The therapeutic benefit of antioxidants on the outcome of acute aluminum phosphide poisoning: a systemic review and meta-analysis

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This systematic review and meta-analysis pool evidence available from clinical trials to verify the effect of antioxidants on the outcome of acute aluminum phosphide (AlP) poisoning. A systematic review complied with "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) Protocols. Meta-analysis was conducted on 10 studies that fulfill eligibility criteria. Four antioxidants were implemented: N-Acetyl cysteine (NAC), L-Carnitine, Vitamin E, and Co-enzyme Q10 (Co Q10). Risk of bias, publication bias, and heterogeneity were assessed to ensure the results' reliability. Antioxidants significantly decrease mortality of acute AlP poisoning around three folds (OR = 2.684, 95% CI: 1.764–4.083; $P < .001$) and decrease the need for intubation and mechanical ventilation by two folds (OR = 2.391, 95% CI 1.480–3.863; $P < .001$) compared with control. Subgroup analysis revealed that NAC significantly decreases mortality by nearly three folds (OR = 2.752, 95% CI: 1.580–4.792; $P < .001$), and vitamin E significantly decreases mortality by nearly six folds (OR = 5.667, 95% CI: 1.178–27.254; $P = .03$) compared with control. L-Carnitine showed a borderline significance ($P = .050$). Co Q10 decreased the mortality compared with the control; however, the difference was not statistically significant ($P = .263$). This meta-analysis provides solid evidence regarding the efficacy of antioxidants in improving the outcome of acute AlP poisoning with reference to NAC. Wide confidence interval and small relative weight affect reliability regarding vitamin E efficacy. Future clinical trials and meta-analyses are recommended. To our knowledge, no previous meta-analysis was conducted to investigate the efficacy of treatment modalities for acute AlP poisoning.

Key words: aluminum phosphide poisoning; antioxidants; L-carnitine; N-acetyl cysteine; vitamin E; co-enzyme Q10.

Introduction

Aluminum phosphide (AlP) is a highly toxic phosphine-generating pesticide that is widely used in many countries. In the last few years, AlP gained popularity as a suicidal agent, with an escalating rise in cases of acute poisoning.[1]

Upon oral intake of AlP, it rapidly liberates the highly toxic phosphine (PH_3) gas that interferes with cellular respiration. PH_3 disrupts mitochondrial functions by inhibiting cytochrome oxidase and adenosine triphosphate (ATP) formation. Furthermore, phosphine induces oxidative stress by enhancing the generation of reactive oxygen species (ROS) and inhibition of enzymatic antioxidants such as catalase (CAT), glutathione reductase (GR), and superoxide dismutase (SOD). Disturbed redox status results in lipid peroxidation, destroying the various cellular structures and enhancing cellular death.[2,3]

Clinically, acute AlP poisoning manifested with severe metabolic acidosis and refractory cardiogenic shock. The management of phosphide poisoning is confined to supportive measures in the absence of an antidote. Unfortunately, acute AlP poisoning is associated with high mortality.[4,5] Thus, adopting therapeutic interventions based on the mechanism of acute AlP poisoning is necessary.[6–8]

Oxidative stress is a well-established mechanism of acute phosphide poisoning.[9,10] Therefore; several clinical trials proposed that antioxidants, including N-acetyl cysteine,[11–16] L-carnitine,[17,18] Vitamin E,[19] and Co-enzyme Q10 (Co Q10),[20] could counteract the fatal phosphine effects. However, clinical studies often have limitations, such as inconsistent results, heterogeneity, and small sample size. Therefore, sporadic trials assess the efficacy of therapeutic intervention with limited validity.[21]

Systematic reviews are done using a standardized approach better than traditional narrative reviews, randomly searching literature with a high possibility of escaping valuable studies. Thus, systematic reviews have been commonly applied in different medical specialties for a long time. However, in toxicology, the first systematic review was in 2014, and a limited number of systematic reviews have been published since then.[22,23]

Meta-analysis is a statistical method that combines the results of multiple individual studies to generate a new hypothesis. A meta-analysis is a powerful tool with the strongest statistical evidence in clinical research. It overcomes the problem of small numbers of patients in sporadic studies and assesses the effects of specific treatments with high precision. Therefore, meta-analysis provides the "platinum standard of evidence".[24,25]

Objectives

The current study adopted a systematic review and meta-analysis to pool the evidence available from clinical trials that studied the

Table 1. List of advanced search strategies in the Scopus, Web of Science, and Pubmed databases.

	Search items of query
Scopus	(acute) AND (aluminum OR aluminium) AND (phosphide) AND (poisoning OR toxicity) AND (antioxid* OR nac OR n-acetyl AND cysteine OR l-carnitine OR vitamin OR co-enzyme)
Web of Science	((((TS = ((acute))) AND TS = ((aluminum) OR (aluminium))) AND TS = ((phosphide))) AND TS = ((toxicity) OR (poisoning))) AND TS = ((antioxid*) OR (NAC) OR (N-acetyl cysteine) OR (L-carnitine) OR (vitamin) OR (co-enzyme))
Pubmed	((((((acute))) AND ((aluminum OR aluminium))) AND ((phoshide))) AND ((poisoning OR toxicity))) AND ((antioxid* OR NAC OR N-acetyl cysteine OR L-carnitine OR vitamin OR co-enzyme))

effect of various antioxidants in improving the outcome of acute AlP poisoning.

