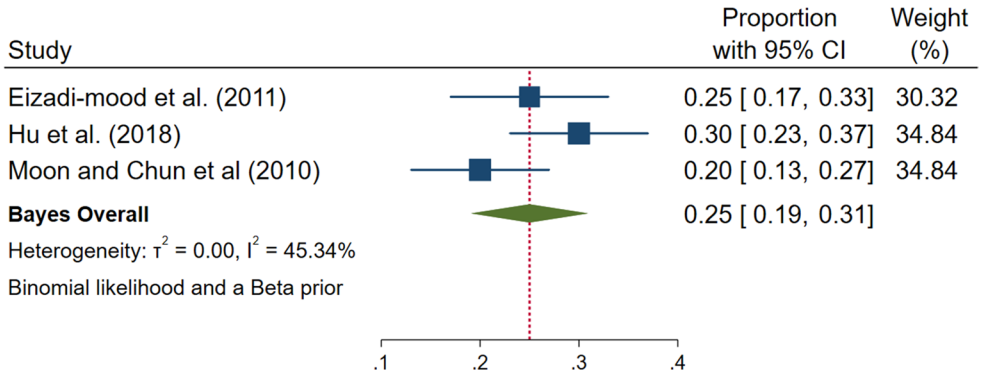


Fig. 2 Proportion of males in the intervention group

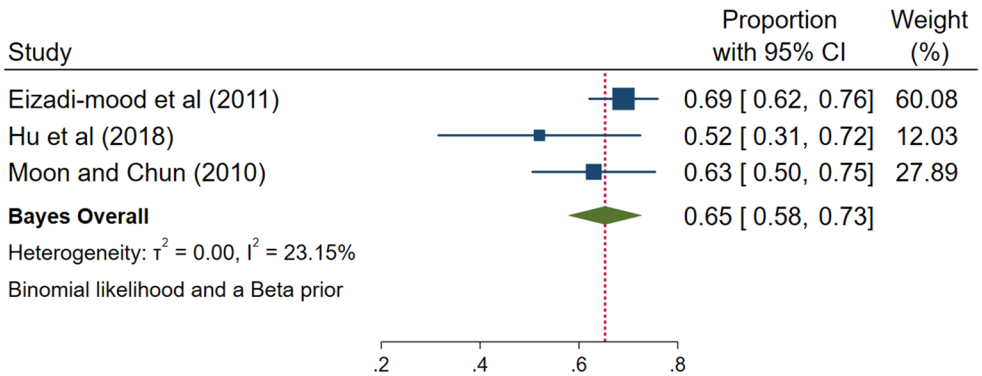


Fig. 3 Proportion of males in the control group

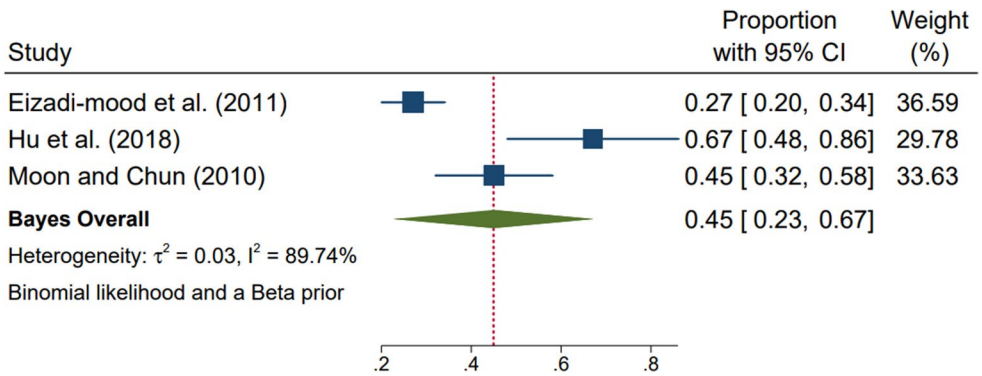


Fig. 4 Proportion of females in the intervention group

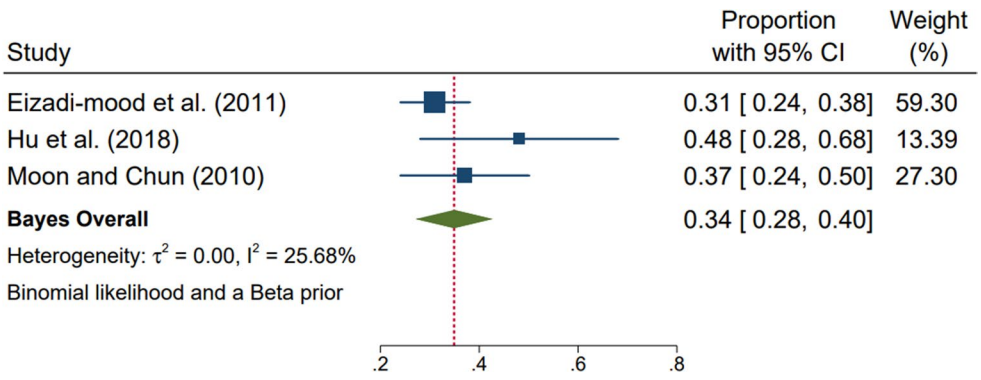


Fig. 5 Proportion of females in the control group

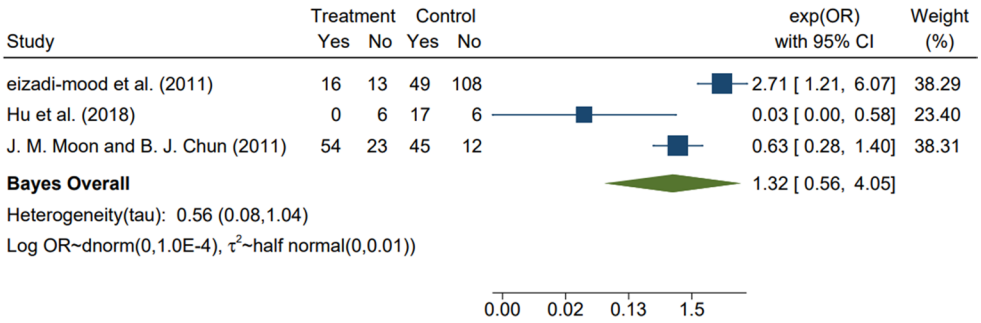


Fig. 6 Forrest plot of Bayesian meta-analysis for mortality rate in the intervention group (vitamins C and/or E) and the control group (routine treatment)

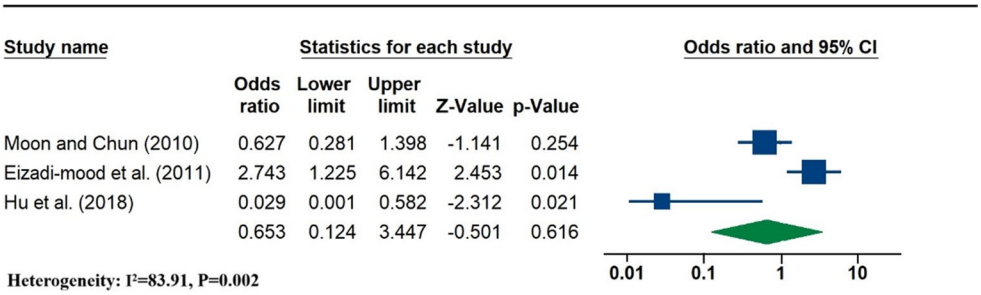


Fig. 7 Forest plot of the frequentist random-effects meta-analysis for mortality rate in the intervention group (vitamins C and/or E) and the control group (routine treatment)

Mortality

A Bayesian random-effects meta-analysis was conducted on the three included studies to compare mortality rates between the intervention and control groups. The pooled OR for mortality in the intervention group relative to the control group was 1.32, with a 95% CI of 0.56–4.05 (Fig. 6).

In addition to the Bayesian analysis, we performed a complementary frequentist random-effects meta-analysis to assess the robustness of the findings. The pooled odds ratio for mortality in the intervention group compared with the control group was 0.653 (95% CI: 0.124–3.447, $P=0.616$), indicating no statistically significant survival benefit (Fig. 7). Statistical heterogeneity was substantial, with an I^2 value of 83.91% (P for heterogeneity = 0.002), confirming considerable between-study variability.

