LITERATURE REVIEW: NON-INDICATED USE OF N-ACETYLCYSTEINE AGAINST OXIDATIVE STRESS-MEDIATED ORGANOPHOSPHATE TOXICITY

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ABSTRACT

Organophosphate poisoning poses a significant health threat due to its ability to induce oxidative stress, cellular damage, and neurotransmitter disruption. Pharmacovigilance plays a crucial role in monitoring and preventing adverse effects associated with medical products, including responses to toxic exposure. This study aims to evaluate the protective role of N-acetylcysteine (NAC) against organophosphate-induced toxicity through a comprehensive literature review. The method employed includes a review of eight experimental studies conducted between 2017 and 2023, involving both in vivo (animal models) and in vitro (cell cultures and human samples) approaches. The results indicate that NAC significantly reduces oxidative stress biomarkers, enhances antioxidant enzyme activity, suppresses apoptosis, and restores inhibited cholinesterase activity. Moreover, NAC improves histopathological alterations in organs exposed to organophosphates, including the liver, kidneys, brain, and testes. In conclusion, NAC demonstrates strong therapeutic potential as a standalone or adjunct agent in managing organophosphate toxicity through its antioxidant, anti-inflammatory, and cytoprotective mechanisms.

Keywords: *N-acetylcysteine, organophosphate toxicity, oxidative stress, antioxidants, pharmacovigilance*

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INTRODUCTION

Pharmacovigilance is a branch of science that has a role in the collection, monitoring, assessment, and prevention of risks related to the safe use of medical products. The discipline involves the identification and analysis of adverse drug reactions (ADRs), which are negative responses arising from drug use in both humans and animals. These reactions are adverse and undesirable, can include lack of drug effectiveness, and can occur at normal doses, due to overdose, or drug abuse (BPOM RI, 2011).

The main sources of information in pharmacovigilance include national reporting systems on suspected ADRs and the results of pharmacoepidemiologic research. Activities in pharmacovigilance aim to detect and address unexpected and potentially harmful adverse drug events (Syamsuri Syakri et al., 2018).

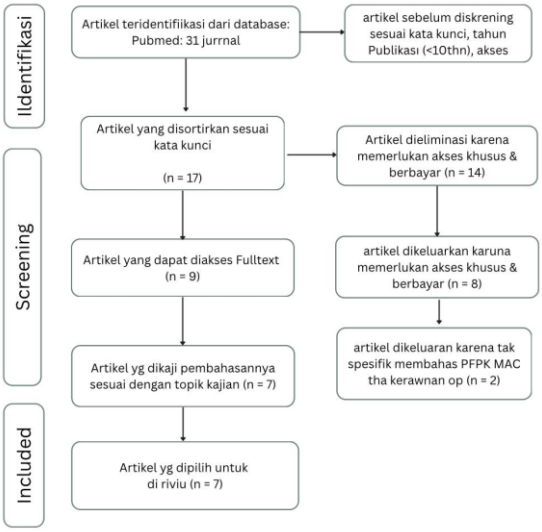
Oxidative stress is an imbalance between the amount of free radicals (pro-oxidants) and antioxidants in the body. This imbalance is generally caused by two main factors, namely antioxidant deficiency or increased free radical production. Free radicals are molecules, atoms, or collections of atoms that have one or more unpaired electrons in their outer orbit, making them highly reactive. A molecule will be stable if all of its electrons are paired, but if there are unpaired electrons, the molecule becomes unstable and has the potential to cause damage to cells or tissues (Ayudiah Rizki Utami et al, 2023).

N-Acetylcysteine or often referred to as NAC has a role in preventing or reducing liver damage caused by the consumption of large amounts of acetaminophen. However, not all forms of acetylcysteine are effective as acetaminophen antidotes. Acetylcysteine also has other uses such as preventing or treating oxidative stress.

A number of studies have indicated that N-Acetylcysteine (NAC), an orally consumed source of antioxidants, has the potential to reduce oxidative stress and provide protection against free radical-induced tissue damage. It is suspected that NAC can increase the secretion of various growth factors that play a role in accelerating the wound healing process (Elisabeth Prajanti Sintaningrum et al, 2020).

