Oil-based gastric lavage in acute Aluminum Phosphide (AlP) poisoning: a systematic review and meta-analysis

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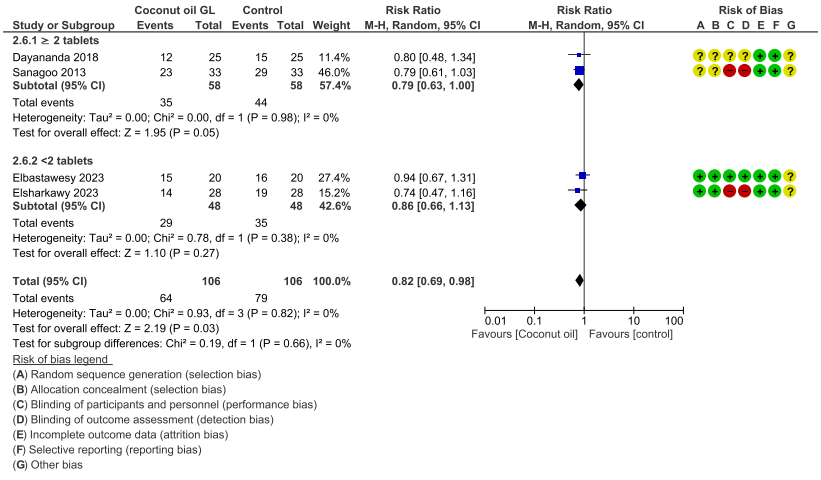
Abstract

Background: The incidence of Aluminum Phosphide (AlP) poisoning constituted one of the most common causes of poisoning death in low- and middle-income countries (LMICs). **Aims**: to evaluate the data available on the safety and efficacy of oil-based gastric lavage (GL) compared with standard therapy for the treatment of AlP poisoning. **Design**: were previously established (**PROSPERO ID: CRD42022296780**); an exhaustive search was carried out in different databases, identifying randomized controlled trials (RCTs). **Settings**: health centers of any level. **Participants**: Any person presented within 6 hours post-exposure to AlP. Interventions: Lavage solution with oils, including liquid paraffin or coconut oil. **Findings:** We identified 7 RCTs. The evidence from 4 RCTs indicates that GL with paraffin oil is an effective treatment for acute AlP poisoning, decreasing the mortality rate (RR = 0.62; 95%CI = 0.48 to 0.81; participants = 226; I2=10%; low-quality evidence). We estimate an NNT of 4. Likewise, this intervention reduces the need for intubation and mechanical ventilation (RR = 0.62; 95%CI = 0.40 to 0.79; participants= 226; I2 = 0%; low-quality evidence). Regarding GL with coconut oil, the evidence from 4 RCTs, indicates a slight reduction in mortality in patients with acute AlP poisoning (RR= 0.82; 95%CI = 0.69 to 0.98; participants= 112; I 2= 0%; very low-quality evidence). Conclusions: Limited evidence suggests that GL with paraffin oil is effective in reducing the mortality rate in acute AlP poisoning. Likewise, limited evidence showed in favor of paraffin oil concerning the need for intubation and mechanical ventilation. This efficacy was not confirmed in terms of length of hospital stay or the total amount of vasoactive agents used. Very limited evidence suggests that GL with coconut oil may have benefits in terms of mortality in patients with acute AlP poisoning. Very limited evidence suggests that both interventions would have a benign safety profile. **Conclusions:** Limited evidence suggests that GL with paraffin oil is effective in reducing the mortality rate in acute AlP poisoning. Likewise, limited evidence showed in favor of paraffin oil concerning the need for intubation and mechanical ventilation. This efficacy was not confirmed in terms of length of hospital stay or the total amount of vasoactive agents used. Very limited evidence suggests that GL with coconut oil may have benefits in terms of mortality in patients with acute AlP poisoning. Very limited evidence suggests that both interventions would have a benign safety profile.



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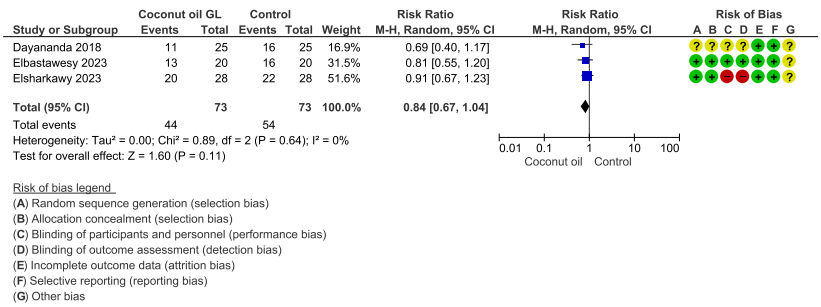

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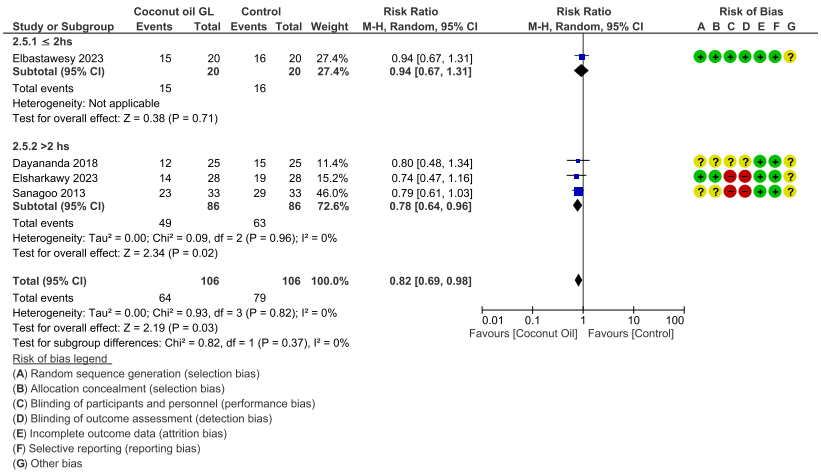

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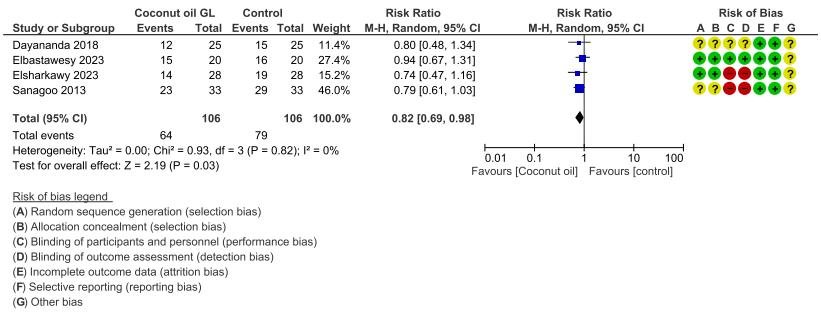