Subgroup and Sensitivity Analyses

To explore potential sources of heterogeneity, predefined subgroup analyses were conducted based on study design (prospective interventional vs. retrospective) and intervention type (high-dose vitamin C alone vs. vitamin C combined with vitamin E). Stratification by study design yielded a lower pooled odds ratio (OR) for mortality in the prospective interventional subgroup, which was based solely on the Hu et al. study, compared with the retrospective subgroup (prospective interventional: OR = 0.029, 95% CI = 0.001–0.582, $P=0.021$; retrospective: OR = 1.31, 95% CI = 0.30–5.56, $P=0.714$). The between-subgroup difference, however, was not statistically significant (P for subgroup difference = 0.634). However, stratification by intervention type revealed a significant and unfavorable

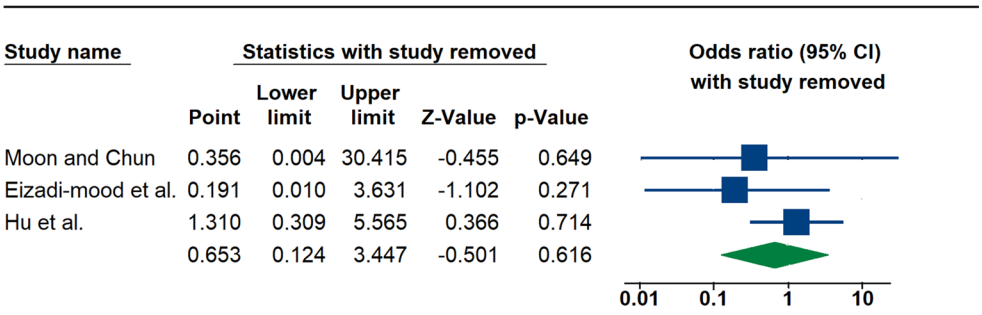


Fig. 8 Forest plot of leave-one-out sensitivity analysis: pooled odds ratio for mortality after sequential exclusion of each study

effect in the vitamin C plus vitamin E subgroup (OR = 2.74, 95% CI = 1.22–6.14, $P = 0.014$), whereas the high-dose vitamin C subgroup showed a non-significant protective estimate (OR = 0.19, 95% CI = 0.01–3.63, $P = 0.271$). The difference between these intervention subgroups was statistically significant (P for subgroup difference = 0.038). Importantly, the vitamin C plus vitamin E subgroup was based on a single study [27], whereas the high-dose vitamin C subgroup included two studies [28, 29]. Given the limited number of contributing studies, this significant difference should be interpreted with extreme caution.

The results of the leave-one-out method sensitivity analysis are presented in Fig. 8. The removal of any single study did not substantially influence the results of the pooled OR for mortality. The direction and statistical significance of the pooled OR remained unchanged. This indicates that the overall findings were not unduly influenced by any individual study.

Publication Bias

> Because only three studies were included, formal assessment of publication bias was not statistically meaningful; the corresponding analyses are provided in Supplementary Material for transparency only and should not be interpreted as evidence for or against publication bias.

Publication bias was assessed using Egger's regression asymmetry test. The result was not statistically significant (Intercept = -3.36, 95% CI = -48.46 to 41.72, t-value = 0.949, P-value = 0.501), indicating no substantial evidence of publication bias among the included studies. The corresponding funnel plot is presented in Supplementary Figure S1. However, as this method is not recommended when fewer than 10 studies are included in a meta-analysis, we supplemented the assessment by performing Begg's tests.

Begg's rank correlation test also showed no significant indication of publication bias (Kendall's Tau = -0.33, z = 0.52, p-value = 0.601). Duval and Tweedie 'trim-and-fill' correction resulted in the imputation of 1 potentially missing study and an adjusted pooled OR of 1.31 (95% CI = 0.23 to 7.43). Finally, the overall assessment does not strongly support the presence of substantial publication bias across the analyzed outcomes.

