



Protective Effects of Artemisinin against Malathion-induced Oxidative Damage in the Brain, Liver and Kidneys of Rats

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10.18805/IJAR.BF-2113

ABSTRACT

Background: The organophosphorus pesticide Malathion (MAL) is widely used in agriculture; however, it is toxic to the liver, kidney and brain tissues of vertebrates. This study investigated how Artemisinin (ART) protects liver, kidney and brain tissues from MAL toxicity in male albino rats.

Methods: Forty Wistar rats, including eight mature males, were randomly assigned to five different groups. The control group received normal saline and the treatment groups received ART (100 mg/kg), MAL (200 mg/kg), MAL + ART (50 mg/kg), or MAL + ART (100 mg/kg) daily for 28 days.

Result: MAL markedly elevated serum concentrations of AST, ALP, ALT, LDH and γ -GT, in addition to cholesterol, urea, uric acid, creatinine and cytokines IL-1 β , IL-6, TNF- α and 8-OHdG ($p < 0.05$). Conversely, levels of total protein, albumin, triglycerides and AChE diminished. The tissue analysis revealed elevated levels of MDA and NO, but GSH and the activity of antioxidant enzymes SOD, GSH-Px, CAT were diminished. ART co-treatment (50 and 100 mg/kg) significantly improved these disturbances ($p < 0.05$), restoring serum biochemical and antioxidant status. ART demonstrates excellent therapeutic potential for treating MAL-induced damage to livers, brains and kidneys, which makes it an attractive solution for organ protection in public health.

Key words: Antioxidants, Artemisinin, Hepatotoxicity, Malathion, Nephrotoxicity, Neurotoxicity.

Abbreviations: ART: Artemisinin; MAL: Malathion; AST: Aspartate aminotransferase; ALT: Aspartate aminotransferase; ALP: Alkaline phosphatase; LDH: Lactate dehydrogenase; γ GT: Gamma-glutamyl transferase; AChE: Acetylcholine esterase; IL-1 β : Interleukin-1 beta; TNF- α : Tumor necrosis factor-alpha; IL-6: Interleukin-6; 8-OHdG: Hydroxy-2'-deoxyguanosine; MDA: Malondialdehyde; NO: Nitric oxide; GSH: Glutathione; GSH-Px: Glutathione peroxidase; SOD: Superoxide dismutase; CAT: Catalase.

INTRODUCTION

The pesticide Malathion (MAL) is a toxic organophosphate compound. The active ingredients of effective pesticides exhibit characteristics such as high stability, low water solubility and a high toxic potential, which lead to various health threats for people and environmental ecosystems (Cech *et al.*, 2023). These toxicants influence and/or interfere with the reproductive and hormonal milieu *via* acting on the hypothalamus, pituitary gland and reproductive organs (Sangha *et al.*, 2023).

The oxidative stress caused by MAL leads to increased apoptotic markers, which results in DNA fragmentation and damage's mitochondrial function (Dos Santos *et al.*, 2016). MAL has been documented to disrupt reproductive and sexual development in animals (Ibrahim *et al.*, 2020). The body experiences organ damage from prolonged exposure, which mainly affects the liver, kidneys and the brain (Selmi *et al.*, 2018; El Okle *et al.*, 2022). Artemisinin (ART) was discovered by the medical community during the 1970s, bringing about the malaria treatment revolution that saved countless lives across the globe (Guo, 2016). ART has established antimalarial effects and displays additional pharmacological properties, including antiviral, antineoplastic, immuno suppressive, antioxidant and neuroprotective effects. Due to its multiple drug-like properties, ART demonstrates potential as a therapeutic

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How to cite this article: Ibtesam, S. (2026). Protective Effects of Artemisinin against Malathion-induced Oxidative Damage in the Brain, Liver and Kidneys of Rats. *Indian Journal of Animal Research*. 60(9): 1656-1664. doi: 10.18805/IJAR.BF-2113.

Submitted: 07-02-2026 **Accepted:** 30-03-2026 **Online:** 15-04-2026

option for autoimmune and inflammatory diseases (Xia *et al.*, 2020; Meng *et al.*, 2021). The literature has documented the therapeutic benefits of ART, but scientists have not studied its ability to protect against MAL toxicity. This research investigated ART's effects on the brain, liver and kidney tissues of rats exposed to MAL, focusing on its antioxidative and cytoprotective properties.

MATERIALS AND METHODS

Chemicals

Pure artemisinin and Malathion were procured from Sigma-Aldrich Chemical Company (USA). Diagnostic kits for the

assessment of serum, brain, hepatic and renal biomarkers were obtained from Bio Diagnostics Co. (Egypt). Enzyme-linked immunosorbent assay (ELISA) kits for the quantification of serum pro-inflammatory cytokines were purchased from R and D Systems (Germany), while 8-OHdG assay kits were supplied by Cayman Chemical Company (USA).

