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Protective effects of lipid emulsion on vital organs through the LPS/TLR4 pathway in acute organophosphate poisoning

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Abstract Organophosphorus poisoning (OP), a prevalent form of pesticide intoxication, induces severe multiorgan dysfunction. While combined lipid emulsion (ILE) and standard treatment (pralidoxime methiodide & atropine) demonstrate improved clinical outcomes, the therapeutic mechanisms remain elusive.

Methods An OP rat model was established for: (1) histopathological assessment via hematoxylin-eosin (H&E) staining; (2) LPS/Toll-like receptor 4 (TLR4) quantification through flow cytometry; (3) inflammatory cytokine measurement using enzyme-linked immunosorbent assay (ELISA); and (4) cytokine mRNA analysis via reverse transcription PCR (RT-PCR). TLR4 pathway validation employed anti-TLR4 intervention.

Results After survived 24 h, multiple organs were damaged in rats with organophosphorus poisoning. Treatment with standard treatment or only lipid emulsion slightly alleviated the symptoms of poisoning, However, when standard treatment was combined with lipid emulsion, the symptoms were significantly alleviated, and the expression level of TLR4 was significantly decreased in the ST + ILE group. After anti-TLR4 was used to block the LPS/TLR4 pathway, liver function and acetylcholinesterase(AchE) levels in rats were significantly improved($P < 0.001$), lung and heart pathology improved, and inflammatory cytokines were reduced; Moreover, the expression level of TLR4 in heart and lung also decreased significantly($P < 0.01$). As a result, the symptoms of organ poisoning were relieved.

Conclusion Lipid emulsion is involved in the protective effect via the LPS/TLR4 pathway on vital organs inacute or organophosphorus poisoning.

Keywords Acute organophosphorus poisoning, Lipid emulsion, LPS/TLR4 pathway, Vital organs

Introduction

Organophosphate insecticides are widely used pesticides in agriculture, especially in developing countries [1, 2]. They hold an important place among patients admitted to emergency services [3, 4]. It is reported that suicide rates have exceeded 1/3 in China and 1/10 globally [5]. According to data, almost 1/7 of the world's suicides, totaling 110,000 out of 798,000 cases, were due to organophosphates [6]. In Jiangsu province of China, there were about 30,789 pesticide poisoning cases between 2007 and 2016, with most of them being caused by organophosphates [7, 8]. Organophosphate poisoning inhibits

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acetylcholinesterase, leading to acetylcholine accumulation and causing muscarinic (e.g., bronchospasm, salivation), nicotinic (e.g., muscle fasciculations, weakness), and central nervous system symptoms (e.g., altered consciousness). Patients with chronic disorders face higher risks due to compromised baseline physiological functions [9, 10]. The traditional treatment method involves atropine and Pyraloxime Methiodide(PAM), which can appropriately reduce mortality and severity rate [11, 12]. However, the current treatment is only partly effective with case fatality often greater than10% even in intensive care units [13]. Therefore finding effective adjuvant drugs to reduce acute organophosphate-induced damage to the organs is urgently required.

Lipid emulsion (ILE) is one of the most commonly used drugs in nutritional replacement or as a therapy. It is composed of soybean oil, egg phospholipids and glycerine, and is available in 10%, 20%, and 30% concentrations [14]. The 20% ILE is utilized as parenteral nutrition for patients who are unable to eat [15]. The clinical rationale for using lipid emulsion therapy in organophosphorus poisoning is based on several potential mechanisms (Lipid Sink Effect, Cardiac Stabilization, CNS Protection), though evidence is primarily extrapolated from experimental models and other poisoning contexts [16–19]. Lipid emulsion is primarily used for lipid-soluble drug/toxin poisoning (e.g., local anesthetics, organophosphates) [16, 20, 21]. It has been reported that animals treated with ILE were found to have reduced liver and pancreatic injury when compared with animals treated with the accepted antidotes alones [22, 23]. A recent international study investigating the therapeutic benefits of intravenous ILE in rats with organophosphorus insecticide poisoning demonstrated that combining ILE with atropine and PAM significantly alleviated poisoning symptoms, reduced mortality rates, accelerated cholinesterase level recovery, and minimized organ damage caused by toxic exposure [24–27]. However, the precise mechanism by which ILE mediates organ protection in acute organophosphate poisoning remains poorly understood. To address this knowledge gap, the present study systematically investigates the molecular pathways through which ILE attenuates toxin-induced organ damage.

Materials and methods

Chemicals

Dichlorvos, also known as 2,2-dichlorovinyl dimethyl dichlorvos (DDVP No. 20200813001, Adama Corporation, China), 20% intravenous Lipid emulsion (ILE No. 80PF033, China), Atropine (No. 1811161, Fresenius Caba, China), PyraloximeMethiodide (PAM, No. 19032701, Kaifeng Pharmaceutical, China), Toll4 blocker (anti-TLR4, No. 66229 MedChem Express New Jersey, USA), CD284 [TLR4 monoclonal antibody, PE (No. 12904180, eBioscience™, USA)].

Fifty male

Sprague-Dawley rats (weight: 250–280 g) were purchased from Shanghai Jihui Experimental Animal Breeding Co., Ltd. (SCXK No.: 2017-0012-005541, China). All animals were housed under specific pathogen-free (SPF) conditions at a controlled temperature of 22–24 °C with ad libitum access to sterilized food and water. To establish the poisoning model, rats were intranasally administered dichlorvos (DDVP) at a dose of 7 mg/kg. Subsequently, the animals were randomly divided into five groups ($n = 10$/group) using a random number table:

1. Mock group: Received 5 mL/kg saline via tail vein injection;
2. ILE group: Administered 20% intravenous lipid emulsion (ILE) at 5 mL/kg via tail vein injection;
3. ST (Standard Treatment) group: Immediately after DDVP injection, rats in this group received intramuscular injections of atropine (10 mg/kg) and pralidoxime (PAM, 40 mg/kg) [28];
4. ST + ILE group: In addition to the standard treatment, this group was administered 20% intravenous lipid emulsion (ILE) at 5 mL/kg via tail vein injection.
5. ST + ILE + anti-TLR4 group: The ST + ILE treatment was further combined with anti-TLR4 antibody (0.5 mg/kg) administered via tail vein injection.