Discussion

The present study provides a quantitative synthesis of the available human evidence on the impact of vitamins C and/or E on mortality in patients with acute paraquat (PQ) poisoning. A total of 3 studies were included in our systematic review [27–29]. Our primary finding indicates that adjunctive therapy with these antioxidants does not confer a statistically significant survival benefit. To further examine the consistency of our findings, we also performed a complementary frequentist meta-analysis, which yielded results consistent with the Bayesian estimate. This result, while not definitive, challenges the straightforward translation of promising preclinical data into clinical practice and underscores the significant gap between experimental models and human pathophysiology.

Vitamin C functions is a powerful scavenger of free radicals and is thought to diminish the concentrations of pro-inflammatory and pro-fibrotic molecules such as IL-6, IL-17, and TGF-β within lung tissues [32]. It is important to highlight that vitamin C has been demonstrated to mitigate the morphological changes induced by PQ in the liver [14]. Despite numerous reports demonstrating the potential therapeutic benefits of vitamins C or E in cases of paraquat poisoning [15, 16, 29, 33], our results showed that adding these vitamins to standard treatment for paraquat-induced toxicity in humans is not effective.

A study by Eizadi-Mood et al. showed that the administration of vitamins C and E for over 2 days in most instances did not yield favorable outcomes in terms of preventing pulmonary fibrosis, as indicated by mortality rate data. Notably, none of the patients who consumed more than 10 mL of paraquat survived. Thus, the primary prognostic determinant appears to be the quantity of paraquat ingested, a finding consistent with previous studies, indicating that plasma paraquat concentrations tended to be higher in patients who did not survive compared to survivors, regardless of the time elapsed after ingestion [27].

According to a study performed in South Korea, there was no difference in the incidence of hepatitis and hypoxia between the control group and the intervention group that received a high-dose regimen of vitamin C for 14 days after admission. In their study, the control group received a solution containing 12.5 g of Fuller's earth via a nasogastric tube every two hours for a total of five times. Additionally, pulse therapy was initiated, involving the administration of 10 milligrams of dexamethasone every eight hours for a duration of 14 days. The pulse therapy regimen included the infusion of 1 gram of cyclophosphamide in 200 milliliters of 5% dextrose saline (DS) over the course of two days, followed by the infusion of 1 gram of methylprednisolone in 200 milliliters of 5% DS over three days. Pain was managed through morphine infusion [29].

A study by Hu et al. showed that there was no statistically significant difference in the incidence rate of lung fibrosis among the survivors in either group ($p > 0.05$). However, it is notable that in their study, 6 patients in the control group succumbed to respiratory failure attributed to severe lung fibrosis, whereas no patients in the intervention group exhibited severe lung fibrosis. This observation suggests that high doses of long-term antioxidants may effectively reduce the occurrence of lung fibrosis in patients [28].

While our human data show no clear benefit, a substantial body of preclinical evidence has provided a strong mechanistic rationale for antioxidant therapy. The discordance between these preclinical findings and our human results is not uncommon in toxicology and can be attributed to several factors. First, animal models often employ acute, high-dose exposures in young, healthy, genetically homogeneous populations, which do not fully replicate the clinical scenario of human poisoning, which often involves ingestion of variable doses, delayed presentation, and a patient population with pre-existing health conditions. Second, the dosing regimens in animal studies are often carefully controlled and optimized, whereas clinical studies may use non-equivalent doses or routes of administration. Third, the endpoints in animal studies are often biochemical (e.g., oxidative stress markers, histopathology) rather than the clinical endpoint of mortality, which is influenced by many complex factors beyond just oxidative stress, including the degree of organ failure, the quality of intensive care, and the effectiveness of other supportive therapies like hemoperfusion.