Experimental design

Forty male Wistar rats (130-160 g) were acclimatized for one week and divided into five groups (n=8). The subjects were kept under controlled conditions (22±2°C, 45±5% humidity, 12-hour light/dark cycle) with unlimited access to food and water during the 28-day study duration. The animal procedures followed the guidelines established by the Ethics Committee of Batterjee Medical Research Center, Batterjee Medical College, Jeddah, Saudi Arabia during 2025. All rats received daily oral treatments *via* gastric gavage for a duration of 28 consecutive days, according to the following experimental protocol: Group 1 (control)-normal physiological saline was administered to the control animals. Group 2 (artemisinin)-rats were treated with 100 mg/kg of artemisinin (Jia *et al.*, 2022). Group 3 (Malathion) -200 mg/kg of MAL was administered (Abdel-Daim *et al.*, 2020). Group 4 (Malathion + artemisinin)-rats received 200 mg/kg of MAL and 50 mg/kg of ART. Group 5 (Malathion + artemisinin)-rats received 200 mg/kg of MAL and 100 mg/kg of ART. The diagram illustrates the five experimental groups, the 28-day treatment period and the comparative analysis between MAL-induced oxidative stress, inflammation and DNA damage, versus the anti-inflammatory, antioxidant and organo-protective effects (Hepato-, Renal- and Neuro-protection) of ART (Fig 1).

Blood, serum and tissue collection

Serum was obtained from cardiac blood at 3000 rpm for 15 minutes. Brain, liver and kidney tissues were collected, rinsed in cold saline and homogenized in ice-cold 50 mM sodium phosphate buffer (pH 7.4) containing 0.1 mM EDTA. Homogenates were subjected to centrifugation (5000 rpm, 30 min, 4°C) and the supernatants were preserved at -80°C for biomarker analysis.

Assessment of serum AChE activity and biochemical analysis

Serum AChE activity was quantified colorimetrically according to the manufacturer's guidelines. Total protein, creatinine, urea and ALP were quantified using the methodologies established by Lowry *et al.* (1951), Larsen (1972), Coulombe and Favreau (1963) and Tietz *et al.* (1983), respectively. Serum ALT and AST levels were evaluated utilizing the Reitman and Frankel (1957) methodology.

Assessment of oxidative DNA damage markers and pro-inflammatory cytokines

A competitive ELISA kit was used to measure 8-OHdG serum concentrations following the instructions provided by the manufacturer. The analysis of 8-OHdG measured both its free state and its DNA-bound state to determine oxidative DNA damage levels. ELISA kits from RandD Systems in Mannheim, Germany, were used to measure the pro-inflammatory cytokines TNF-α, IL-1β and IL-6, according to the manufacturer's guidelines.

The assessment of tissue lipid peroxidation and the activity of antioxidant enzymes

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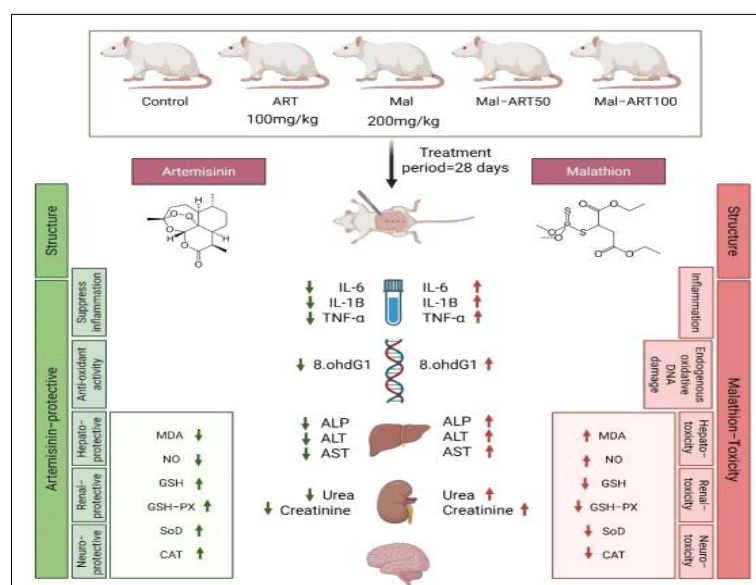


Fig 1: Schematic representation of the experimental design and the protective mechanisms of ART against Mal-induced multi-organ toxicity.