Twenty-four hours after initial treatment, all rats were euthanized by decapitation under anesthesia induced by intraperitoneal injection of ketamine hydrochloride (Ketalar®, Istanbul, Turkey; 50 mg/kg) and xylazine (Rompun®, Bayer, Leverkusen, Germany; 5 mg/kg). The time of death was recorded, and lung and heart tissues were surgically excised for histological analysis.

Histological analysis

The heart and lung tissues were removed and preserved in 10% formalin solution. Following routine histologic procedures, they were embedded in paraffin, from which 4–5 μm thick sections were obtained and stained using the Hematoxylin-Eosin (H&E) method. The inflammatory reaction in the heart and lung tissue was assessed based on muscle fiber appearance, red blood cell and inflammatory cell counts. Histopathological examination was conducted on the lung and heart tissue sections to evaluate tissue congestion, muscle fiber arrangement, and presence of inflammatory cells.

Measurement of cytokine gene expression

Total RNA was extracted from rat lung and heart homogenates following the manufacturer's instructions. First-strand cDNA synthesis was carried out using SuperScript II Reverse Transcriptase (NO. R222–01, China), followed by reverse transcription PCR using SYBR Green Master Mix (NO. Q411–02, China) in a Step One Plus PCR system. Tissue samples were obtained from 5 rats in each group, with the experiment being repeated three times. Primer design and synthesis were performed by GS Corp (Nanjing, China), The primer sequences are as follows:

Gene	Up primer(5′-3′)	Down primer(5′-3′)
IL-6	5′-ACAAGTCCGGAGAGGAGACT-3′	5′-TTGCCATTGCACAACTCTTTTC-3′
NF-κB	5′-TATGGACAACTATGAGGTCTCTGG-3′	5′-GGCTGCCTGGATCACTTCAA-3′
TNF-α	5′-ATGGGCTCCCTCTCATCAGT-3′	5′-GCTTGGTGGTTTGCTACGAC-3′
β-actin	5′-CCCATCTATGAGGGTTACGC-3′	5′-TTTAATGTCACGCACGATTTC-3′

Reverse transcription PCR was conducted using a LightCycler® 480 system (Roche Molecular Biochemicals) with identical amplification conditions. The expression of the target gene was normalized to that of β-actin and presented as fold-change in mRNA expression (fold-change = 2-△△CT).

Baseline biochemical parameters were recorded for all rats prior to dichlorvos (DDVP) poisoning

Blood samples were collected via tail vein puncture at two time points: pre-exposure and 4 h post-poisoning. Serum acetylcholinesterase (AChE) activity and hepatic function markers were quantified using standardized enzymatic assays at the Experimental Research Center.

Cytokine assessment in serum

Serum samples (approximately 0.5 ml) were collected from the orbital cavity of five rats in each group,24 h after poisoning. The levels of cytokines, including IL-6 (NO. JL20268, Jianglai Biology, China), TNF-α (NO. JL10484, Jianglai Biological, China), and NF-κB (NO. JL18090, Jianglai Biological, China), were quantified using ELISA kits. The experiment was repeated three times.

Preparation of single-cell suspensions from the lung and heart

The rats were anesthetized and their lungs and hearts were flushed in situ with 20 mL of phosphate-buffered saline (PBS) via cannulation of the heart to remove the intravascular blood pool. Lung tissues and hearts were then incubated at 37 °C for 1 h on a rocker with a solution containing 200 μg/mL collagenase D and 40 μg/mL DNase I (Roche Molecular Biochemicals, China) in 10 mL of RPMI 1640 medium supplemented with 10% fetal calf serum. Single-cell suspensions from the digested lung or heart tissue were collected through density-gradient centrifugation using lymphocyte separation solution. The cells were resuspended in RPMI 1640 medium.

Flow cytometry

To identify TLR4 in the lungs and hearts of rats, each aliquot of parenchymal cells was blocked with anti-mouse CD284 and incubated on ice for 20 min with specific monoclonal antibodies or isotype-matched controls. Subsequently, flow cytometry analysis was performed on 100,000 stained parenchymal cells to identify TLR4 as CD284.

Statistical analysis

Statistical analysis was conducted using SPSS version 22.0 software, confirming that the data followed a normal distribution pattern. Measurement data are presented as mean ± standard deviation (x ± s). Single factor multilevel group one-way analysis of variance was used for comparison, and further pairwise comparisons among groups employed the LSD-t method. A significance level of $P < 0$ 0.05 was considered statistically significant.

Results

General index and biochemicals in serum

In this experiment, 50 rats were utilized for the study. Baseline body weight and temperature did not exhibit significant differences among the five groups (Table 1). There were no notable variations in weight and temperature observed across the 5 groups ($P > 0.05$, Table 1).

In acute organophosphorus-poisoned rats, the vital organs were severely damaged after 4 h of poisoning. The serum levels of AchE also significantly declined (Table 2). The liver function markers ALT/AST/LHD showed a significant increase, indicating impaired liver function after 24 h of poisoning. However, treatment with standard treatment or ILE improved liver function. When standard treatment was combined with ILE, the ALT/AST/LHD levels decreased significantly compared to the ST or ILE group, and AchE levels in the serum increased. Additionally, AchE levels were significantly higher in the ST + ILE + anti-TLR4 group than in the ST + ILE group.