Several important limitations must be acknowledged. First, the small number of eligible studies limits the statistical power and generalizability of our findings. Second, substantial clinical and methodological heterogeneity exists across studies, including differences in vitamin dosing regimens (vitamin C alone vs. combined with vitamin E), administration routes, treatment durations, and control group protocols. Third, the subgroup analyses performed to explore potential sources of heterogeneity were based on a very limited number of studies; specifically, the prospective interventional subgroup was derived from a single study (Hu et al., 2018), and the vitamin C plus vitamin E subgroup was also based on a single study (Eizadi-Mood et al., 2011). Consequently, these subgroup findings essentially reflect that study's individual estimate rather than a pooled effect, and any observed differences between subgroups should be interpreted with extreme caution. Fourth, the predominance of retrospective cohort designs introduces inherent biases, including selection bias, confounding by indication, and secular trends in critical care management over time. Furthermore, the restriction to English-language publications may have introduced language bias, potentially excluding relevant studies published in other languages, particularly from regions with high paraquat poisoning prevalence.

Conclusion

This systematic review and Bayesian meta-analysis of three eligible human studies demonstrates that adjunctive therapy with vitamins C and/or E does not significantly reduce mortality in patients with paraquat-induced toxicity. While preclinical evidence provides a mechanistic rationale for antioxidant therapy, the current human evidence is limited by the small number of studies, heterogeneous designs, and high risk of bias, particularly in the single interventional study. Further research, including large-scale, well-designed randomized controlled trials with standardized high-dose vitamin C protocols, adequate sample sizes, and consistent outcome definitions, may provide more conclusive evidence regarding the efficacy of vitamin C supplementation in the management of paraquat poisoning.

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Declarations

Ethics Approval The study protocol was reviewed and approved by the Ethics Committee of Isfahan University of Medical Sciences (approval code: IR.MUI.PHANUT.REC.1402.052).

Competing Interests The authors declare no competing interests.