GSH levels were quantified according to the procedures established by Uchiyama and Mihara (1978); Green *et al.* (1982) and Beutler *et al.* (1963), respectively. The activities of SOD, GSH-Px and CAT were assessed using the techniques defined by Nishikimi *et al.* (1972); Paglia and Valentine (1967) and Aebi (1984).

Statistical analysis

The research data underwent a one-way analysis of variance (ANOVA) followed by Duncan's multiple range test for post hoc comparisons, as this method demonstrated better results for multiple group assessments in this study design. The Statistical Package for the Social Sciences (SPSS) software version 22 was used to perform all statistical calculations. Results are expressed as mean $\pm$ SEM, with statistical significance set at $p < 0.05$.

RESULTS AND DISCUSSION

Effects of ART on tissue serum biochemical parameters in MAL-intoxicated rats

ART alone (100 mg/kg) showed no significant differences from controls, except for elevated AChE. MAL exposure significantly increased serum AST, ALT, ALP, LDH, γ -GT, cholesterol, urea, uric acid and creatinine, while decreasing total protein, albumin, triglycerides and AChE ($p < 0.05$). ART co-treatment effectively mitigated these alterations, with the MAL-ART100 group largely returning to normal levels, excluding AST (Table 1).

Inflammatory cytokines and DNA oxidation marker

Relative to the control group, rats exposed to MAL exhibited significantly elevated serum IL-1 β , IL-6, TNF- α and 8-OHdG levels ($p < 0.05$). ART alone (100 mg/kg) showed no

Table 1: Effects of ART administration on serum biochemical parameters in MAL-intoxicated rats.

Treatments	Control	ART100	MAL	MAL-ART50	MAL-ART100
AST u/mL	56.23 $\pm$ 1.98 ^a	53.58 $\pm$ 1.43 ^a	142.68 $\pm$ 3.26 ^d	99.82 $\pm$ 2.38 ^b	66.63 $\pm$ 1.49 ^c
ALT u/mL	32.69 $\pm$ 1.43 ^a	31.95 $\pm$ 1.92 ^a	55.78 $\pm$ 2.64 ^c	43.31 $\pm$ 0.85 ^b	36.85 $\pm$ 1.65 ^a
ALP U/L	75.86 $\pm$ 2.53 ^a	73.24 $\pm$ 2.13 ^a	180.44 $\pm$ 6.58 ^c	119.39 $\pm$ 3.50 ^b	81.36 $\pm$ 1.18 ^a
LDH U/L	205.98 $\pm$ 7.33 ^a	202.04 $\pm$ 4.25 ^a	528.09 $\pm$ 19.45 ^c	344.77 $\pm$ 10.66 ^b	210.08 $\pm$ 4.24 ^a
γ GT U/L	3.87 $\pm$ 0.12 ^a	3.89 $\pm$ 0.08 ^a	9.09 $\pm$ 0.33 ^c	5.97 $\pm$ 0.15 ^b	3.89 $\pm$ 0.10 ^a
Albumin (g/L)	4.28 $\pm$ 0.12 ^c	4.24 $\pm$ 0.09 ^c	3.31 $\pm$ 0.07 ^a	3.95 $\pm$ 0.09 ^b	4.22 $\pm$ 0.05 ^c
Total protein (g/L)	7.73 $\pm$ 0.02 ^c	7.61 $\pm$ 0.15 ^c	5.43 $\pm$ 0.19 ^a	6.81 $\pm$ 0.11 ^b	7.48 $\pm$ 0.14 ^c
Cholesterol (mg/dL)	75.10 $\pm$ 3.76 ^a	74.27 $\pm$ 2.61 ^a	166.71 $\pm$ 5.65 ^c	115.02 $\pm$ 3.85 ^b	83.29 $\pm$ 1.75 ^a
Triglycerides (g/L)	127.56 $\pm$ 3.07 ^c	128.23 $\pm$ 3.05 ^c	75.19 $\pm$ 1.74 ^a	101.25 $\pm$ 2.72 ^b	121.04 $\pm$ 2.23 ^c
Urea (mg/dL)	23.75 $\pm$ 1.56 ^a	23.98 $\pm$ 1.58 ^a	71.43 $\pm$ 4.65 ^c	46.30 $\pm$ 2.20 ^b	25.27 $\pm$ 23.04 ^a
Uric acid (mg/dL)	26.56 $\pm$ 1.99 ^a	26.67 $\pm$ 0.79 ^a	79.13 $\pm$ 2.77 ^c	49.37 $\pm$ 1.60 ^b	27.94 $\pm$ 26.36 ^a
Creatinine mg /dL	0.67 $\pm$ 0.04 ^a	0.65 $\pm$ 0.02 ^a	4.72 $\pm$ 0.19 ^b	2.01 $\pm$ 0.15 ^b	0.91 $\pm$ 0.04 ^a
AChE (U/L)	222.07 $\pm$ 5.19 ^c	230.54 $\pm$ 6.66 ^d	76.30 $\pm$ 3.03 ^a	136.83 $\pm$ 3.14 ^b	212.61 $\pm$ 6.94 ^c

Data are means $\pm$ SEM (n = 8 per group). Values with different superscript letters in the same row are significantly different at $p < 0.05$.