Methods

In the current study, a systematic review was performed in compliance with the requirements of the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocols.[26] The study was approved by the Research Ethics Committee of the Faculty of Medicine, Alexandria University (IRB Number: 00012098, FWA Number: 00018699, Approval Serial Number: 0305138).

(i) Study design types

The study included all published clinical studies that used antioxidants in the management of acute AlP poisoning and fulfilled illegibility criteria.
Participants: patients with acute AlP poisoning.
Intervention: antioxidant therapy along with conventional supportive measures.
Control: conventional supportive measures.
Outcome:

(a) Primary outcome: mortality percentage.
(b) Secondary outcome: the need for endotracheal intubation and mechanical ventilation.

(ii) Exclusion criteria

(a) Non-human studies that include in vitro and animal studies.
(b) Registered ongoing clinical trials that are unpublished at the time of conduction of the study.
(c) Co-exposure to other toxicants with AlP.
(d) One group without comparison arm, case series, and case reports.
(e) When additional interventions are used other than conventional supportive measures and antioxidants.

(iii) Information sources

The electronic retrieval method was implemented, and the retrieval time started from the established database on 2022 February 25. The retrieval database included advanced searches in Scopus, PubMed (National Library of Medicine), Web of Science (Clarivate), and Egyptian journals that were accessed through the Egyptian Knowledge Bank (EKB). The retrieved studies were in the English language.

(iv) Search strategy

The advanced search strategies of the Scopus, Web of Science, and Pubmed databases were performed, as illustrated in Table 1. Egyptian articles were retrieved from EKB using the exact keywords.
(v) Study selection

The search results were exported into reference management software (EndNote™ X8), and duplicated studies were omitted. Two reviewers screened titles and abstracts separately to exclude studies according to the eligibility criteria. Then, the reviewers obtained the full text for the articles and assessed them again based on the inclusion criteria.[27]

(vi) Data extraction

The two reviewers comprehensively read the full text of articles that fulfill the inclusion criteria. Then, they extracted relevant data in a designed Excel sheet that consisted of the following sections:

(a) General research data: title, authors, and year of publication.
(b) Study design: intervention (type of antioxidant) and the number of patients in intervention and control groups.
(c) Base-line or on-admission characteristics of the patients in intervention and control groups.
(d) Outcome: mortality percentage and need for endotracheal intubation and mechanical ventilation.

(vii) Data analysis

Data analysis was done by comprehensive meta-analysis software version 2. Effect size odds ratio for mortality proportion, the proportion of intubation, and Odds ratio (OR) were presented with an estimate of precision using a 95% confidence interval (CI).

Risk of bias assessment is a quality assessment that establishes transparency of generated hypothesis. The modified Cochrane Collaboration tool was used to assess the risk of bias for each included study.[28]

Heterogeneity denotes variations in observed effect(s) among researches, which, if excessive, suggest uncontrolled factors influencing the observed effect(s). In the current study, the heterogeneity was assessed using Cochrane Q statistic, which has Chi-Square statistic, and I^2 statistic and P-value, statistical heterogeneity was considered with I^2 of >50% or $P < .1$.[29]

The summary of the meta-analysis results was presented graphically using the forest plot.[30] Subgroup analysis was considered based on the type of antioxidants for each subgroup.

Publication bias means that studies with small sample sizes could have less chance of publication than larger studies. The funnel plot is a graphical method to assess the presence of publication bias by plotting effect sizes against their precisions. The symmetry of the funnel plot denotes the absence of publication bias.[31]

Results

The search in Scopus, Web of Science, PubMed, and Egyptian Journals yielded 204, 13, 20, and 16 articles, respectively. One article was obtained by direct author contact. After removing duplicate articles and excluding articles that did not meet the
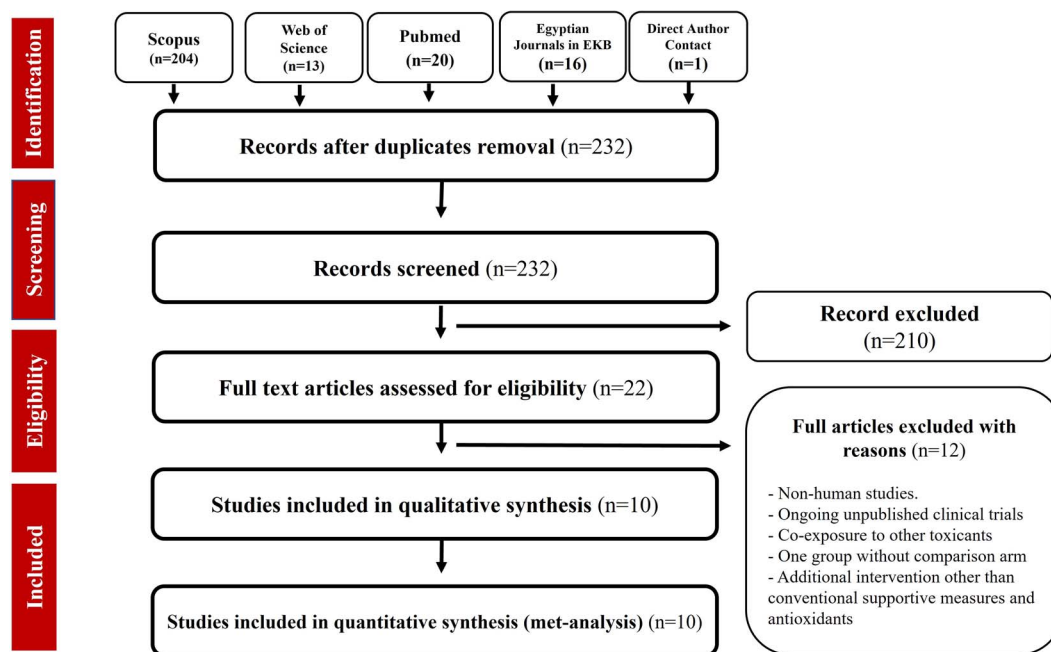
Fig. 1. PRISMA flow diagram describing the phases of the current systematic review. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