References

1. Hart TB. Paraquat—a review of safety in agricultural and horticultural use. Hum Toxicol. 1987;6(1):13–8.
2. Sukumar CA, Shastry AB. Paraquat: the poison potion. Indian J Crit care Med. 2015;23(S4):0.
3. Suntres ZE. Role of antioxidants in paraquat toxicity. Toxicology. 2002;180(1):65–77.
4. Dorooshi G, Zolfaghari S, Eizadi-Mood N, Gheshlaghi F. A new treatment approach for acute paraquat poisoning. J Res Pharm Pract. 2018;7(2):115–6.
5. Gonzales JN, Lucas R, Verin AD. The acute respiratory distress syndrome: mechanisms and perspective therapeutic approaches. Austin J Vasc Med. 2015;2(1):1009.
6. Khosya S, Gothwal S. Two cases of paraquat poisoning from Kota, Rajasthan, India. Case Rep Crit care. 2012;2012(1):652146.
7. Delirrad M, Majidi M, Boushehri B. Clinical features and prognosis of paraquat poisoning: a review of 41 cases. Int J Clin Exp Med. 2015;8(5):8122.
8. Gil Hwook, Hong JR, Jang SH, Hong SY. Diagnostic and therapeutic approach for acute paraquat intoxication. J Korean Med Sci. 2014;29(11):1441.
9. Hsieh YW, Lin JL, Lee SY, Weng CH, Yang HY, Liu SH, et al. Paraquat poisoning in pediatric patients. Pediatr Emerg Care. 2013;29(4):487–91.
10. Weng CH, Hu CC, Lin JL, Lin-Tan DT, Huang WH, Hsu CW, et al. Sequential organ failure assessment score can predict mortality in patients with paraquat intoxication. PLoS ONE. 2012;7(12):e51743.
11. Dinis-Oliveira R, Duarte JA, Sánchez-Navarro A, Remião F, Bastos ML, Carvalho F. Paraquat poisonings: mechanisms of lung toxicity, clinical features, and treatment. Crit Rev Toxicol. 2008;38(1):13–71.
12. Gawarammana IB, Buckley NA. Medical management of paraquat ingestion. Br J Clin Pharmacol. 2011;72(5):745–57.
13. Sabzghabaee AM, Eizadi-Mood N, Montazeri K, Yaraghi A, Golabi M. Fatality in paraquat poisoning. Singap Med J. 2010;51(6):496–500.
14. Awadalla EA. Efficacy of vitamin C against liver and kidney damage induced by paraquat toxicity. Exp Toxicol Pathol. 2012;64(5):431–4.
15. Okolonkwo BN. The effect of combined vitamin treatment on paraquat-inflicted liver damage. Asian J Biochem Genet Mol Biol. 2022;12(4):132–8.
16. Okolonkwo BN, Brisibe N, Maureen I. Antidotal Effect of Vitamin E and C in the Management of Paraquat Intoxication in Rat. Healthc Stud. 2023;1(1):24–9.
17. Miazek K, Beton K, Śliwińska A, Brożek-Płuska B. The effect of β-carotene, tocopherols and ascorbic acid as anti-oxidant molecules on human and animal in vitro/in vivo studies: A review of research design and analytical techniques used. Biomolecules. 2022;12(8):1087.
18. Traber MG, Stevens JF. Vitamins C and E: beneficial effects from a mechanistic perspective. Free Radic Biol Med. 2011;51(5):1000–13.
19. Minakata K, Suzuki O, Saito S, Harada N. Effect of dietary paraquat on a rat mutant unable to synthesize ascorbic acid. Arch Toxicol. 1996;70(3):256–8.
20. Mesripour A, Satari S, Meamar R, Akbari V. Evaluating the Impact of Vitamins C and E Treatment on Paraquat-Induced Acute Toxicity in Animal: A Systematic Review and Meta-Analysis. J Shahid Sadoughi Univ Med Sci. 2025;33(12):9671–9383.
21. Poljsak B, Ionescu JG. Pro-oxidant vs. antioxidant effects of vitamin C. Handb Vitam C Res Dly Requir Diet sources Advers Eff. 2009;153–83.
22. Fenech M, Dreosti I, Aitken C. Vitamin-E supplements and their effect on vitamin-E status in blood and genetic damage rate in peripheral blood lymphocytes. Carcinogenesis. 1997;18(2):359–64.
23. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev. 2021;10(1):1–11.
24. Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ott Ott Hosp Res Inst. 2011;2(1):1–12.
25. Prasad M. Introduction to the GRADE tool for rating certainty in evidence and recommendations. Clin Epidemiol Glob Heal. 2024;25:101484.
26. Flemyng E, Theresa HM, Boutron I, Higgins JPT, Hróbjartsson A, Nejstgaard CH, et al. Using Risk of Bias 2 to assess results from randomised controlled trials: guidance from Cochrane. BMJ Evidence-Based Med. 2023;28(4):260–6.
27. Eizadi-Mood N, Sabzghabaee AM, Yaraghi A, Montazeri K, Golabi M, Sharifian A et al. Effect of antioxidants on the outcome of therapy in paraquat-intoxicated patients. Trop J Pharm Res. 2011;10(1):27–31.
28. Hu S, Qiao C, Yuan Z, Li MIN, Ye J, Ma H, et al. Therapy with high–dose long–term antioxidant free radicals for severe paraquat poisoning: A pilot study. Exp Ther Med. 2018;16(6):5149–55.
29. Moon JM, Chun BJ. The efficacy of high doses of vitamin C in patients with paraquat poisoning. Hum Exp Toxicol. 2011;30(8):844–50.
30. Rahmani AH, Forouzandeh H, Tadayon Khatibi M. Medical management and outcome of paraquat poisoning in Ahvaz, Iran: A hospital-based study. Asia Pac J Med Toxicol. 2015;4(2):74–8.

31. Hong SY, Hwang KY, Lee EY, Eun SW, Cho SR, Han CS, et al. Effect of vitamin C on plasma total antioxidant status in patients with paraquat intoxication. Toxicol Lett. 2002;126(1):51–9.
32. Rodrigues da Silva M, Schapochnik A, Peres Leal M, Esteves J, Bichels Hebeda C, Sandri S, et al. Beneficial effects of ascorbic acid to treat lung fibrosis induced by paraquat. PLoS ONE. 2018;13(11):e0205535.
33. Okolonkwo BN, Jonathan N, Adjekuko OC, Zebedee LU. Ameliorative effect of vitamin E on Paraquat induced haematological disorder in male albino rats. 2022:26(2):9–17.

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