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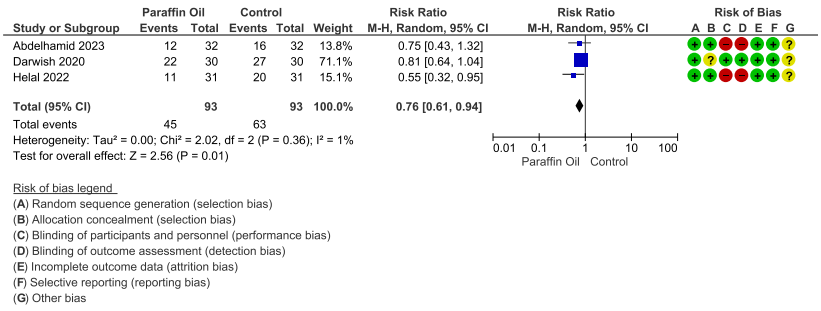

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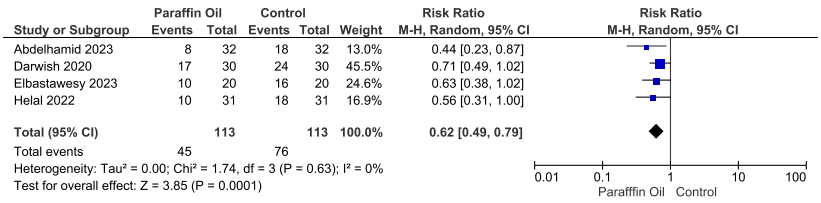

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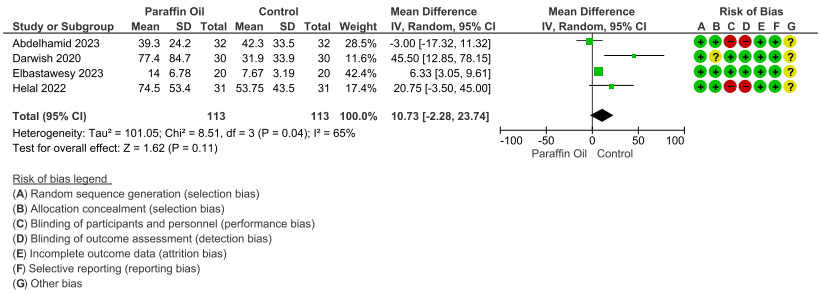

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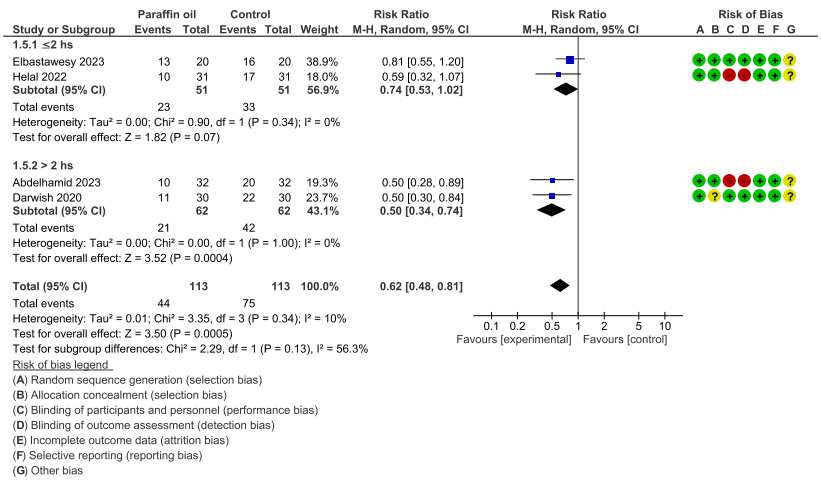

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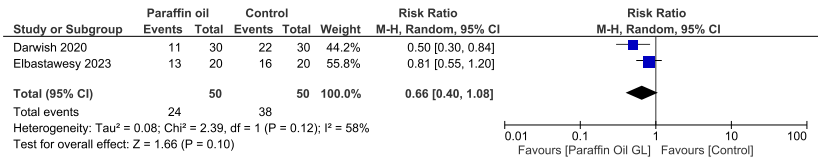

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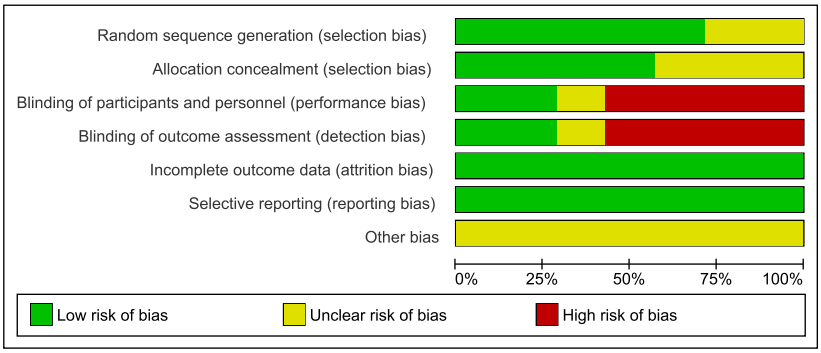
Oil-based gastric lavage in acute Aluminum Phosphide (AlP) poisoning: a systematic review and meta-analysis



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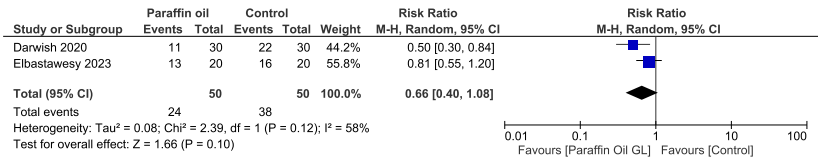