inclusion criteria, 10 articles were included in the meta-analysis, as illustrated in the PRISMA flow chart (Fig. 1).

Assessment of risk of bias

The risk of bias was assessed using the modified Cochrane Collaboration tool. The bias was judged as high, low, or unclear for individual elements from five domains (selection, reporting, performance, detection, attrition).[28–32] All studies included in the meta-analysis had a low or unclear risk of bias, except the study of Taghaddosinejad et al. 2016 had a high risk of selection bias, as demonstrated in Fig. 2.

Data of included studies

Table 2 revealed general publication data of the studies included in the meta-analysis. The studies included 465 patients; 227 received the conventional supportive measures (control groups), and 238 received conventional supportive measures along with antioxidant therapy (intervention groups).

Four types of antioxidants were used in these studies as follows:

(i) N-Acetyl cysteine (NAC): Tehrani et al. (2013),[11] Agarwal et al. (2014),[12] Taghaddosinejad et al. (2016),[13] Bahalla et al. (2017),[14] El-Ebiary and Abuelfadl (2017),[15] and Emam et al. (2020).[16]
(ii) L-Carnitine: Elgazzar et al. (2019)[17] and Mabrouk et al. (2019).[18]
(iii) Vitamin E: Halvaei et al. (2017).[19]
(iv) Co-enzyme Q 10 (Co Q10): Darwish et al. (2020).[20]

On-admission data

Table 3 illustrates the admission data most relevant to acute AlP poisoning, including the mean patients' age, exposure data, vital signs, and Arterial Blood Gases (ABG).

Almost no statistical differences were recorded between each study's control and intervention groups regarding baseline data. The classical clinical features of acute AlP poisoning were present in almost all studies, including decreased systolic and diastolic blood pressures and decreased pH and bicarbonate levels.

In addition, the studies investigated other laboratory parameters less relevant to acute AlP poisoning, which include liver enzymes [alanine transaminase (ALT), aspartate transaminase AST), and renal function test (creatinine, urea, blood urea nitrogen (BUN)]. There were no statistical differences between each study's control and intervention groups regarding these parameters (Supplementary Table 1).

Outcome (Table 4)

Out of 10 studies, 5 clinical studies showed significantly lower mortality percentages in intervention groups compared with control groups. These studies include Tehrani et al. (2013),[11] Agarwal et al. (2014),[12] El-Ebiary and Abuelfadl (2017),[15] and Emam et al. (2020),[16] which used NAC, and Halvaei et al. (2017),[19] which use Vitamin E.

Out of seven studies, three clinical studies showed a significantly lower need for intubation and mechanical ventilation in intervention groups compared with control groups. These studies include Tehrani et al. (2013),[11] which used NAC, Elgazzar et al. (2019),[17] which used L-Carnitine, and Halvaei et al. (2017),[19] which used Vitamin E.

Effects of antioxidants on outcomes of acute AlP poisoning
Primary outcome (mortality percentage)

Overall, 10 studies with 465 participants were included in the meta-analysis. The effect size of antioxidants was assessed at first pooling in all possible studies.