Table 1 Baseline characteristics ($n = 10$/ group, x ± s)

Group	Mock	ILE	ST	ST + ILE	ST + ILE + anti-TLR4	*P*
Weight(g)	265.5 ± 9.45	263.4 ± 5.42	260.7 ± 6.50	264.2 ± 8.12	260.4 ± 9.57	0.7758
T (°C)	36.66 ± 0.25	36.69 ± 0.25	36.75 ± 0.21	36.76 ± 0.17	36.81 ± 0.19	0.5707

Table 2 After organophosphorus rats were poisoned, five groups of rats survived 24 h; liver function in blood and ache secreted detected after poisoned 4 h in serum(x ± sd *n* = 10/ group, U/L). Values are presented as mean ± SD

Group	Mock	ILE	ST	ST + ILE	ST + ILE + anti-TLR4	*P*
ALT	229.60 ± 9.09	214.90 ± 15.80	150.60 ± 7.95	127.00 ± 7.75	105.6 ± 16.77	< 0.0001
AST	242.90 ± 20.40	197.90 ± 17.77	175.70 ± 10.75	140.10 ± 19.30	103.1 ± 14.99	< 0.0001
LDH	539.50 ± 25.01	413.80 ± 31.36	352.20 ± 30.92	315.40 ± 22.29	275.2 ± 11.03	< 0.0001
AchE	137.4 ± 73.67	306.307 ± 66.01	441.7 ± 174.37	536.4 ± 229.38	721.9 ± 6.48	< 0.0001

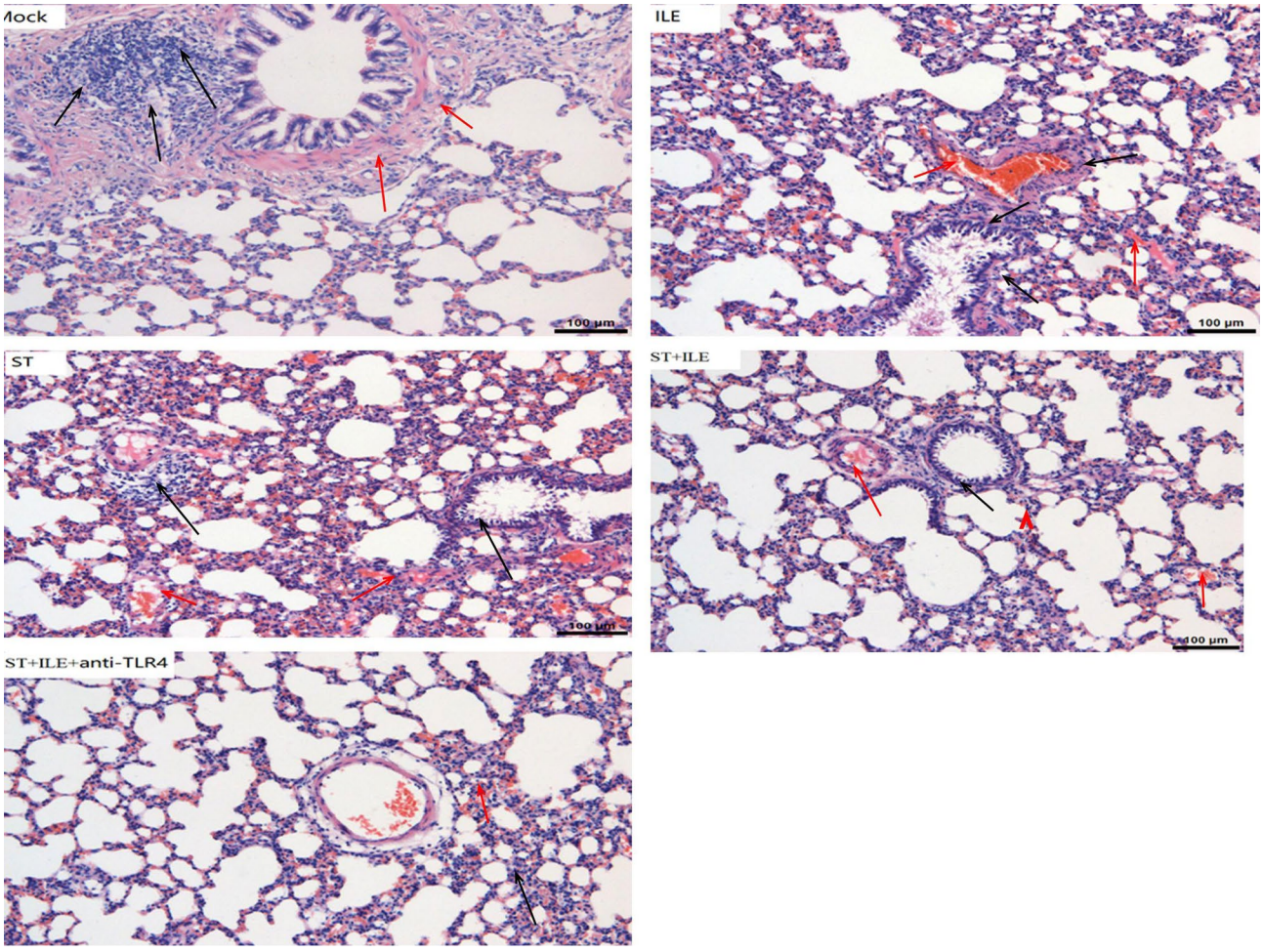

Fig. 1 Histological examination of lung tissues from organophosphorus-poisoned rats at 24 h. Lung tissues were collected and stained with hematoxylin and eosin (H&E). Black arrows indicate inflammatory cellinfiltration, and red arrows highlight erythrocyte extravasation (HE, ×100 objective)

Furthermore, the ALT/AST/LHD levels of liver function significantly decreased in the ST + ILE + anti-TLR4 group compared to the ST + ILE + anti-TLR4 group (Table 2).

Pathological

Pulmonary pathology of organophosphorus poisoning: The mock group exhibited widened alveolar septa with edema and interstitial hyperemia, inflammatory cell infiltration, perivascular loose edema, and exudation. In the ILE group, the alveolar septum was widened with interstitial hyperemia and inflammatory cell infiltration. The ST group showed slightly widened alveolar septa with a small amount of inflammatory cell infiltration and red blood cell exudation. In the ST + ILE group, there was a small amount of inflammatory cell infiltration and red blood cell infiltration. The ST + ILE + anti-TLR4 group displayed slightly widened alveolar septa with a small amount of inflammatory cell infiltration and red blood cell exudation in the lungs (HE, ×100 objective) (Fig. 1). Cardiac pathology of organophosphorus poisoning: In the mock group, disordered muscle fiber arrangement was observed along with damaged muscle fibers, leakage of a large number of red blood cells between tissues, as well as inflammatory cell infiltration and cellular edema. The ILE group exhibited widened alveolar septa with interstitial hyperemia and inflammatory cell infiltration.