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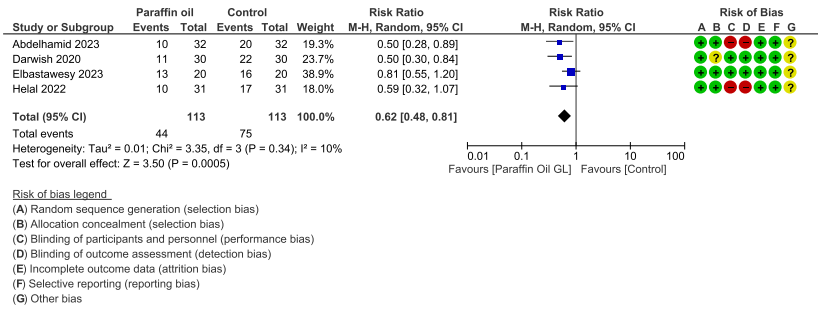

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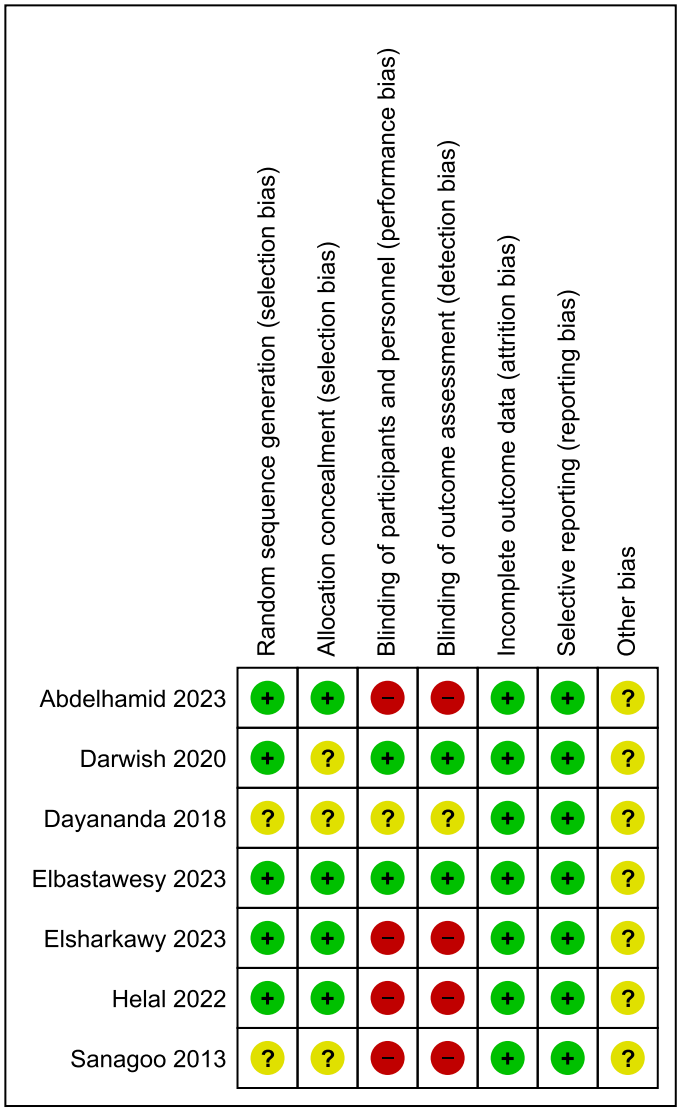

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PRISMA_2020_flow_diagram_new_SRs_v2.docx available at https://authorea.com/users/581400/articles/664487-oil-based-gastric-lavage-in-acute-aluminum-phosphide-alp-poisoning-a-systematic-review-and-meta-analysis

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INTRODUCTION

The deepening of the commodification of nature, within the framework of an extractivist model, has extended the use of technologies such as pesticides, predominantly in low- and middle-income countries (LMICs), increasing the damage and inequalities that this model has produced up to now (1). The use of aluminum phosphide (AlP) has become popular in these countries, to respond to the growing demand for food worldwide, because it's highly effective without significative adverse effects on seed viability, non-persistent under most environmental conditions, and low cost (2). The incidence of AlP poisoning is low in high-income countries (3), but it constitutes one of the most common causes of poisoning death in Iran (4), India (5), Albania (6), Sri Lanka, and Morocco (7).

Description of the condition

Deliberate exposure to pesticides is one of the most common methods of suicide in LMICs (8). Fatal cases due to intentional exposure to AlP exceed 50% (9), which is comparable to other highly lethal suicide methods, such as firearms, used in high-income countries (10). In India, based on the results of an analysis of autopsy records over 25 years (from April 1977 to 2002), it was found that since 1992, AlP became the most common suicidal agent responsible for 68.4% of all deaths from poisoning (11) (12). By contrast, in high-income countries (HIC) the incidence is low, in circumstances of accidental exposure (13) (14).

Commonly known as rice tablet or wheat pill, AlP (CAS: 20859-73-8) is a dark gray or yellow inorganic crystalline compound with garlic, fish, or raw liver odor, available as a tablet or pellet bag (15). Although it is stable when dry, in contact with moisture it is hydrolyzed to phosphine (PH3, hydrogen phosphide, phosphorus trihydride), a highly toxic gas.

The mechanism of PH3 toxicity is through an irreversible metabolic crisis and/or the indirect effect of increased oxidative stress (16) (17) (18). The formation of reactive oxygen species (ROS), causes lipid peroxidation and protein denaturation, with severe cellular damage (19) (20) (21). In patients with severe acute AlP poisoning, cardiotoxicity is the main cause of morbidity and mortality (22) (23) (24). The reported mortality rate in ingestions ranges from 31 % (13) to 91% (25).

Gastric lavage (GL) with potassium permanganate (KMnO4) magnesium sulfate (MgSO4), or even activated charcoal, has been used for many years, with a low level of certainty about its evidence (26). These strategies involve aqueous solutions, which could induce more PH3 liberation (27) (28).

Description of the intervention

Although GL is a treatment that has been used for more than 200 years in the management of acute poisoning, there is low certainty of its benefit (29). Some authors recommend that must be performed within the first 30-60 minutes after ingestion, in massive intake of highly lethal xenobiotics with no effective specific antidote or alternative therapies (e.g., hemodialysis). Nevertheless, due to evidence of persistence of significant amounts of xenobiotics in the stomach after 60 minutes post-ingestion, some other authors recommend GL in patients up to 6 hours after ingestion (30).

How the intervention might work

Some *in vitro* studies suggest that lipids, mainly vegetable oils or liquid paraffin, inhibit the release of PH3 (31), and some case reports have used this strategy successfully (32). In theory, surrounding AlP with a lipid environment could decrease the release of PH3 (26).