METHODS

The method used in writing this literature review refers to a systematic literature review approach. The literature search process was conducted through several scientific databases such as PubMed, ScienceDirect, and Google Scholar using a combination of keywords "N-acetylcysteine", "organophosphate toxicity", "oxidative stress", and "protective effect". The limitations of the literature used were English or Indonesian articles published in the last 10 years (2013-2023). The literature selection process was based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) principles, which includes four stages: identification, screening, eligibility checking, and inclusion. In the identification stage, articles were collected based on a predetermined keyword search. Next, screening was conducted by evaluating titles and abstracts, and eliminating irrelevant or duplicate articles. Successful articles were then fully evaluated to ensure content suitability to the topic of discussion, particularly those examining the protective effect of N-acetylcysteine against organophosphate compound toxicity. Articles that met all inclusion criteria were then analyzed further. The research design in the selected articles generally used an experimental approach, either in vivo using experimental animals such as albino rats, or in vitro using human cell cultures or blood samples. The studies applied a true experimental or controlled laboratory experiment design with randomization or purposive sampling methods. Statistical analysis used in the articles included One-way ANOVA test followed by post hoc tests such as Tukey's test, Duncan's Multiple Range Test, HSD (Honestly Significant Difference), and Scheffe test. Some studies also used Student's t-test to compare two groups of data. The choice of statistical methods in these studies reflects an effort to ensure the validity of the results and specifically identify the protective effects of N-acetylcysteine against various toxicity parameters, including biochemical, histological, and oxidative stress parameters.



RESULTS

The preparation of this *literature review* is done through analysis of articles that have been selected in accordance with the focus and objectives of the study. The literature reviewed focuses on the use of N-acetylcysteine (NAC) in treating organophosphate poisoning. The final results obtained after reviewing scientific articles using *PubMed* were 7 articles. The range of study publication years was from 2017 to 2023. In general, there are two main methods used in the study, namely using in vitro (cells and enzymes) and in vivo (test animals)

models with a focus on exposure to different organophosphates, such as fenitrothion, chlorpyrifos, malathion, dimethoate, and pirimiphos methyl. The parameters measured were mainly oxidative stress biomarkers, antioxidant status, and related enzyme activities

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Table 1. Summary Comparison of Study Results

No.	Research Name & Year	Journal Name	Research Title	Variables Examined	Study Design	Research Sample	Statistical Methods	Research Conclusion
1	Rasha T. Alam, Tamer S. Imam, Azza M. A. Abo-Elmaaty, Ahmed Hamed Arisha	ELSEVIER	Amelioration of fenitrothion induced oxidative DNA damage and inactivation of caspase-3 in the brain and spleen tissues of male rats by N-acetylcysteine	Effects of fenitrothion exposure and protection by N-Acetylcystein	*True Experimental Study*	80 male Sprague rats with *random sampling* technique	*One-way ANOVA & Tukey's post hoc test*	N-Acetylcysteine administration is effective in repairing nerve and immune cell damage caused by fenitrothion in male rats.
2	Sahar M. Mahmoud, Ahmed E. Abdel Moneim, Marwa M. Qayed, Mabil A. El-Yamany	Environmental Science and Pollution Research	Potential role of N-acetylcysteine on chlorpyrifos-induced neurotoxicity in rats	Effects of N-Acetylcysteine administration on adult male rat brain	*Experimental Laboratory*	28 adult male albino rats with *random sampling* technique	*One-way ANOVA & Tukey's post hoc test*	N-Acetylcysteine effectively protects rat brain tissue from chlorpyrifos exposure
3	Pochuen Shieh, Chung-Ren Jan, Wei-Zhe Liang	ELSEVIER	The protective effects of the antioxidant N-acetylcysteine (NAC) against oxidative stress-associated apoptosis evoked by the organophosphorus insecticide malathion in normal human astrocytes	The effects of malathion on normal human astrocytes and the role of N-Acetylcysteine in these effects	*Experimental In Vitro Laboratory*	*Gibco Human Astricytes* (GHA) with *Purposive Sampling*	*One-way ANOVA & Tukey's HSD (Honestly Significantly Different)*	The protective effect of N-Acetylcysteine makes it a potential drug to prevent malathion-induced cytotoxicity in GHA cells
4.	Axxa A.A. Galal, Raghda A. Ramadan, Mohamed M.M.	ELSEVIER	Protective effect of N-acetylcysteine on fenitrothion-	Protective effect of N-Acetylcysteine on fenitrothion	*True Experimental In Vivo*	32 adult male albino rats with *random allocation* technique.	*One-way ANOVA & Duncan's Multiple Range*	N-Acetylcysteine administration can protect fenitrothion