The ST group showed slightly widened alveolar septa with a small amount of inflammatory cell infiltration and red blood cell exudation. In the ST + ILE group, there was a small amount of inflammatory cell infiltration and erythrocyte exudation. The ST + ILE + anti-TLR4 group displayed slightly widened alveolar septa with a small amount of inflammatory cell infiltration and red blood cell exudation (HE, ×100 objective) (Fig. 2).

Cytokine assessment and cytokine gene expression

Following organophosphorus poisoning, there was a significant increase in serum levels of the pro-inflammatory cytokines IL-6, TNF-α, and NF-κB. The Mock Group had significantly higher levels compared to those in the ILE Group before decreasing in the ST Group. The most significant decrease was observed in the ILE Group (Figure 3).

Flow cytometry

Flow cytometry analysis revealed a significant increase in LPS/ TLR4 expression in lung tissue and heart following organophosphate poisoning after 24 h of survival. In the mock group, LPS/TLR4 expression was significantly higher compared to the ILE and ST groups, with the most significant decrease observed in the ILE group. However, the blocking group exhibited the lowest TLR4 expression, which decreased significantly after treatment with ILE combined with atropine and PAM. The expression of TLR4 in the heart mirrored that of the lung (Fig. 4).

Discussion

Organophosphorus poisoning is a common type of pesticide poisoning, and the standard treatment involves PAM and atropine, supplemented by gastric lavage, blood perfusion, and other comprehensive treatments [29]. However, the prognosis is often unsatisfactory [25]. Organophosphorus poisoning can lead to damage in important organs. Research has shown that during the

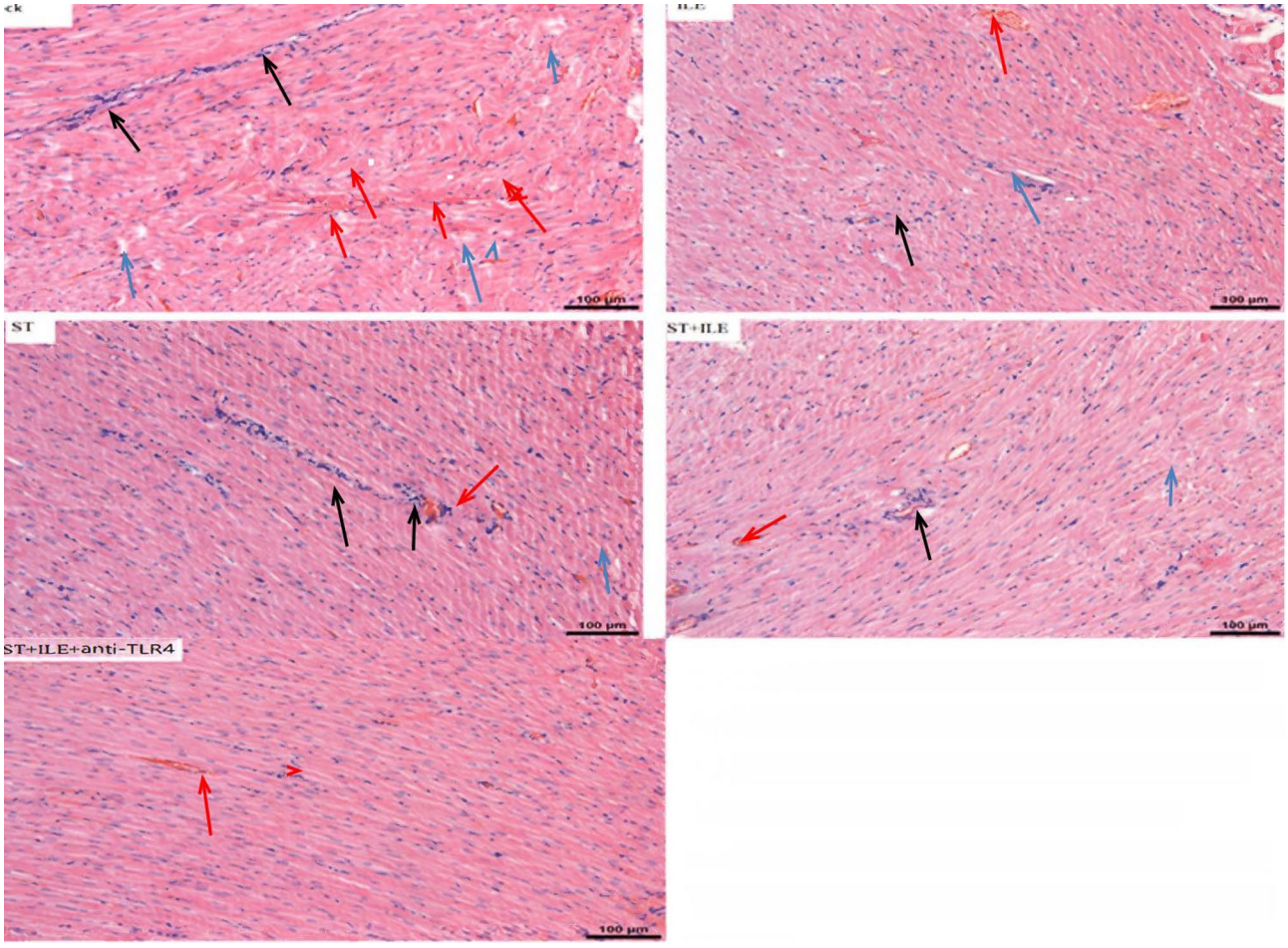

Fig. 2 Histological examination of heart tissues from organophosphorus-poisoned rats at 24 h. Heart tissues were collected and stained with hematoxylin and eosin (H&E). Black arrows indicate inflammatory cell infiltration, blue arrows denote muscle fiber rupture, and red arrows highlight erythrocyte extravasation (HE,×100 objective)