The statistical heterogeneity was assessed using Cochran's Q test. Cochran's Q value of 4.8 with $P = .85$ indicates no statistically significant heterogeneity of the intervention effects across the studies, I^2 statistic that reflects the percentage of variation attributed to between-study heterogeneity showed 0% variation ($I^2 = .000$, $Tau^2 = .000$), So, the fixed-effect model was applied.
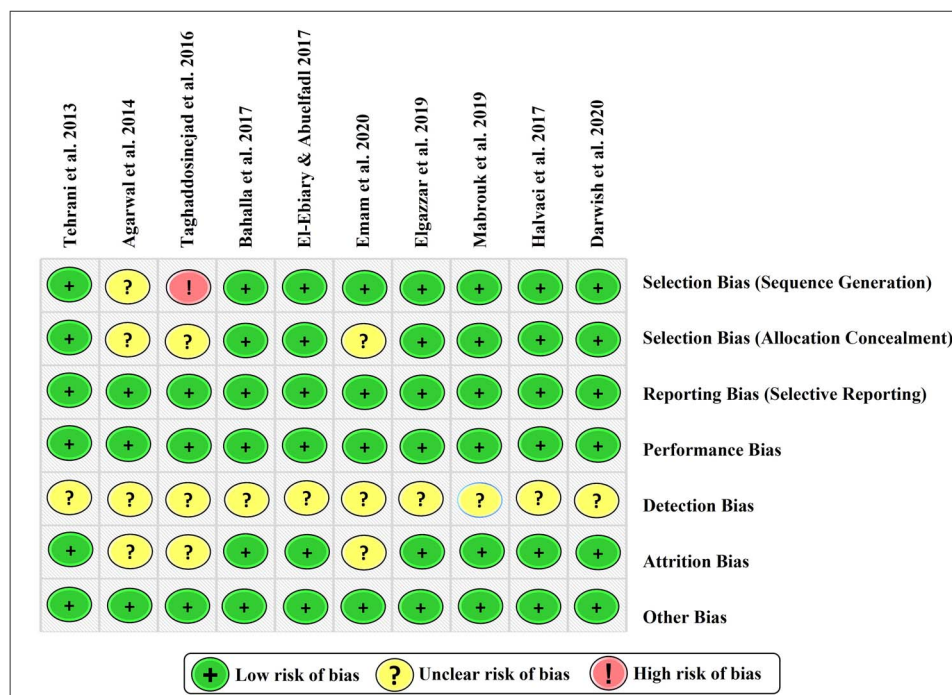
Fig. 2. Risk of bias assessment of the studies included in a meta-analysis using the modified Cochrane Collaboration tool.

Table 2. Description of the clinical studies included in the meta-analysis.

Studies included in meta-analysis	Country	Groups	Antioxidant	Sample size
Tehrani et al. 2013[11]	Iran	Control		15
		Intervention	NAC	22
Agarwal et al. 2014[12]	India	Control		22
		Intervention	NAC	24
Taghaddosinejad et al. 2016[13]	Iran	Control		23
		Intervention	NAC	23
Bahalla et al. 2017[14]	India	Control		26
		Intervention	NAC	24
El-Ebiary & Abuelfadl 2017[15]	Egypt	Control		15
		Intervention	NAC	15
Emam et al. 2020[16]	Egypt	Control		30
		Intervention	NAC	30
Elgazzar et al. 2019[17]	Egypt	Control		25
		Intervention	L-Carnitine	25
Mabrouk et al. 2019[18]	Egypt	Control		25
		Intervention	L-Carnitine	25
Halvaei et al. 2017[19]	Iran	Control		16
		Intervention	Vit E	20
Darwish et al. 2020[20]	Egypt	Control		30
		Intervention	Co Q10	30

The meta-analysis showed a significant difference between antioxidants and control in favor of antioxidants in decreasing mortality among patients with acute AlP poisoning (OR = 2.684, 95% CI: 1.764–4.083; $P < .001$), as shown in Fig. 3.

Subgroup analysis

The meta-analysis showed a significant difference between antioxidants and control in favor of antioxidants in decreasing mortality among patients with acute AlP poisoning in both vitamin E, and NAC subgroups. Vitamin E significantly decreased the mortality by nearly six folds compared with the control (OR = 5.667, 95% CI: 1.178–27.254; $P = .030$). In addition, NAC significantly decreases the mortality by nearly three folds

compared with the control (OR = 2.752, 95% CI: 1.580–4.792; $P < .001$). Nevertheless, the L-Carnitine subgroup showed a borderline statistical significance in decreasing mortality compared with the control (OR = 2.451, 95% CI: .998–6.019; $P = .05$). On the other hand, Co Q10 showed no statistically significant difference in reducing mortality (OR = 1.902, 95% CI: .617–5.863; $P < .263$) (Fig. 4).

Assessment of publication bias

The presence of publication bias was assessed visually by funnel plot. There was no visual asymmetry on visual inspection (Fig. 5). Statistically, Trim and fill analysis showed that when using the random effects model, no studies were missing to the left of

Table 3. Baseline data (on admission) of acute AlP-poisoned patients in the studies included in the meta-analysis.