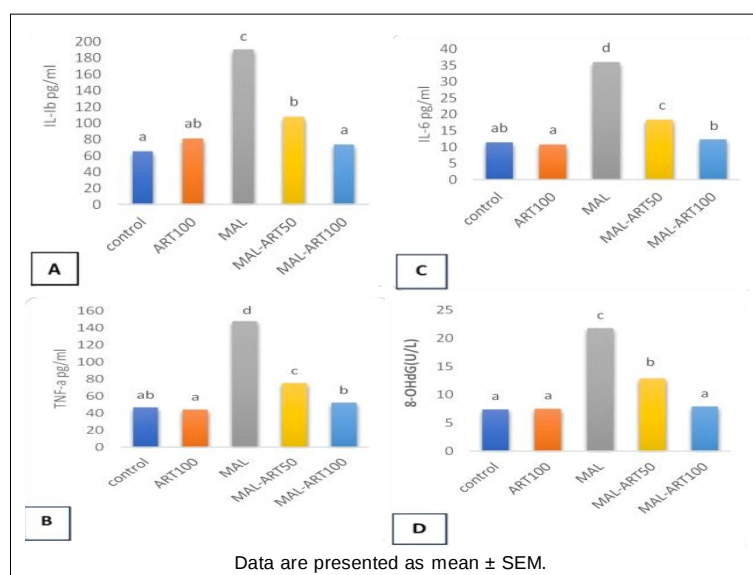


Fig 2: The protective effect of ART against MAL-induced changes in the serum levels of IL-1 β (A), TNF- α (B), IL-6 (C) and 8-OHdG (D) in rats.

significant variations, while ART co-treatment (50 and 100 mg/kg) significantly reduced these parameters ($p < 0.05$). Furthermore, the MAL-ART100 group showed no significant differences compared to the control group (Fig 2).

Lipid peroxidation in the liver and the antioxidant status

Relative to the control group MAL significantly elevates hepatic MDA and NO concentrations while depleting GSH and antioxidant enzyme activities ($p < 0.05$). ART alone (100 mg/kg) caused no significant changes. In comparison with the MAL group ART co-treatment (50 and 100 mg/kg) markedly reduced oxidative stress markers and restored antioxidant status (Fig 3).

Lipid peroxidation in the kidney and antioxidant status

Compared to the control group MAL intoxication significantly increased renal MDA and NO concentrations while depleting GSH and antioxidant enzyme activities ($p < 0.05$). ART alone (100 mg/kg) showed no significant variations. In comparison with the MAL group, ART co-treatment (50 and 100 mg/kg) significantly mitigated oxidative abnormalities,

reinstating GSH levels and enhancing antioxidant enzyme activity (Fig 4).

Lipid peroxidation in the brain and antioxidant status

Compared to the control group, cerebral MAL-intoxication markedly increased MDA and NO levels while diminishing GSH and antioxidant enzyme activity ($p < 0.05$). ART alone (100 mg/kg) produced no statistically significant changes ($p < 0.05$). Compared to the MAL group ART Co-treatment (50 and 100 mg/kg) alleviated these oxidative changes, reinstating GSH levels and enhancing the activities of SOD, GSH-Px and CAT (Fig 5).

Herbal materials, serving as models for numerous synthetic medications, illuminate the structures of their active substances and are thus essential components of contemporary medicine (Girisgin *et al.*, 2023). This research aimed to determine the potential of ART to protect against MAL toxicity in rats.