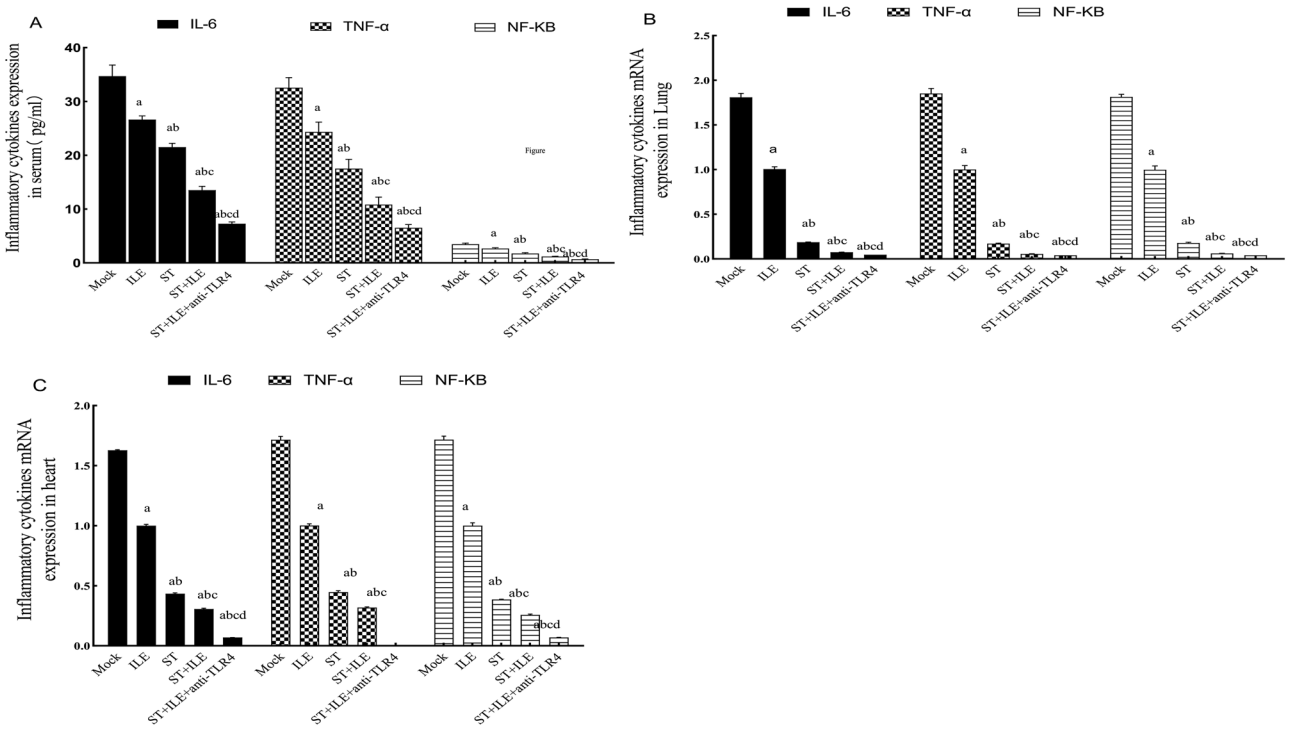

Fig. 3 Rats exposed to organophosphorus pesticides survived for 24 h, resulting in increased production of inflammatory cy-tokines. Serum samples were collected and analyzed for levels of IL-6, TNF-α, and NF-κB using ELISA (**A**). The expression of inflammatory mediators mRNA(IL-6, TNF-α, and NF-κB) in lung and heart tissues was quantified (**B, C**). These data are representative of five independent experiments ($n = 5$ rats/group). Statis-tical significance is indicated as follows: aP < 0.01 vs. Mock group; bP < 0.01 vs. ILE group; cP < 0.01 vs. ST group; dP < 0.01 vs. ST + ILE group

treatment of AOPP, the combination of standard treatment and ILE can reduce the use of atropine. Tuzcu et al. found that ILE reduces pancreatic damage caused by organophosphate poisoning [30, 31], while Malarvannan et al. identified the protective effect of ILE on kidneys in acute organophosphate poisoning [32]. In this study, organophosphate poisoning resulted in damage to the liver, heart, lungs and other vital organs. The combination of standard treatment with ILE alleviated poisoning symptoms and significantly decreased inflammatory cytokines at both protein and mRNA levels. This confirms that ILE combined with standard treatment exerts a protective role on important organs [33, 34]. The exact mechanism of action for ILE in AOPP is not yet clear; however there are common theories including:1) "ILE pool" theory: where ILE introduced into circulation replaces toxic substances in plasma as droplets which then play a detoxification effect [35]; 2) Metabolic theory: where ILE blocks damage effects and promotes mitochondrial activity within cells leading to altered distribution of ILE-soluble organophosphorus pesticides in the body promoting metabolism or discharge of poison [36, 37]. Studies have indicated that the infusion of intravenous lipid emulsion (ILE) into the liver and spleen endothelial network results in the absorption of long-chain triglycerides. This leads to the accumulation of organic phosphorus, A potent ILE-soluble drug, in the liver and spleen under the influence of ILE. Consequently, ILE has the potential to alter the distribution of organic phosphorus in the body and inhibit immune function and inflammatory response.

Toll-like receptor 4 (TLR4) is a member of the TLR family and has been identified as a key pattern recognition receptor for lipopolysaccharide (LPS) [38, 39]. It plays a crucial role in linking inflammation response with metabolic syndrome [40–42]. Activation of TLR4 by LPS derived from Gram-negative bacteria induces inflammatory signaling, contributing to inflammatory immunity [37, 43–45]. The expression of LPS increases during stress and inflammatory responses, leading to activation of the LPS/TLR4 pathway, intracellular NF-κB activation and production of inflammatory cytokines such as TNF-α and IL-6. These cytokines play critical roles in responding to external stimuli and tissue damage [40, 46]. Organophosphorus insecticides are known to be lipophilic; therefore, ILE may serve as a novel therapeutic agent due to its similar lipophilic properties. Additionally, ILE inhibits macrophage activation through binding with phospholipids and high-density lipoproteins present in vivo or vitro conditions which neutralize cytokine responses. Studies on healthy volunteers have demonstrated that supplementation with ILE after endotoxin