Studies included in meta-analysis	Groups	Age (year)	Time till admission (minute)	Amount of AlP (gram)	SBP (90–120 mmHg).	DBP (60–80 mmHg)	Pulse (60–100 beat/minute)	pH (7.35–7.45)	PaCO2 (35–45 mmHg).	HCO3 (22–26 mEq/l)
Tehrani et al. 2013[11]	Control	24.7 ± 6.4	78.9 ± 59.6	5.4 ± 3.3	87.3 ± 13.6	—	94.6 ± 21.1	7.35 ± .08	—	16.8 ± 4.1
	Intervention	23.5 ± 7.8	102.1 ± 63	4.8 ± .9	93.7 ± 17.8	—	88.7 ± 17.1	7.36 ± .13	—	19.2 ± 5.8
Agarwal et al. 2014[12]	Control	27.74 ± 8.86	—	—	NS	NS	NS	7.2 ± .2	33.7 ± 12	14.1 ± 7.8
	Intervention	—	—	—	—	—	—	7.2 ± .2	31.3 ± 15.1	13.7 ± 6.1
Taghaddosinejad et al. 2016[13]	Control	28.39 ± 1.11	—	—	106.63 ± 2.4	—	80.36 ± 3.9	—	—	—
	Intervention	26.65 ± 1.06	—	—	100.15 ± 3.9	—	82.76 ± 3.1	—	—	—
Bahalla et al. 2017[14]	Control	S*	NS	—	NS	—	—	—	—	—
	Intervention									
El-Ebiary & Abuelfadl 2017[15]	Control	NS	168	1.680	NS	NS	NS	7.3 ± .1	23.8 ± 5.6	—
	Intervention		180	1.680				7.4 ± .1	27.2 ± 8.1	—
Emam et al. 2020[16]	Control	24.43 ± 9.66	70.8 ± 35	NS	94.83 ± 21.19	57.33 ± 15.44	104.27 ± 20.51	7.28 ± .13	30.43 ± 6.76	18.15 ± 4.40
	Intervention	24.40 ± 10.55	75 ± 37	NS	92.16 ± 21.95	56.33 ± 16.00	104.57 ± 20.51	7.27 ± .14	30.46 ± 6.94	18.05 ± 4.24
Elgazzar et al. 2019[17]	Control	23.9 ± 7.6	120	1.680	NS	NS	NS	7.21 ± .02	30.7 ± 9.4	13.9 ± 5.5
	Intervention	22.9 ± 7.8	90	1.680				7.23 ± .10	35.0 ± 6.1	16.2 ± 5.1
Mabrouk et al. 2019[18]	Control	26.6	120	—	89.5	57.5	97.2	7.2 ± .10	31.4 ± 9.1	14.9 ± 6.3
	Intervention	25.3	120	—	96	56.7	96	7.3 ± .10	35.2 ± 5.6	17.1 ± 5.7
Halvaei et al. 2017[19]	Control	26.31 ± 8.90	74.06 ± 43.29	2.64	89.81 ± 13.29	60.67 ± 1.91	95.07 ± 15.04	7.38 ± .09	27.81 ± 7.30	16.88 ± 4.24
	Intervention	24.95 ± 8.11	98.25 ± 76.66	2.15	89.16 ± 17.95	55.76 ± 11.03	90.50 ± 16.68	7.40 ± .07	31.81 ± 7.06	20.06 ± 5.47
Darwish et al. 2020[20]	Control	22.8 ± 7.03	193.2 ± 78	1.39 ± .6	91.43 ± 24.14	56.19 ± 17.46	108.33 ± 24.26	7.37 ± .10	27.87 ± 7.84	16.03 ± 4.47
	Intervention	21.5 ± 4.98	147 ± 63	1.93 ± 1.2	90.00 ± 12.33	59.23 ± 12.30	96.47 ± 31.27	7.37 ± .14	26.97 ± 7.42	16.50 ± 4.27

NS, non-significant difference among categorized data of intervention and control group (mean values were not mentioned). S*, significant difference among categorized data of intervention and control group (mean values were not mentioned).

Table 4. Outcome of acute AlP-poisoned patients in the studies included in the meta-analysis.

Studies included in meta-analysis	Groups	Mortality %	P	Intubation and mechanical ventilation %	P
Tehrani et al. 2013[11]	Control	60	< .05*	73.30	0.040*
	Intervention	36		45.40	
Agarwal et al. 2014[12]	Control	82	0.046*	—	—
	Intervention	54		—	
Taghaddosinejad et al. 2016[13]	Control	43.47	0.36	—	-
	Intervention	30.43		—	
Bahalla et al. 2017[14]	Control	88.5	0.91	—	-
	Intervention	87.5		—	
El-Ebiary & Abuelfadl 2017[15]	Control	80	0.01*	80	0.058
	Intervention	33		47	
Emam et al. 2020[16]	Control	43.30	< .05*	20.00	0.754
	Intervention	20		23.30	
Elgazzar et al. 2019[17]	Control	80	0.123	56	0.009*
	Intervention	60		20	
Mabrouk et al. 2019[18]	Control	80	0.208	40	0.225
	Intervention	64		24	
Halvaei et al. 2017[19]	Control	50	0.02*	62	< .05*
	Intervention	15		30	
Darwish et al. 2020[20]	Control	36.67	0.26	56.7	0.21
	Intervention	23.33		40	