Why it is important to do this review

In addition to the lack of an effective antidote, there is no standardized approach to gastrointestinal decontamination, and conventional techniques could worsen the clinical condition (27). The results of new RCTs have been published, which could provide greater precision to the quality of the evidence available to date. The systematic integration of this new evidence could clarify certain inconsistencies, which allows illustration of the decision-makers and managers of public policies, patients, and health professionals, with current evidence about oil-based GL's benefits and risks for treating people with AlP poisoning.

Objectives

This systematic review aims to evaluate the data available to date on the safety and efficacy of oil-based GL compared with standard therapy for the treatment of people with AlP poisoning.

METHODS

This review was prepared following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA). The research question was structured according to the PICOT criteria (33).

Types of studies

We included randomized controlled trials (RCTs) of at least 6 weeks of overall study duration

Inclusion criteria: articles with original data from RCT examining the use of oil-based GL for the treatment of people with AlP poisoning. The search won't be restricted by language or status of publication

Exclusion criteria: a) repetitive data; b) old published data for the same study; c) unavailability of the complete report for reference in case of lack of clarity of information in the abstract; d) Case series; e) Case reports; f) Nonsystematic reviews; g) Editorials; h) Letters to the editor

Types of participants

Inclusion criteria: Any person presented within 6 hours post-exposure to AlP. Also, studies that were developed in health centers of any level of care in the inpatient setting were included.

Exclusion criteria: Studies that enrolled patients who presented with a delay time greater than 6 hs after AlP exposure or hose that took place in the outpatient setting were excluded.

Types of interventions

Intervention

Inclusion criteria: Lavage solution with oils, including liquid paraffin, coconut oil, olive oil, almond oil, or corn oil, that was given through the nasogastric tube or orally administered, in any dosage schedule, as monotherapy, or in combination with another pharmacotherapy such as KMnO4, MgSO4, NaHCO3, or activated charcoal, if these interventions were provided equally in the experimental and control groups.

Exclusion criteria: Lavage solution with any drugs not listed above

Comparator

Inclusion criteria: Placebo, any other pharmacotherapy and/or standard care available for the treatment of people with AlP poisoning

Exclusion criteria: No comparison; non-concordant historical controls

Types of outcome measures

Primary outcomes

Mortality: percentage of death and survival within each group

Secondary outcomes:

Length of hospital stays: mean of total hospital or ICU stay (hours);

*Need of mechanical ventilation:*indication of endotracheal intubation / mechanical ventilation;

Need for vasopressors: administration of vasopressors or inotropic drugs;

Adverse Events (AEs) due to the intervention

Search methods for identification of studies

The search strategy was agreed upon by the authors and replicable, obtaining all relevant studies. The review was done in duplicate to establish the eligibility of the studies. Two researchers were involved in screening (ODS, CDN) using the Covidence tool (*https://www.covidence.org*). We use Medeley Cite (*https://mendeley.com*) as software to manage references. An exhaustive search of the scientific literature was carried out in each of the following databases from the beginning of the report until November 2023, identifying RCTs that evaluated the efficacy of varenicline for the treatment of people with AUD regardless of its publication status: PubMed (https://PubMed.ncbi.nlm.nih.gov), Cochrane Library (https://www.cochranelibrary.com/), SciELO (https://SciELO.org/es/), Science Direct (https://www.ScienceDirect.com/), Google Scholar (https://scholar.google.com/) Europe PMC (https://europepmc.org/), Trip Database (https://www.tripdatabase.com/), LILACS (https://LILACS.bvsalud.org/es/) and Index Medicus for South-East Asia Region, IMSEAR (https://imsear.searo.who.int/handle/123456789/205654)

We also searched the following trial registry platforms:

- ClinicalTrials.gov (https://ClinicalTrials.gov/)

- WHO International Clinical Trials Registry Platform, ICTRP (https://www.who.int/clinical-trials-registry-platform)

- European Union Clinical Trials Register, EUCTR (*https://www.clinicaltrialsregister.eu/ctr-search/search*)

Electronic searches. PubMed search strategy: ((aluminum phosphide [MeSH] OR aluminum phosphide [tiab] OR celphos [tiab] OR delicia gastoxin [tiab] OR phostoxin [tiab] OR quick phos [tiab]) AND ("poisoning" [MeSH] OR poisoning [tiab] OR poisonings [tiab]) AND (gastric lavage [MeSH] OR gastric lavage [tiab] OR irrigation, gastric [tiab] OR gastric irrigation [tiab] OR gastric irrigations [tiab] OR irrigations, gastric [tiab] OR lavage, gastric [tiab] OR gastric lavages [tiab] OR lavages, gastric [tiab]))

This search strategy aims to achieve the highest possible sensitivity, which can result in relatively low precision. The remaining search strategies are detailed in the section Appendices

Searching other resources. It is also planned to manually retrieve articles considered relevant in non-indexed literature in the cited databases, such as dissertations or theses, using the Gray Matters-Canada‘s Drug and Health Technology Agency (CADTH) gray literature registry (*https://www.cadth.ca*) and Grey Source (*http://greynet.org/greysourceindex.html*). In addition, it was planned to maintain contact with relevant people and organizations to obtain information on unpublished or ongoing studies. We also hand-searched the reference lists of included studies and any current relevant systematic reviews

Data collection and analysis. The methods were established before their implementation and their registration was made before the start of data extraction in PROSPERO (*https://www.crd.york.ac.uk/PROSPERO/*); ID: CRD42023417503.

Selection of studies. Data extraction was done using a predefined electronic form including study characteristics, details of participants, interventions, comparators, and outcomes. The results were filtered by RCT using the following filter provided by the Cochrane Handbook for Systematic Reviews (35): ((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) NOT (animals [mh] NOT humans [mh]).

Data extraction and management. Two authors (ODS, CDN) extracted the data independently using the web application Rayyan QCRI (36). Any disagreement was resolved by consensus or discussion with another author (MJO). We extracted data about the type of participants, the dose and duration of treatment, the outcome measures, the randomization procedure, concealment of allocation, and the completeness of follow-up.

Assessment of risk of bias in included studies. The risk of bias in the RCTs was assessed by the tool described in the Cochrane Handbook 2022 (36). The risk of bias was assessed using the tool provided in RevMan 5.4. The following biases were evaluated, according to RoB2 terminology:

a) bias arising from the randomization process;

b) bias due to deviations from intended interventions;

c) bias due to missing outcome data;

d) bias in the measurement of the outcome;

e) bias in the selection of the reported result.