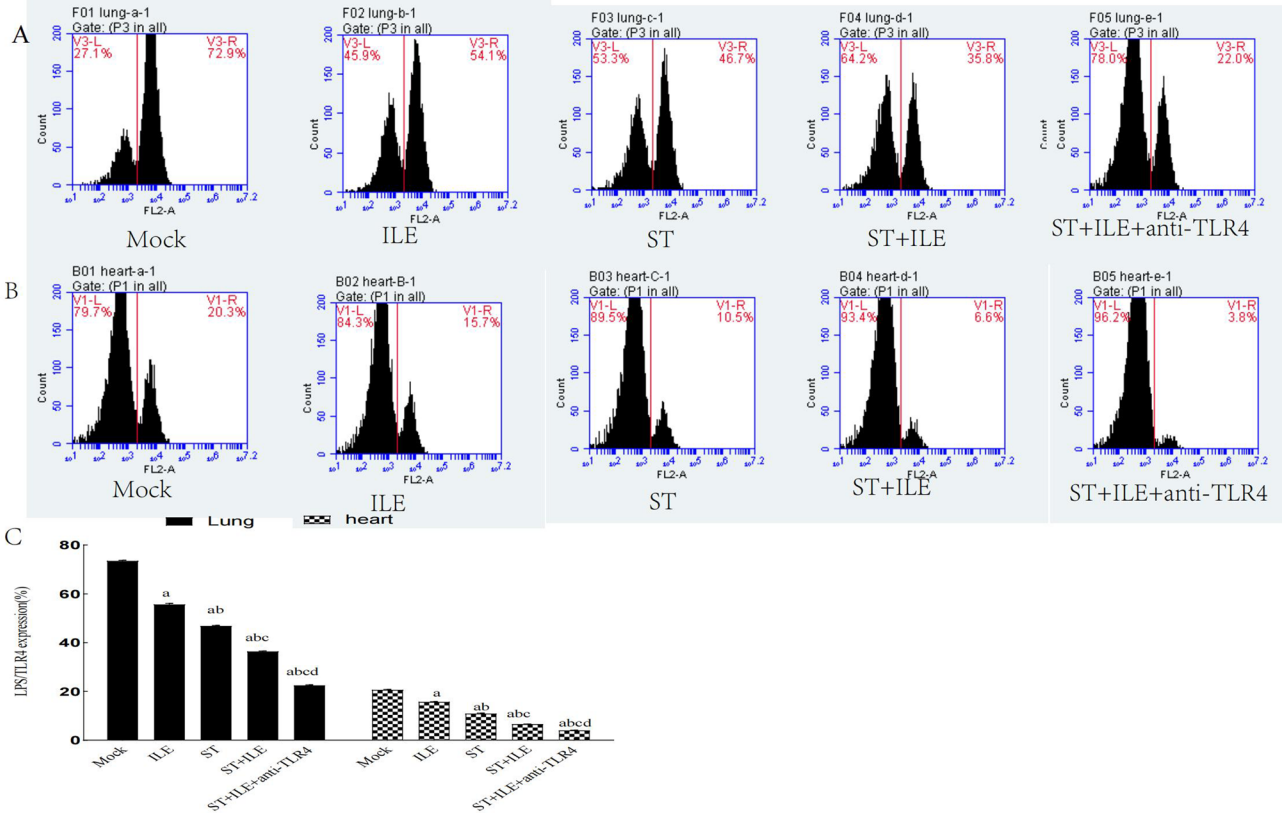

Fig. 4 Representative flow cytometry images showing TLR4 expression in lung (**A**) and heart (**B**) tissues of organophosphorus pesticide-poisoned rats at 24 h post-exposure. Corresponding LPS/TLR4 expression levels in surviving rats are presented. Statistical significance is denoted as follows: aP < 0.01 vs. Mock group; bP < 0.01 vs. ILE group; cP < 0.01 vs. ST group; dP < 0.01 vs. ST + ILE group. Corresponding LPS/TLR4 expression levels in surviving rats are presented (**C**)

stimulation resulted in significant effects on immune function modulation [47]. The action with lipophilics reduces the levels of Interleukin-6 (IL-6) and Tumor necrosis factor-α (TNF-α) [48]. However, after the action with lipophilics, ILE loses its ability to inhibit the release of IL-6 and TNF-α. It was observed that ILE or lipopolysaccharide (LPS) alone does not release IL-6 and TNF-α [49]. Our experimental data revealed significant upregulation of TLR4 and inflammatory protein expression in cardiac and pulmonary tissues following organophosphate intoxication. Notably, TLR4 expression dynamics exhibited a strong positive correlation ($p < 0.01$) with serum concentrations of pro-inflammatory mediators, including IL-6, TNF-α, and NF-κB. Therapeutic intervention with PAM, atropine, and intravenous lipid emulsion (ILE) substantially attenuated tissue expression of TNF-α, IL-6, and NF-κB ($p < 0.05$ vs. Mock group), with these molecular changes directly associated with improved clinical outcomes (reduced mortality, accelerated cholinesterase recovery). Mechanistically, the LPS/TLR4 signaling axis was identified as a central driver of AOPP pathology. Immunohistochemical analysis demonstrated that both standard therapy (ST) and ILE monotherapy reduced TLR4 overexpression in vital organs, yet the combined ST + ILE regimen achieved superior suppression. To establish causal linkage, we employed a TLR4-specific inhibitor in parallel with standard therapies. Pharmacological blockade of the LPS/TLR4 pathway yielded multifactorial benefits:

These findings delineate a pathogenic cascade wherein organophosphates activate the LPS/TLR4 pathway, triggering mediated cytokine storms that culminate in multiorgan dysfunction. Therapeutic targeting of this axis, particularly through ILE-enhanced detoxification, represents a promising strategy for mitigating AOPP-induced tissue injury.g to secretion of inflammatory cytokines and subsequent damage to vital organs.

In summary, Our findings suggest that combining ILE with standard therapy (pralidoxime/atropine) enhances organ protection in acute organophosphate poisoning, potentially through suppressing the TLR4 pathway and reducing inflammatory cytokines. However, key limitations include: Small sample size and lack of clinical validation; Absence of long-term outcome data; Undefined risks of drug-lipid interactions; Future studies should prioritize mechanistic validation (e.g., TLR4 knockout models), clinical translation trials, and extended safety assessments.

Abbreviations

ALT	Glutamic pyruvic transaminase
AST	Aspartate transaminase
HE	Hematoxylin-eosin
ILE	Lipid emulsion
LHD	Glutamic pyruvic transaminase
LPS	Lipopolysaccharide
OP	Organophosphorus poisoning
PAM	Pyraloxime Methiodide
TLR4	Toll-like receptor 4

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None.