No.	Research Name & Year	Journal Name	Research Title	Variables Examined	Study Design	Research Sample	Statistical Methods	Research Conclusion
	Metwally, Sawsan M.A. El-Sheikh		induced toxicity: The antioxidant status and metabolizing enzymes expression in rats	toxicity			*Test*	toxicity in non-target organisms and humans
5.	Jitender Kumar Bhardwaj, Priyanka Saraf, Priya Kumari, Meenu Mittal, Vijay Kumar	WILEY	N-Acetyl-cysteinemediated inhibition of spermatogonial cells apoptosis againstmalathion exposure in testicular tissue	Dose- and time-dependent effects of malathion-induced toxicity on the mitigating effects of N-acetyl-L-cysteine on testicular tissue	*Experimental In Vitro Laboratory*	Testicular tissue obtained from goat (Capra hicus)	*One-way ANOVA & Duncan's Post Hoc Test*	Malathion increases oxidative stress by increasing ROS generated due to lipid peroxidation and reduces FRAP activity in testicular tissue which is responsible for increased cell permeability to pro-apoptotic signaling molecules that facilitate the initiation and execution of apoptosis.
6	Manel Jallouli, Ines El Bini Dhouib, Hanene Dhouib, Montassar Lasram, Najoua Gharbi, Saloua El Faaza	ENVIRON SCI POLLUT RES	Disruption of steroidogenesis after dimethoate exposure and efficacy of N-acetylcysteine in rats: an old drug with new approaches	Reprotoxic effects of DMT and protective role of N-acetylcysteine (NAC) in male rats. DMT (20 mg/kg/body weight) was administered daily to male rats.	*Experimental Laboratory*	48 male rats divided into 4 test groups	*Student's t test*	DMT exposure can result in oxidative changes in the testes associated with increased lipid peroxidation, impaired testosterone secretion, along with decreased expression of steroidogenic genes in male rats.
7	Piotr Adamczuk, Konrad Jamka, Hubert Bojar, Joanna Szala-Rycaj, Aleksandra Szewczyk, Krzysztof	Annals of Agricultural and Environmental Medicine	The effect of the antioxidant N-acetylcysteine on cholinesterase activity in the brain and	Effect of NAC on functional status of target cholinesterases in brain and blood during	*In Vivo Laboratory Experiment*	144 male swiss rats divided into 2 test groups	*Student's t test, ANOVA, Post hoc tukey test*	NAC may be used to enhance the potential of OBID to reactivate brain AChE inhibited by PM.

No.	Research Name & Year	Journal Name	Research Title	Variables Examined	Study Design	Research Sample	Statistical Methods	Research Conclusion
	Bogumil Sawicki, Grzegorz Raszewski		blood during Pirimiphos methyl poisoning in the course of treatment with atropine alone, and with atropine and obidoxime	treatment with atropine (ATR) and/or obidoxime (OBID) in pirimiphos methyl-induced toxicity.				Therefore, these positive impacts of NAC may prompt consideration for the inclusion of NAC into treatment protocols in cases of pirimiphos methyl poisoning.

DISCUSSION

Literature review conducted by the author obtained 7 journals that studied the effect of N-acetylcysteine as an antidote in organophosphate compound poisoning. The literature was obtained through Pubmed and has been selected according to the requirements and keywords that have been determined. The author then made comparisons between one journal and another to be able to make generalizations.

In the first literature, NAC administration can reduce neurotransmitters in the brain such as GABA, Serotonin, and dopamine in combination treatment. This is due to exposure to fenitrothion, which is an organophosphate compound, for 30 days orally which can reduce the number of erythrocytes as well as damage to other blood components. The antioxidant activity of NAC has been hypothesized to increase the neurotransmitters glutamate and dopamine. NAC also reduces the production of various neuro-inflammatory markers thereby reducing inflammation in brain tissue (Alam et al, 2019). Further literature also states that NAC acts as a free radical scavenger and antioxidant resulting in an increase in BDNF, a dimeric protein part of the neurotrophin molecule found in the brain, as an inhibitor of the progression of neurodegenerative disorders. Captured free radicals can help stop the release of ROS thus preventing cell apoptosis and injury to the brain (Mahmoud et al, 2019).