The first part of this tool involves describing what was reported by the authors of each included trial. The second part consists of assigning a judgment related to the risk of bias for each domain. Two authors (ODS, CDN) independently assessed the risk of bias in the included studies. When necessary, the authors of the evaluated study were contacted for any clarification in this regard. We plan to perform a funnel plot to assess publication bias. The quality of the evidence was evaluated with the GRADE system, through the GRADE pro-GDTT tool (*https://gradepro.org/*). The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system initially classifies the quality of evidence as high or low, depending on the methodological design, from RCTs (initially of high quality) or observational studies. Subsequently, the authors rate the certainty of the evidence, which is applied to each outcome, according to different domains (risk of bias, imprecision, inconsistency, indirectness, and publication bias) with the option to lower their level of certainty one or two levels. In rare circumstances, the authors can increase the certainty (if there is a large magnitude of effect, dose-response gradient or all residual confounding would decrease the magnitude of effect). GRADE thus establishes four levels of certainty of the evidence: very low, low, moderate, and high.

Measures of treatment effect. We will follow the intention-to-treat (ITT) principle, to assess the effect of intervention allocation, and maintain the benefit of the randomization, regardless of whether the interven-

tions are received as intended. Dichotomous outcomes were analyzed by risk ratio calculation (RR), while for continuous outcomes we estimated the mean difference (MD). We calculate each summary measure's corresponding confidence interval of 95% (IC 95%). We will use the standardized mean difference (SMD) when studies use different instruments. As an absolute measure, the Number Needed to Treat (NNT) will be determined as the inverse of the Absolute Risk Reduction (1/ARR). We consider the possibility and implications of skewed data when analyzing continuous outcomes, particularly in small sample trials, where the true distribution may be asymmetrical

Unit of analysis issues. The level at which randomization occurred in each of the RCTs was taken into account so that the number of observations coincided with the number of randomized units. If we included clinical trials with multiple arms and one arm was considered more than once in the same comparisons (e.g., different dosing schedules of the same therapeutic agent compared to the same control group), we combined all relevant treatment arms in a single group and compared with the control to avoid double counting of participants in control groups.

The statistical method usually used to combine the results of multiple studies is to weight them by the amount of information they provide (more specifically, by the inverse variances of their effect estimates). Those trials that contribute more weight are mentioned.

Dealing with missing data. We carefully considered the implications of missing individual participant outcome data (due to loss to follow-up or exclusions from analysis). Important numerical data, such as selected and randomized participants, as well as ITT or per-protocol analysis (PP), was carefully evaluated. In addition, losses to follow-up will be assessed and questions related to missing data will be critically appraised. Guessing about the results of participants who were lost was avoided. Whenever possible, we have contacted the authors of the different clinical trials to try to complete the incomplete information. When missing data were considered to affect the final result, the study was excluded from the meta-analysis. A sensitivity analysis is planned to assess how sensitive the results are to reasonable changes in the assumptions considered. We also plan to address the potential impact of missing data on the review findings in the Discussion section.

Assessment of heterogeneity

Heterogeneity (or inconsistency) was interpreted graphically (forest plot), through the Q test, Chi^2 (χ^2), and mainly according to the value of I^2. The I^2 statistic was used to measure the magnitude of heterogeneity. It indicates what percentage of the observed variability in the effect estimates is due to heterogeneity, beyond what is expected by chance (by sample size).

The I^2 is the proportion of the total variability, beyond chance, explainable by heterogeneity and is categorized as follows:

0% to 40%: might not be important;

30% to 60%: may represent moderate heterogeneity;

50% to 90%: may represent substantial heterogeneity;

75% to 100%: considerable heterogeneity.

It should be noted that the importance of the observed value of I^2 depends on the magnitude and direction of the effects and the strength of the evidence for heterogeneity. We regard heterogeneity as substantial if the I^2 was greater than 50% or the P value for the Chi2 test for heterogeneity is less than 0.10. If we find considerable levels of heterogeneity (75% or higher), we will explore the forest plot to identify studies that contribute to the greatest heterogeneity

Assessment of reporting biases

We have followed standard Cochrane methodology (Cochrane Handbook 2022) to assess the reporting bias, and we plan to perform a funnel plot to assess publication bias.

Data synthesis

If the studies were considered homogeneous, the data were pooled to perform a meta-analysis using the Review Man tool (RevMan 5.4), to assess the degree of statistical heterogeneity.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was performed when the $\mathbf{I^2}$ value was greater than 30%. The analysis was performed according to:

I) Patients who presented with a latency fewer or equal to 2 hs versus those who arrived more than 2 hours after AlP exposure

II) Patients who ingested less than 2 tablets of AlP versus those who ingested more than 2 tablets

The choice of these characteristics was motivated by clinical hypotheses, supported by evidence from sources other than the included trials.

Sensitivity analysis

We plan to perform a sensitivity analysis to assess the robustness of the results, such as the impact of assumptions, imputed data, borderline decisions, and clinical trials with a high risk of bias. Therefore, sensitivity analysis was carried out taking into consideration: a) low risk of bias studies and high risk of bias studies; b) random effects vs. fixed effects; c) RR vs. Odds Ratio (OR)

In the overall judgment of the risk of bias, trials were considered to be at **high risk of bias** if these were at high risk in at least one domain for this result or were judged to have some concerns across multiple domains. We present the results in the **random-effect model (RE),** which will default to a fixed model when there is a lack of heterogeneity

FINDINGS

Description of studies

Results of the search. The flow diagram proposed by the PRISMA statement, (*Figure 1* : PRISMA study flow diagram) outlines the identification, selection, eligibility, and inclusion process.

Included studies. Full details of the included studies are given in the*Included Studies* tables. We identified 11 full-text articles evaluated for eligibility (n=11) and four articles were excluded; the justification is reported in the attached tables (Supporting Information). We also obtained primary data from one unpublished clinical trial (37). This review included seven RCTs (n=7), 3 comparing coconut oil versus standard treatment, 3 comparing paraffin oil versus standard treatment, and 1 RCT comparing coconut oil versus paraffin oil and standard therapy.