Author contributions
Haiyan Hu is expected to have made substantial contributions to the conception design of the work; OR the acquisition, analysis, interpretation of data; the creation of new software used in the work; have drafted the work or substantively revised it. Gang Li have approved the submitted version (and any substantially modified version that involves the author's contribution to the study); AND to have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
All experiments involving animals were conducted in strict accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals and the ARRIVE guidelines. The study protocol was reviewed and approved by the Animal Protection Ethics Committee of Zhejiang Provincial People's Hospital (Approval No. HB20200011909002LG-A). No human participants, human tissues, or human data were involved in this study.

Consent for publication
Not applicable. This study did not involve human participants.

Competing interests
The authors declare no competing interests.

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References

1. Chowdhary S, Bhattacharyya R, Banerjee D. Acute organophosphorus poisoning. Clin Chim Acta. 2014;431:66–76.
2. Mundhe SA, Birajdar SV, Chavan SS. The clinico-demographic study of morbidity and mortality in patients with organophosphate compound poisoning at tertiary care hospital in rural India. Int J Adv Med 2017;4(3).
3. Liu SH, Lin JL, Weng CH, Yang HY, Hsu CW, Chen KH, Huang WH, Yen TH. Heart rate-corrected QT interval helps predict mortality after intentional organophosphate poisoning. PLoS ONE. 2012;7(5):e36576.
4. Maksimovic ZM, Jovic-Stosic J, Vucinic S, Perkovic-Vukcevic N, Vukovic-Ercegovic G, Skrbic R, Stojiljkovic MP. Acute organophosphate and carbamate pesticide poisonings - a five-year survey from the National poison control center of Serbia. Drug Chem Toxicol. 2023;46(1):113–21.
5. Liu S, Page A, Yin P, Astell-Burt T, Feng X, Liu Y, Liu J, Wang L, Zhou M. Spatiotemporal variation and social determinants of suicide in China, 2006–2012: findings from a nationally representative mortality surveillance system. Psychol Med. 2015;45(15):3259–68.
6. Aman S, Paul S, Chowdhury FR. Management of organophosphorus poisoning: standard treatment and beyond. Crit Care Clin. 2021;37(3):673–86.
7. Mew EJ, Padmanathan P, Konradsen F, Eddleston M, Chang SS, Phillips MR, Gunnell D. The global burden of fatal self-poisoning with pesticides 2006-15: systematic review. J Affect Disord. 2017;219:93–104.
8. Wang N, Jiang Q, Han L, Zhang H, Zhu B, Liu X. Epidemiological characteristics of pesticide poisoning in Jiangsu Province, China, from 2007 to 2016. Sci Rep. 2019;9(1):8604.
9. Jokanovic M, Oleksak P, Kuca K. Multiple neurological effects associated with exposure to organophosphorus pesticides in man. Toxicology. 2023;484:153407.
10. Eddleston M, Buckley NA, Eyer P, Dawson AH. Management of acute organophosphorus pesticide poisoning. Lancet. 2008;371(9612):597–607.
11. Reddy BS, Skaria TG, Polepalli S, Vidyasagar S, Rao M, Kunhikatta V, Nair S, Thunga G. Factors associated with outcomes in organophosphate and carbamate poisoning: a retrospective study. Toxicol Res. 2020;36(3):257–66.
12. Eyer P, Buckley N. Pralidoxime for organophosphate poisoning. Lancet. 2006;368(9553):2110–1.
13. Eddleston M, Eyer P, Worek F, Mohamed F, Senarathna L, von Meyer L, Juszczak E, Hittarage A, Azhar S, Dissanayake W, et al. Differences between organophosphorus insecticides in human self-poisoning: a prospective cohort study. Lancet. 2005;366(9495):1452–9.
14. Basarslan SK, Alp H, Senol S, Evliyaoglu O, Ozkan U. Is intralipid fat emulsion a promising therapeutic strategy on neurotoxicity induced by malathion in rats? 2014.
15. Cao D, Heard K, Foran M, Koyfman A. Intravenous lipid emulsion in the emergency department: a systematic review of recent literature. J Emerg Med. 2015;48(3):387–97.
16. Fettiplace MR, Weinberg G. The mechanisms underlying lipid resuscitation therapy. Reg Anesth Pain Med. 2018;43(2):138–49.
17. Eddleston M, Chowdhury FR. Pharmacological treatment of organophosphorus insecticide poisoning: the old and the (possible) new. Br J Clin Pharmacol. 2016;81(3):462–70.
18. Harvey M, Cave G, Chanwai G, Nicholson T. Successful resuscitation from bupivacaine-induced cardiovascular collapse with intravenous lipid emulsion following femoral nerve block in an emergency department. Emerg Med Australas. 2011;23(2):209–14.
19. Zhao M, Zhang T, Li G, Qiu F, Sun Y, Zhao L. Associations of CYP2C9 and CYP2A6 polymorphisms with the concentrations of valproate and its hepatotoxin metabolites and valproate-Induced hepatotoxicity. Basic Clin Pharmacol Toxicol. 2017;121(2):138–43.
20. Joson M, Castor FRM, Micu-Oblefias CV. Role of intravenous lipid emulsion therapy and packed red blood cell transfusion as adjuvant treatment in the management of a child with severe organophosphate poisoning (chlorpyrifos). BMJ Case Rep. 2022;15(4).
21. Wong SW, Kwon MJ, Choi AM, Kim HP, Nakahira K, Hwang DH. Fatty acids modulate Toll-like receptor 4 activation through regulation of receptor dimerization and recruitment into lipid rafts in a reactive oxygen species-dependent manner. J Biol Chem. 2009;284(40):27384–92.
22. Shen S, Wang K, Zhi Y, Shen W, Huang L. Gypenosides improves nonalcoholic fatty liver disease induced by high-fat diet induced through regulating LPS/TLR4 signaling pathway. Cell Cycle. 2020;19(22):3042–53.
23. Turkdogan KA, Duman A, Avcil M, Akoz A, Canakci SE, Kantekin B. Treatment methods following suicidal self-administration of IV organophosphate: what can additional lipid administration change? Am J Emerg Med. 2017;35(9):1388. e1383-1388 e1385.
24. Esen M, Uysal M. Protective effects of intravenous lipid emulsion on malathion-induced hepatotoxicity. Bratisl Lek Listy. 2018;119(6):373–8.
25. Uysal M, Karaman S. In vivo effects of intravenous lipid emulsion on lung tissue in an experimental model of acute malathion intoxication. Toxicol Ind Health. 2018;34(2):110–8.
26. Pannu AK, Garg S, Bhalla A, Dhibar DP, Sharma N. Lipid emulsion for the treatment of acute organophosphate poisoning: an Open-Label randomized trial. Clin Toxicol (Phila). 2022;60(5):602–8.
27. Omar S, Sooka PN, Khoza S, Van Rooyen MC, Mashamba L, Madi S, Mathivha LR, George JA. Hemoperfusion for clinically suspected organophosphate and carbamate poisoning in critically ill patients: A randomized trial. Blood Purif. 2023;52(2):157–65.
28. Felippe ISA, Muller CJT, Siqueira AA, Dos Santos L, Cavadino A, Paton JFR, Beijamini V, Sampaio KN. The antidotes Atropine and pralidoxime distinctively recover cardiorespiratory components impaired by acute poisoning with Chlorpyrifos in rats. Toxicol Appl Pharmacol. 2020;389:114879.