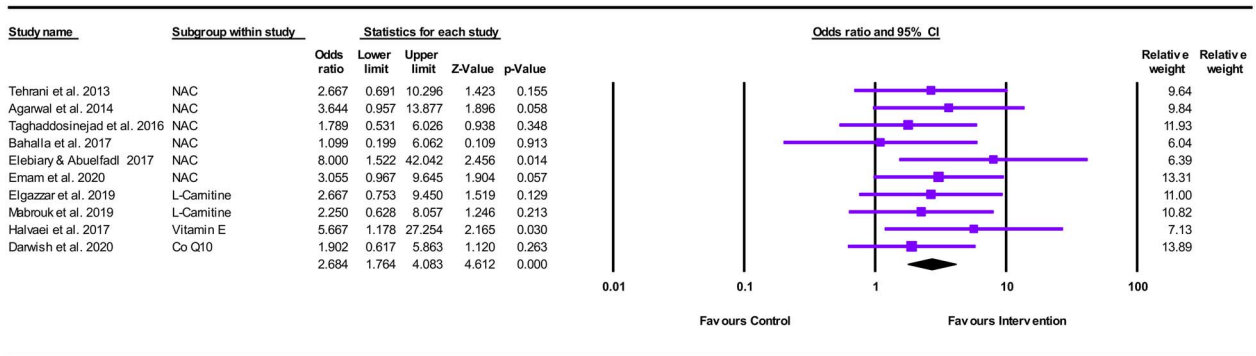*Significant difference between intervention and control group.

Fig. 3. Forest plot illustrating the effect of antioxidants on reducing mortality in acute AlP poisoning.
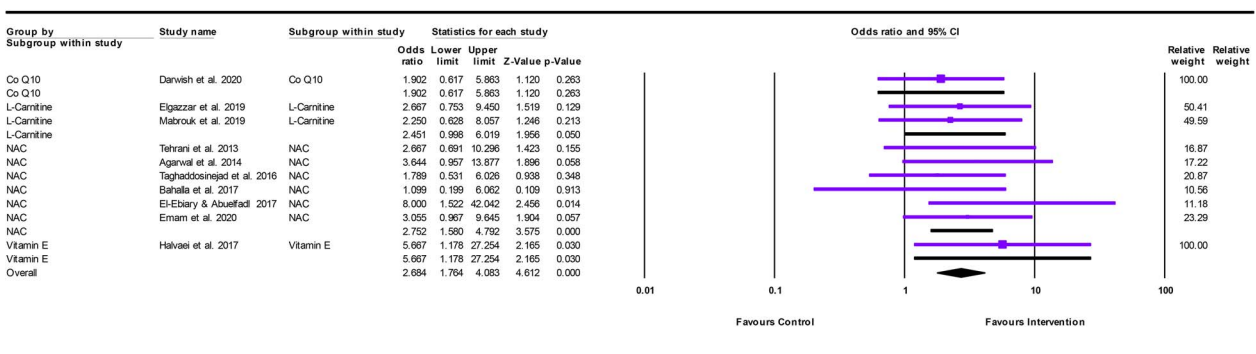

Fig. 4. Forest plot illustrating the effect of each type of antioxidant on reducing mortality in acute AlP poisoning (subgroup analysis).

the mean, suggesting no bias against the effect of antioxidants (adjusted effect size exactly as observed .98; 95% CI: .568: 1.47, $P < .001$).

Secondary outcome (need for intubation and mechanical ventilation)

The statistical heterogeneity was assessed using Cochran's Q test. Cochran's Q value of 6.6 with $P = .356$ indicates no statistically significant heterogeneity of the intervention effects across the studies, I^2 statistic that reflects the percentage of variation attributed to between-study heterogeneity showed a 9.605% variation ($I^2 = 9.605$, $Tau^2 = .043$), So, the fixed-effect model was applied.

The meta-analysis showed a significant difference between antioxidants and control in favor of antioxidants in decreasing the number of patients with acute AlP poisoning who need intubation
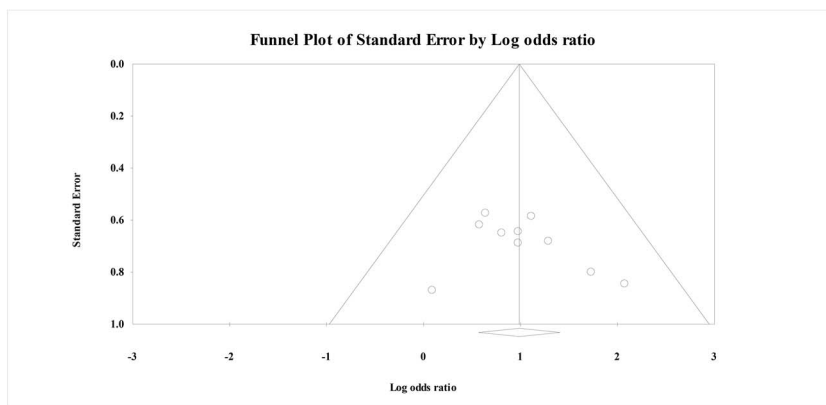
Fig. 5. Funnel plot for the meta-analysis of the effects of antioxidants on reducing mortality in acute AlP poisoning.
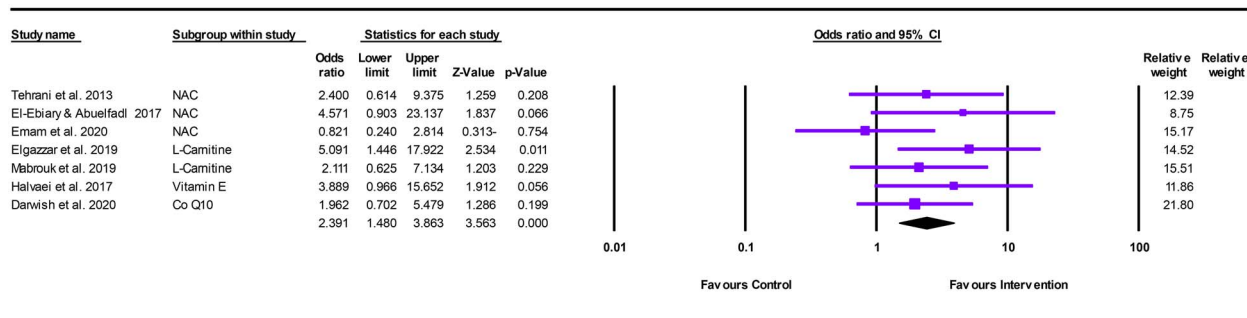