In summary, the distinctive characteristics are presented in the following table (Table 1):

Trials	**Study design**	**Participants and Interventions**	**Amount ingested**	**Risk of bias and Comments**
Sanagoo 2013 [37] **(Iran,** from March to July) **Unpublished**	RCT **Single-blind** 2 parallel-group	Patients of any age of both genders, with acute AlP poisoning (N= 66) within the **first 3 h** of exposition All people received **standard treatment** -Group I: **Coconut oil** (N=33) -Group II: Control group (N=33)	Mean Group I**:** **2.6** Group II: 2.3	The diagnosis **was not biochemically validated.** Random sequence generation and allocation concealment were **not detailed AEs were not reporte**d as a specific outcome
Dayananda 2018 [38] (**India**, from March 2014 to August 2016)	RCT ¿? 2 parallel groups	Adults of both sexes, with acute AlP poisoning **(N= 50).** All people received **standard treatment** -Group I: **Coconut oil** -Group II: Control group	Mean Group I: **2.24** Group II: **2.48**	Blinding, random sequence generation and allocation concealment were **not detailed AEs were not reporte**d as a specific outcome

Trials	**Study design**	**Participants and Interventions**	**Amount ingested**	**Risk of bias and Comments**
Darwish 2020 [39] (**Egypt**, between June 2018 and May 2019)	RCT **Double-blind** 3 parallel groups	Patients aged more than 18 years of both genders, with acute AlP poisoning within the **first 6 h** of exposition **(N= 90).** All people received **standard treatment** -Group I: KMNO4 solution (1:10 000) This group was a **historical control** (N=30) -Group II: **Paraffin oil** (N=30) -Group III: Co Q10 + **Paraffin oil** (N=30)	Mean (SD) Group I: **0.97** ± 0.50 Group II: **0.83** ± 0.36 Group III: **1.15** ± 0.73	The diagnosis **was not biochemically validated**. The allocation concealment method was **not described. AEs were not reporte**d as a specific outcome.
Helal 2022 [40] (**Egypt** 2020, from June to November)	**RCT Single-blind** 2 parallel-group (**Phase 2)**	Patients aged more than 18 years of both genders, with acute AlP poisoning within the first **0.5 to 2.5 h** of exposition **(N= 62)**. All people received **standard treatment** -Group I (N=31): **Paraffin oil** -Group II (N=31): Control group	Mean (SD) **Group I: 1.1** ± 0.18 **Group II: 1.3** ± 0.43	This was a single-blind study, and the outcomes are likely to be influenced by the lack of blinding **AEs were not reporte**d as a specific outcome

Trials	Study design	Participants and Interventions	Amount ingested	Risk of bias and Comments
Abdelhamid 2023 [41] (**Egypt**, from January to December 2020)	RCT **Single-blind** 3 parallel groups	Adults of both sexes, with acute AlP poisoning within the **first 6 hs of exposition (N=96).** All people received **standard treatment** -Group I (N=32): N-acetyl cysteine (NAC) -Group II (N=32): NAC + L- carnitine -Group III (N=32): NAC **+ Paraffin oil**	Mean (SD) Group I**: 1.47** ± 0.8 Group II: **1.47** ± 0.6 Group III: **1.8** ± 0.6	The diagnosis **was not biochemically validated** This was a single-blind study, and the outcomes are likely to be influenced by the lack of blinding **AEs were not reporte**d as a specific outcome
Elbastawesy 2023 [42] (**Egypt** between January, and June 2021)	RCT **Double-blind** 3 parallel groups	Patients aged more than 12 years of both genders, with acute AlP poisoning within the **first 2 h** of exposition **(N= 60).** All people received **standard treatment** -Group I (N=20): **Paraffin oil** -Group II (N=20): **Coconut oil** -Group III (N=20): Control group	Mean (SD) **Group I: 1.0** ± 0 **Group II: 0.83** ± 0.4 **Group III: 0.83** ± 0.4	This was the trial rated with the **lowest risk of bias AEs were reporte**d as a specific outcome

Trials	Study design	Participants and Interventions	Amount ingested	Risk of bias and Comments
Elsharkawy 2023 (43) (**Egypt,** between December to November 2021)	RCT **Single-blind** 3 parallel groups (**Phase 2)**	Patients aged more than 18 years of both genders, with acute AlP poisoning within the **first 6 h of exposition (N= 84).** All people received **standard treatment** -Group I (N=28): Control group -Group II (N=28): **Coconut oil** -Group III (N=28): **Coconut oil + CoQ10**	Mean (SD) **Group I: 0.75** ± 0.4 **Group II: 0.83** ± 0.4 **Group III: 0.6** ± 0.4	The diagnosis **was not biochemically validated** This was a single-blind study, and the outcomes are likely to be influenced by the lack of blinding **AEs were not reporte**d as a specific outcome

Risk of bias in included studies . The Characteristics of included studies tables give full details of the risk of bias among the included studies. A bias assessment across domains for each key outcome for each included study is represented in *Figure 2 (Risk of bias summary review of authors' judgments about each risk of bias item for each included study)* and*Figure 3*(Risk of bias graph review authors' judgments about each risk of bias item presented as percentages across all)

Effects of interventions

Paraffin oil vs. standard treatment

Mortality. Four RCT (39) (40) (41) (42) comparing GL with paraffin oil to standard therapy, covering 226 participants with acute AlP poisoning, 113 of whom received paraffin oil, delivering a RR of 0.62, 95% CI 0.48 to 0.81 (*Figure 4* : Forest plot of comparison: Paraffin oil versus standard therapy, outcome: 1.1 Mortality) with a level of heterogeneity not relevant (I^2 = 10%). Likewise, the analysis remained robust in other summary statistics, delivering an OR of 0.31 (95% CI 0.18 to 0.54; I^2= 0%). Following the sensitivity analysis, by removing from the analysis the trials classified as having a high risk of bias (40) (41) a major decrease in the estimate of the effect is found (RR 0.66; 95% CI: 0.40 to 1.08) also with an increase of the I^2 value to 58% (*Figure 5* : Forest plot of comparison: Sensitivity Analysis outcome 1.1). Only two trials reported biochemical validation of the diagnosis of acute poisoning (40) (42), by the silver nitrate test, which could detect phosphine gas in stomach aspirate (44).

Subgroup: latency from exposure to AlP

Two trials reported the inclusion of patients with acute poisoning within 6 hours of AlP exposure (39) (41), one within 2.5 hours (40), and one within 2 hours (42). Although one of these (40) would enroll patients within 2.5 hours post-exposure, all participants consulted before 2 hours, so we pooled these results with the most recent trial (42). Treating these trials as a subgroup of the main analysis (analysis 1.1, outcome 1:

Mortality) the pooled analysis at the latency from exposure to AlP fewer or equal to 2 hs delivers an RR of 0.74 (95% CI 0.53 to 1.02; participants = 102) with a low level of heterogeneity (*Figure 6* : Forest plot of subgroup analysis: latency from exposure to AlP). The remaining trials (39) (41), with those patients who arrived more than 2 hours after AlP exposure, delivered a RR of 0.50 (95% CI 0.34 to 0.74; participants = 124; I^2 = 0%).