29. Liu L, Ding G. Effects of different blood purification methods on serum cytokine levels and prognosis in patients with acute severe organophosphorus pesticide poisoning. Ther Apher Dial. 2015;19(2):185–90.
30. Tuzcu K, Alp H, Ozgur T, Karcioglu M, Davarci I, Evliyaoglu O, Karakus A, Hakimoglu S. Oral intralipid emulsion use: a novel therapeutic approach to pancreatic beta-cell injury caused by malathion toxicity in rats. Drug Chem Toxicol. 2014;37(3):261–7.
31. Celik MM, Alp A, Dokuyucu R, Zemheri E, Ozkanli S, Ertekin F, Yaldiz M, Akdag A, Ipci O, Toprak S. Protective Effects of Intralipid and Caffeic Acid Phenethyl Ester on Nephrotoxicity Caused by Dichlorvos in Rats. J Anal Methods Chem. 2015;2015:491406.
32. Malarvannan G, Belpaire C, Geeraerts C, Eulaers I, Neels H, Covaci A. Organophosphorus flame retardants in the European eel in Flanders, Belgium: occurrence, fate and human health risk. Environ Res. 2015;140:604–10.
33. Eddleston M. CON: oximes should not be used routinely in organophosphorus insecticide poisoning. Br J Clin Pharmacol. 2022;88(12):5070–3.
34. Yu S, Yu S, Zhang L, Gao Y, Walline J, Lu X, Ma Y, Zhu H, Yu X, Li Y. Efficacy and outcomes of lipid resuscitation on organophosphate poisoning patients: A systematic review and meta-analysis. Am J Emerg Med. 2019;37(9):1611–7.
35. Zhou Y, Zhan C, Li Y, Zhong Q, Pan H, Yang G. Intravenous lipid emulsions combine extracorporeal blood purification: a novel therapeutic strategy for severe organophosphate poisoning. Med Hypotheses. 2010;74(2):309–11.
36. Dong N, Liu J, Wang Z, Gao N, Pang L, Xing J. Development of a practical prediction scoring system for severe acute organophosphate poisoning. J Appl Toxicol. 2020;40(7):889–96.
37. Murakami K, Kamimura D, Hasebe R, Uchida M, Abe N, Yamamoto R, Jiang JJ, Hidaka Y, Nakanishi Y, Fujita S, et al. Rhodobacter azotoformans LPS (RAP99-LPS) is a TLR4 agonist that inhibits lung metastasis and enhances TLR3-Mediated chemokine expression. Front Immunol. 2021;12:675909.
38. Zhang J, Tan YQ, Wei MH, Ye XJ, Chen GY, Lu R, Du GF, Zhou G. TLR4-induced B7-H1 on keratinocytes negatively regulates CD4(+) T cells and CD8(+) T cells responses in oral lichen planus. Exp Dermatol. 2017;26(5):409–15.
39. Kumar V, Stewart JH. cGLRs join their cousins of pattern recognition receptor family to regulate immune homeostasis. Int J Mol Sci. 2024;25(3).
40. Vaure C, Liu Y. A comparative review of toll-like receptor 4 expression and functionality in different animal species. Front Immunol. 2014;5:316.
41. Plociennikowska A, Hromada-Judycka A, Borzecka K, Kwiatkowska K. Co-operation of TLR4 and raft proteins in LPS-induced pro-inflammatory signaling. Cell Mol Life Sci. 2015;72(3):557–81.
42. Yuan Y, Gong X, Zhang L, Jiang R, Yang J, Wang B, Wan J. Chlorogenic acid ameliorated Concanavalin A-induced hepatitis by suppression of Toll-like receptor 4 signaling in mice. Int Immunopharmacol. 2017;44:97–104.
43. Shapira S, Harb OS, Caamano J, Hunter CA. The NF-kappaB signaling pathway: immune evasion and immunoregulation during toxoplasmosis. Int J Parasitol. 2004;34(3):393–400.
44. Bianchi ME. DAMPs, pamps and alarmins: all we need to know about danger. J Leukoc Biol. 2007;81(1):1–5.
45. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. Cell. 2010;140(6):805–20.
46. Wallace FA, Miles EA, Calder PC. Comparison of the effects of linseed oil and different doses of fish oil on mononuclear cell function in healthy human subjects. Br J Nutr. 2003;89(5):679–89.
47. Gwaltney-Brant S, Meadows I. Intravenous lipid emulsions in veterinary clinical toxicology. Vet Clin North Am Small Anim Pract. 2018;48(6):933–42.
48. Bonaterra GA, Driscoll D, Schwarzbach H, Kinscherf R. Krill Oil-In-Water emulsion protects against Lipopolysaccharide-Induced Proinflammatory activation of macrophages in vitro. Mar Drugs. 2017;15(3).
49. Litz RJ, Roessel T, Heller AR, Stehr SN. Reversal of central nervous system and cardiac toxicity after local anesthetic intoxication by lipid emulsion injection. Anesth Analg. 2008;106(5):1575–7.

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