Fig. 6. Forest plot illustrating the effect of antioxidants on reducing the need for endotracheal intubation and mechanical ventilation in acute AlP poisoning.

and mechanical ventilation (OR = 2.391, 95% CI: 1.480–3.863; $P < .001$) (Fig. 6).

Assessment of publication bias

The presence of publication bias was assessed visually by funnel plot. There was no visual asymmetry on visual inspection (Fig. 7). Statistically, Trim and fill analysis showed that when using the random effects model, no studies were missing to the left of the mean, suggesting no bias against the effect of antioxidants (adjusted effect size exactly as observed .88; 95% CI: .58: 1.65, $P < .001$).

Discussion

Acute AlP poisoning remains one of the most gravid toxicities associated with poor prognosis. Currently, supportive measures are implemented empirically in attempts to rescue AlP-poisoned patients. Phosphine, the toxic constituent of AlP, is proven to exert its toxic effects through interference with cellular respiration and induction of oxidative stress.[33,34] Thus, individual clinical studies have evaluated the efficacy of different antioxidants in improving the outcome of acute AlP poisoning. Each study applied a single antioxidant in a relatively limited number of AlP-poisoned patients.[11–20] The results of these different studies did not yield an uninformed conclusion regarding the effect of antioxidants in improving the prognosis of acute AlP poisoning. Also, no previous studies compared the effects of different antioxidants in managing these cases.

A meta-analysis is a powerful statistical tool adopted to combine the results of multiple studies to provide a conclusion.[35] The current study started with a comprehensive performance of a

systematic review in compliance with the requirements of the reporting rules in PRISMA protocols. Then, all published clinical studies that used antioxidants in managing acute AlP poisoning were included in a meta-analysis according to the eligibility criteria.[36]

The meta-analysis encompasses 10 published articles that implemented four antioxidants. NAC was used in six studies; Tehrani et al. (2013),[11] Agarwal et al. (2014),[12] Taghaddosinejad et al. (2016),[13] Bahalla et al. (2017),[14] El-Ebiary and Abuelfadl (2017),[15] and Emam et al. (2020).[16] Two studies used L-Carnitine: Elgazzar et al. (2019)[17] and Mabrouk et al. (2019).[18] Although Vitamin E was used in a study by Halvaei et al. (2017),[19] Co Q 10 was used in a study conducted by Darwish et al. (2020).[20]

Each antioxidant has a different mechanism by which it exerts its antioxidant effect. NAC is a potent antioxidant that acts as a disulfide bonds reductant, ROS scavenger, and glutathione precursor.[37] L-Carnitine (4-N-trimethylammonium-3-hydroxybutyric acid) is a vital structure in mitochondrial membranes essential for cellular respiration. Also, L-Carnitine scavenger ROS and decreases lipid peroxidation.[8,38,39] Vitamin E, or tocopherol, is a powerful antioxidant that decreases the generation of ROS during fat oxidation and free radical reactions.[40] Considering Co Q10 or Ubiquinone, it is a constituent of mitochondrial membranes essential in oxidative phosphorylation and energy production at the cellular level. Also, Co Q10 selectively enhances systolic cardiac function.[41,42]

It was noticed that 6 studies out of 10 used NAC. The popularity of NAC could stand behind the increasing number of studies that used NAC in relation to other antioxidants. It is worth mentioning that NAC is a mucolytic commonly used to manage various bronchopulmonary diseases. In clinical toxicology, NAC is an effective
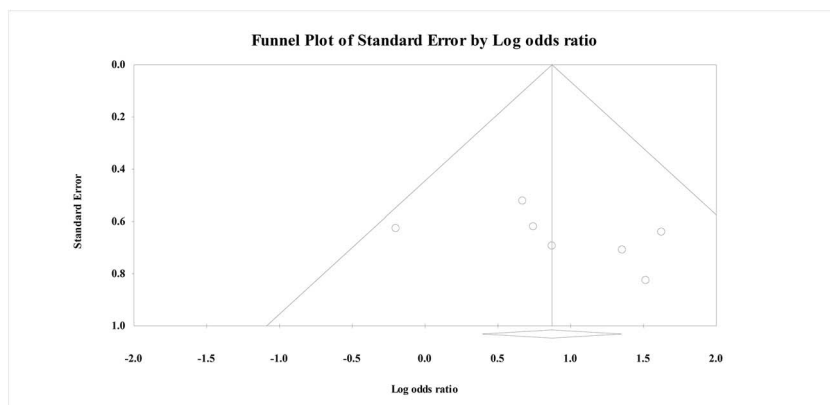
Fig. 7. Funnel plot for the meta-analysis of the effects of antioxidants on reducing the need for endotracheal intubation and mechanical ventilation in acute AlP poisoning.