The third literature states that exposure to malathion, an organophosphate insecticide, can cause cell cycle arrest and cytotoxicity. This results in cells experiencing oxidative stress due to increased intracellular ROS levels accompanied by decreased glutathion and antioxidant enzymes. In this literature, NAC was shown to reverse the oxidative stress response and prevent cell apoptosis. Assisted by GHA cells, NAC can initiate inhibition of the mitochondrial apoptotic pathway by involving the cell cycle and ROS response. The results of this study indicate that NAC has the potential as a potential compound as a preventative for brain injury due to malathion exposure (Shieh et al, 2019). In the fourth literature, it is stated that fenitrothion (TNF) contamination of soil, water, and food products has hepatotoxic, nephrotoxic, and neurotoxic effects. This compound caused subjects to experience decreased food intake, water intake, body weight, as well as changes in the expression

of cytochrome P450 (CYP1A1) and gluthathion S-transferase (GSTA4-4) metabolic enzymes. FNT also causes oxidative stress, hepatotoxicity, nephropathy, encephaloathy, and increased pro-inflammatory cytokines in liver, kidney, and brain tissues. Increased FNT levels can increase the presence of injury biomarkers in the kidney and liver and acetylcholinesterase inhibition in the brain. Through this study, the administration of NAC was shown to ameliorate all of these problems, so it can be concluded that NAC can protect cells from FNT toxicity in non-target organisms, including humans (Galal et al, 2019).

In the fifth literature, the study conducted by Bhardwaj et al. (2019) highlighted the effects of malathion toxicity on goat testicular tissue in vitro and the mitigating role of N-acetyl-L-cysteine (NAC). The results showed that malathion exposure increased oxidative stress through increased ROS and lipid peroxidation, and decreased FRAP (Ferric Reducing Antioxidant Power) activity. This leads to increased cell permeability to pro-apoptotic molecules and facilitates the initiation and execution of apoptosis in spermatogonial cells. The administration of NAC proved to be able to inhibit the apoptotic process, so that NAC has the potential as a protective agent against malathion-induced testicular damage. These findings are in line with previous journals that also highlighted the antioxidant role of NAC in reducing oxidative stress and apoptosis due to organophosphate exposure.

In the sixth piece of literature, Jallouli et al. (2016) examined the effects of dimethoate (DMT) exposure on steroidogenesis and the protective role of NAC in male rats. DMT exposure was shown to cause oxidative changes in the testes, increased lipid peroxidation, impaired testosterone secretion, and decreased steroidogenic gene expression. NAC administration was able to significantly ameliorate these changes, both at the biochemical and gene expression levels. This study strengthens the evidence that NAC not only acts as an antioxidant, but can also maintain endocrine and reproductive functions impaired by organophosphate exposure. When compared with the sixth journal, these two studies both highlight the protective effects of NAC on the reproductive system undergoing oxidative stress due to organophosphates, despite using different types of organophosphates.

The seventh literature, conducted by Adamczuk et al. (2023), discussed the effect of NAC on cholinesterase activity in the brain and blood during the treatment of pirimiphos methyl poisoning in rats, either with atropine alone or a combination of atropine and obidoxime. The results showed that NAC could enhance the effectiveness of obidoxime in reactivating brain acetylcholinesterase (AChE) inhibited by pirimiphos methyl. This finding is very important because it shows the potential use of NAC as part of the organophosphate poisoning treatment protocol, especially in increasing the effectiveness of cholinesterase reactivators. When compared to previous journals, the focus of this study is more on the pharmacological aspects and combination therapy, whereas previous journals highlighted the protective effects at the cellular and tissue levels.

So through all the literature that the author reviewed, organophosphate poisoning is known to cause neurotransmitter disorders, oxidative stress on cells due to increased ROS, and initiate cell apoptosis. The use of NAC as a main or supporting therapy can reduce the effects caused by OP because

NAC can act as a free radical scavenger, antioxidant, and anti-inflammatory.

CONCLUSION

Results from various literature studies indicate that N-Acetylcysteine (NAC) has great potential as a protective agent against poisoning caused by organophosphate (OP) compounds. NAC works as an antioxidant and anti-inflammatory that can reduce oxidative stress, repair tissue damage, and support the recovery of nerve function through increasing the activity of enzymes such as acetylcholinesterase. In addition, NAC can also enhance the effectiveness of standard therapies such as atropine and obidoxime. With its various therapeutic benefits, NAC has promising prospects for use in pharmacovigilance practice, both as a primary treatment and as a complement in OP poisoning therapy.

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