Subgroup: amount of AlP ingested

The mean number of ingested tablets among the four trials was fewer than two (Table 1).

Length of hospital stay. In this particular outcome, we pooled the findings of four RCTs (39) (40) (41) (42), delivering an MD 10.73 (95% CI -2.28 to 23.74) with a high level of heterogeneity (I^2= 65%), shown in *Figure 7* (Forest plot of comparison: Paraffin oil versus standard therapy, outcome: 1.2 Length of hospital stay). The sensitivity analysis with additional adjustments following other summary statistics, delivering an SMD of 0.51 (95% CI 0.02 to 1.01; I^2=70%. Removing trials classified as high risk of bias from the analysis (40) (41) yielded an MD of 22.41 (95% CI: -15.35 to 60.18) while maintaining a high level of heterogeneity (I^2 = 82%).

Need for mechanical ventilation. Pooling the four cited studies (39) (40) (41) (42), an RR of 0.62 (95% CI 0.49 to 0.79) was obtained, with negligible heterogeneity (I^2=0%), shown in *Figure 8* (Forest plot of comparison: Paraffin oil versus standard therapy, outcome 1.3 Need for mechanical ventilation). In addition, the estimates were maintained with adjustments for other summary measures (OR= 0.30, 95% CI of 0.17 to 0.53). Continuing with the sensitivity analysis, the robustness of the estimates is shown by obtaining an RR of 0.68 (95% CI of 0.51 to 0.91) excluding the trials classified as having a high risk of bias (40) (41), shown in *Figure 9* (Forest plot of comparison: Sensitivity analysis, outcome 1.3 Need for mechanical ventilation).

Need and amount of vasopressor agents. Regarding the need for vasopressors, pooling the four RCTs (39) (40) (41) (42), an RR of 0.79 (95% CI= 0.51 to 1.21) was obtained, with a considerable heterogeneity (I^2=89%). In one of the studies the need for vasoactive agents was not predefined as outcomes and the authors reported that all participants eventually required vasopressors (42). Following a sensitivity analysis, excluding this trial, and pooling the remaining RCTs deliver a RR of 0.76 (95%CI= 0.61 to 0.94) with negligible heterogeneity (I^2 = 1%), shown in *Figure 10* (Forest plot of comparison: Sensitivity analysis, outcome 1.4 Need for vasopressors agents). Concerning the amount of vasopressors, only two clinical trials reported this outcome. (40) (42). In one of the RCTs (40), the total amount (mg) was significantly lower in the paraffin oil group compared to the control group (mean of 46.5 ± 16.7 mg vs. 68.4 ± 25.4 mg respectively; p= 0.016). On the contrary, in the other trial, the amounts were higher in the intervention group, but with no significant difference (42). Contradictory results have been attributed to the higher rate of morality in the control group.

Adverse events (AEs): Only one study detailed AEs as a predefined outcome (42). Diarrhea occurred in 15% of the participants in the paraffin oil group (n=3), with a non-significant difference compared with the standard treatment. In another study, it was only reported that no AEs were due to the use of paraffin (40). No study reported serious AEs.

Coconut oil vs. standard treatment

Mortality. In the case of the GL with coconut oil, four RCTs (37)(38)(42)(43) compared this intervention with standard treatment, including 212 participants with acute AlP poisoning, 106 of whom received coconut oil, giving an RR of 0.82 (95% CI 0.69 to 0.98), with a non-relevant level of heterogeneity (I^2=0%), shown in *Figure 11* (Forest plot of comparison: Coconut oil versus standard therapy, outcome: 2.1 Mortality). In the sensitivity analysis through other summary measures, the estimates are maintained with an OR of 0.50 (95% 0.27 to 0.93, I^2=0%). However, continuing with the sensitivity analysis, the only trial rated as low risk of bias (42), reported a non-significant lower mortality in the coconut oil group (RR= 0.94, 95% IC = 0.67 to 1.31).

Subgroup: latency from exposure to AlP

Three trials (37)(38)(43) reported the inclusion of patients with latency from AlP exposure greater than 2 hours. Pooling the results as a subgroup of the main analysis (analysis 2.1, outcome 1: Mortality) presents an RR of 0.78 (95% CI of 0.64 to 0.96; participants = 172; I^2 = 0%) shown in*Figure 12* . Once again, the only trial (42) that included patients within 2 hours of latency is the one with the lowest risk of bias and found no statistically significant differences in mortality between the two groups.

Subgroup: amount of AlP ingested

Two studies (37)(38) reported a mean ingestion between participants of two or more AlP tablets, and treating these as a subgroup of the main analysis (analysis 2., outcome: mortality) gives an RR of 0.79 (95% CI of 0.63 to 1.00), shown in *Figure 13* . Likewise, the two remaining trials (42)(43), which reported lower amounts, give an RR of 0.86 (95% CI of 0.69 to 1.13).

Length of hospital stay. Only two studies (42)(43) reported the length of hospital stay, so it was not possible to estimate a pooled measure. In the study rated as the lowest risk of bias (42), the length of hospital stay was significantly greater in the coconut group (mean of 13.67 days ± 6.38) than in the standard treatment group (7.67 days ± 3.19).

Need for mechanical ventilation. Three of the clinical trials (38)(42)(43) reported the need for intubation and mechanical ventilation. By combining their results, a difference in favor of lavage with coconut oil was obtained, not statistically significant (RR= 0.84, 95% CI= 0.67 to 1.04; $I^{2=}$ 0%) shown in *Figure 14*

*Need and amount of vasopressor agents.*Only one of the studies reported the need for vasopressors as a specific outcome, and a slight decrease in the requirement for these agents was evidenced between the coconut oil group and the control group, with no significant differences (38). In another study, the amount of vasoactive agents were also lower in the coconut oil group, although with no significant difference compared to the control group (43). In contrast, in the study with the lowest risk of bias, the median amounts of vasopressors were relatively higher in the intervention group, although with a non-significant difference (42).