antidote in treating acute acetaminophen poisoning. Also, NAC prevents the development of hepatotoxicity and cardiotoxicity following acute zinc phosphide poisoning.[37] Thus, NAC is convenient in healthcare institutes, and prescribed for managing different disorders. In the field of research, NAC is one of the widely used antioxidants in in vitro and in vivo studies, as well as clinical studies.[43] Most researchers considered NAC an ideal antioxidant that efficiently ameliorates oxidative stress.[44,45]

The clinical studies included in the meta-analysis were conducted in Egypt,[46] Iran,[4] and India[47] that pointing to a high prevalence of acute pesticide poisoning, including AlP, in these developing agricultural countries. The mean ages of the patients in all studies were less than 30 years, which could be explained by the popularity of AlP as a suicidal agent among youth. Hypotensive shock and metabolic acidosis were evident in nearly all included studies on admission which represent classical manifestations of acute AlP poisoning. The statistical comparability between control and intervention groups was proved considering almost all baseline data of the included studies that ensure the reliability of their results.

The outcome of individual clinical studies highlighted the controversy regarding the ability of antioxidants to improve the outcome of acute AlP poisoning; therefore, this meta-analysis was conducted to formulate a universal conclusion in this context.

To ensure statistical inference, the current meta-analysis started with the assessment of the risk of bias for each included study using the modified Cochrane Collaboration tool.[28] In addition, the heterogeneity was assessed and was found to be accepted. Lastly, publication bias was excluded as the funnel plot was symmetrical.[31]

The current meta-analysis proved that antioxidants significantly decreased the mortality of AlP-poisoned patients by nearly three folds. In addition, antioxidants significantly decrease the number of patients who need intubation and mechanical ventilation in relation to control by two folds.

Further subgroup analysis was done to evaluate the effect of each antioxidant on decreasing AlP-related mortality. The results revealed that Vit E and NAC significantly reduced mortality by almost six and three folds, respectively, compared with the control. However, a wide CI (1.178–27.254) and small relative weight (7.13%) could affect the reliability regarding the efficacy of vitamin E in decreasing the mortality of acute AlP poisoning, which needs future clinical trials and meta-analyses.

On the other hand, the L-Carnitine subgroup showed a borderline statistical significance in decreasing mortality compared

with the control ($P = .05$). Also, Co Q10 decreased the mortality compared with the control; however, the differences were not statistically significant.

The current meta-analysis was restricted to the 10 clinical studies that complied with eligibility criteria and were published at the time of study conduction. This meta-analysis investigated the effects of four types of antioxidants, two of which, vitamin E and Co Q10, were represented by one study each. Many antioxidants' efficacy in managing acute AlP poisoning, such as melatonin, vitamin C, and curcumin, could not be assessed. Thus, it is necessary to conduct clinical studies that implement various antioxidants in managing acute AlP poisoning. These future clinical studies should extend to investigating the efficacy of antioxidants not previously mentioned in published clinical trials, along with promising antioxidants that are not extensively investigated, such as L-Carnitine, vitamin E, and Co Q10. The availability of a large number of clinical studies will enable the conduct of more comprehensive meta-analyses in the future.

Despite the current study being limited to 10 available studies, it provides solid evidence regarding the efficacy of antioxidants in improving the prognosis of AlP-poisoned patients. This meta-analysis recommends the addition of NAC to national and international guidelines for the management of acute AlP poisoning. This research is the first meta-analysis to investigate the effect of one of the treatment modalities of acute AlP poisoning. Therefore, further meta-analyses are needed to verify the efficacy of all other treatment modalities in improving the patients' outcome, then the adoption of evidence-based guidelines for managing acute AlP poisoning will be possible.

Conclusions

The current meta-analysis pooled the evidence available from published clinical studies for the effects of antioxidants in improving the outcome of AlP-poisoned patients. Meta-analysis proved that antioxidants decrease mortality of acute AlP poisoning three folds in relation to control. Subgroup analysis proposed NAC as the best antioxidant that reduced mortality by three folds. Also, antioxidants significantly decrease the need for intubation and mechanical ventilation by two folds. This meta-analysis provides solid evidence regarding the therapeutic benefit of antioxidants on the outcome of acute AlP poisoning. Subsequently, based on this meta-analysis, NAC should be included as a standard treatment in treating acute AlP-poisoned patients.

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Author contribution statement

Dr Zahraa Khalifa Sobh contributed to the research concept, work design, advanced search of databases, data extraction, results interpretation, and manuscript drafting. Dr Asmaa Abd Elhameed Ahmed contributed to the advanced search of databases, data extraction, statistical analysis, results interpretation, and manuscript drafting. All authors revised and approved the final manuscript.

Supplementary data

Supplementary material is available at *TOXRES* Journal online.

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Data availability

The dataset used in the study is available from the corresponding author upon reasonable request.

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