Adverse events (AEs): In this comparison as well, only the study rated as having a low risk of bias reported AEs as a specific outcome (42). Nausea occurred in 20% of the participants in the coconut oil group (n=4), with a non-significant difference compared to the control group. In another trial, it was reported that no AEs were observed throughout the study (43).

Paraffin oil vs. Coconut oil

Only one study (42) compared two oil-based GL techniques, reporting a**lower *mortality* rate with paraffin** compared to coconut oil but without statistically significant differences (RR= 0.87, 95% CI= 0.58 to 1.30). Likewise, there was no significant difference between the paraffin oil and coconut oil groups in terms of *length of hospital stay* and the *need for mechanical ventilation.***Diarrhea** and **nausea** (1 with paraffin and 4 with coconut oil) were observed in a small number of participants, again, without significant differences between both interventions.**No severe AEs were reported** .

Quality of the evidence

The evidence quality was evaluated by the **GRADE system** . (*Figure 15* : GRADE Evidence profile).

Potential biases in the review process

Some trials, only reported the median, minimum, and maximum values, and/or the first and third quartiles (when data do not follow a normal distribution), instead of reporting the sample mean and the standard deviation (SD). Being these measures necessary to pool results in a consistent format, a statistical method was used for its estimation (45). We note that even if the means and SD can be satisfactorily estimated from the proposed formulas, it's still a question of to what extent it makes sense to use them if they do not represent the true distribution and dispersion of the data.

Information on the safety of oil-based GL comes exclusively from the RCT. Studies with other designs, which could be valuable in providing pharmacovigilance information on adverse effects, were not included.

Also, we were unable to perform a funnel plot to detect*publication bias* .

DISCUSSION

Summary of main results

The currently available evidence from **4 RCTs (** 39) (40) (41) (42) indicates that **GL with paraffin oil** is an **effective treatment** for acute AlP poisoning, decreasing the **mortality rate** compared with the standard therapy (**RR = 0.62** ; 95%CI = **0.48 to 0.81** ; participants = 226; I^2=10%;*low-quality evidence*)**.** In the subgroup analysis, this effect was only maintained among those participants with the **longest latency** ([?] 2 hs) of AlP exposure (**RR = 0.50** ; 95% CI= **0.34 to 0.74;** participants=124; studies = 2; very low-quality evidence). However, these results are probably influenced by the small number of clinical trials, possibly unsuitable for performing a subgroup analysis or for a meta-regression.

Likewise, the evidence indicates that this intervention reduces the **need for intubation and mechanical ventilation** (RR = **0.62** ; 95%CI = **0.40 to 0.79** ; participants= 226; I^2 = 0%;*low-quality evidence*) . These benefits have not been reflected in the**length of hospital stay** (MD= 10.73; 95%CI = -2.28 to 23.74; I^2 = 65%). The level of heterogeneity could be explained by the results of one of the trials, in which the duration of hospital stay was significantly longer in the **paraffin oil group** because of a higher percentage of survivors (39). The exclusion of this trial gives an MD of 5.64 (95% CI -2.20 to 13.47) decreasing the level of heterogeneity (I^2 = 33%).

Finally, the **need for vasopressors** was **lower** among the participants who received GL with **paraffin oil (** RR=**0.76** ; 95%CI**= 0.61 to 0.94;** studies**= 3;**I^2**= 1%; *low-quality evidence***)

We calculated an NNT from the **mortality** rate of GL with**paraffin oil** (38.9% in the paraffin oil versus 66.4% in the control group), estimating an **NNT of 4** (3.6).

Regarding **GL with coconut oil** , the available evidence from **4 RCTs** (37)(38)(42)(43), indicates a slight reduction in **mortality** in patients with acute AlP poisoning (**RR= 0.82** ; 95%CI = **0.69 to 0.98** ; participants= 112; I^2= 0%; very low-quality evidence). Again, through the subgroup analysis, this effect was only observed among those with **more than 2 hs latency** from AlP exposure (RR= **0.78** ; 95%CI = **0.64 to 0.96;** studies = 3; very low-quality evidence). This effect was not reflected in the other outcomes considered.

Only one RCT that compared both interventions reported AEs among its predefined outcomes and showed a benign safety profile (42). The most frequently reported non-serious AE were gastrointestinal symptoms (diarrhea and nausea) observed in a small number of participants, without significant differences between the two interventions and the control group. No serious AEs were reported.

The included RCTs excluded participants with pre-existing chronic diseases such as cardiovascular diseases, and renal or hepatic disorders. In addition, patients with post-cardiac arrest, pregnant, and lactating women were also excluded.

Overall completeness and applicability of evidence

We do not perform a funnel plot because as a rule of thumb, tests for funnel plot asymmetry should be used only when at least 10 studies are included in the main analysis (46).

CONCLUSIONS

Implications for practice

Limited evidence suggests that GL with paraffin oil is effective in reducing the mortality rate in acute AlP poisoning, showing a relative risk reduction of 38% compared with standard treatment. Likewise, limited evidence showed a relative risk reduction of 38% in favor of paraffin oil concerning the need for intubation and mechanical ventilation. This efficacy was not confirmed in terms of length of hospital stay or the total amount of vasoactive agents used

Very limited evidence suggests that GL with coconut oil may have benefits in terms of mortality in patients with acute AlP poisoning. However, current evidence does not confirm these benefits about the need for mechanical ventilation, hospital length, or vasopressor requirements.

Very limited evidence suggests that both interventions would have a benign safety profile. However, only one trial reported AEs as a predefined outcome, these being gastrointestinal, mild, and transient.

Implications for research

More information is needed on the balance of benefits and adverse effects before general recommendations can be made. Further research should fully consider evaluation in people with pre-existing conditions and explore variations in drug regimens.

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DECLARATION OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

Omar De Santi: Conceptualization (Lead), Data curation (Lead), Formal analysis (Lead), Investigation (Lead), Methodology (Lead), Project administration (Lead), Resources (Equal), Software (Equal), Supervision (Lead), Validation (Equal), Visualization (Equal), Writing – original draft (Lead); Cecilia A. Di Niro: Data curation (Equal), Formal analysis (Equal), Methodology (Equal), Resources (Equal), Software (Equal), Validation (Equal), Writing – original draft (Equal); Marcelo J. Orellana : Formal analysis (Equal), Investigation (Equal), Methodology (Equal), Software (Equal), Validation (Equal); Heba Lashin: Data curation

(Equal), Resources (Equal), Validation (Equal); Vanina Greco*:* Supervision (Equal). All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this review and meta-analysis were included in this article and are attached as **Supporting information.**

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