The present study showed that after receiving 200 mg/kg body weight of MAL for 28 days, rats exhibited biochemical changes reflecting liver and DNA damage, kidney problems,

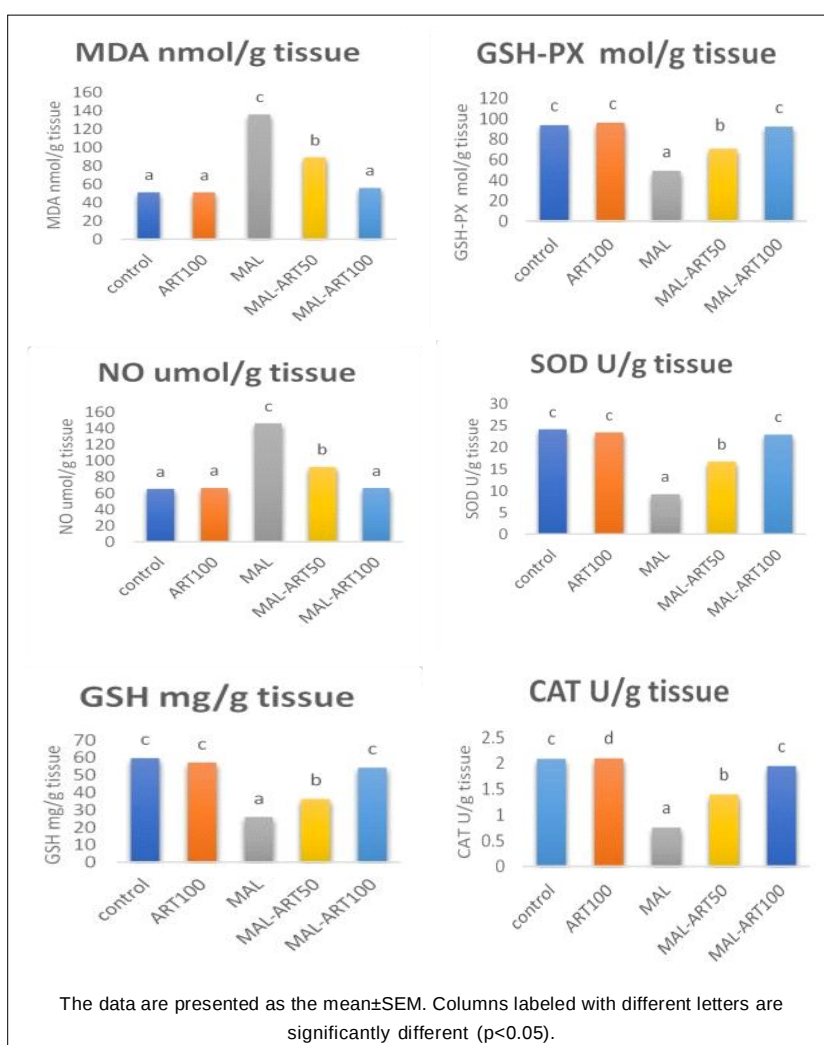


Fig 3: Illustrates the antioxidant effects of ART on MAL-induced hepatotoxicity.

brain toxicity and elevated inflammatory cytokine levels. In contrast, the ART treatment protected rats from MAL toxicity when used at 50 mg/kg body weight and 100 mg/kg body weight.

This research demonstrated that serum levels of ALT, AST, ALP and γ -GT enzymes increase in rats exposed to MAL. Liver tissue sustains structural damage due to hepatocellular necrosis and degenerative changes, which leads to impaired plasma membrane permeability. According to Alkhalaf *et al.* (2024), MAL causes serum liver enzyme levels to increase. The measurement of liver enzyme activity serves as a vital tool for detecting MAL-induced liver damage. The serum levels of albumin, total protein, triglycerides and cholesterol decreased significantly in rats that were exposed to MAL. This work also confirmed previous research by demonstrating that MAL exposure leads to elevated serum levels of urea, creatinine and uric acid, which indicates kidney function impairment (Gur and Kandemir, 2023). The serum creatinine elevation stems from reduced renal clearance, which indicates an impaired glomerular filtration performance. It is commonly acknowledged

that elevated serum creatinine levels, which indicate a reduction in glomerular filtration efficiency, are a trustworthy biochemical indicator of renal failure (Lopez-Giacoman and Madero, 2015).

Exposure to MAL may harm brain function, which is reflected in substantial decreases in AChE enzyme activity in brain tissue. These research results support previous studies that investigated MAL toxicity (Gupta *et al.*, 2023).

The present study also showed that MAL (200 mg/kg) exposure causes severe DNA damage and inflammation as reflected through elevated 8-OHdG, TNF- α , IL-1 β and IL-6 levels in different organ tissues. These findings support earlier scientific studies regarding the toxicity of MAL (Abdel-Daim *et al.*, 2020) and demonstrate that MAL exposure causes substantial decreases in GSH levels and GSH-Px, SOD and CAT enzyme activities while simultaneously increasing MDA and NO concentrations in hepatic, renal and cerebral tissues. This study confirmed the results documented by Gur and Kandemir (2023). The impairment of antioxidant defense system efficiency relative to reactive oxygen species production creates oxidative stress

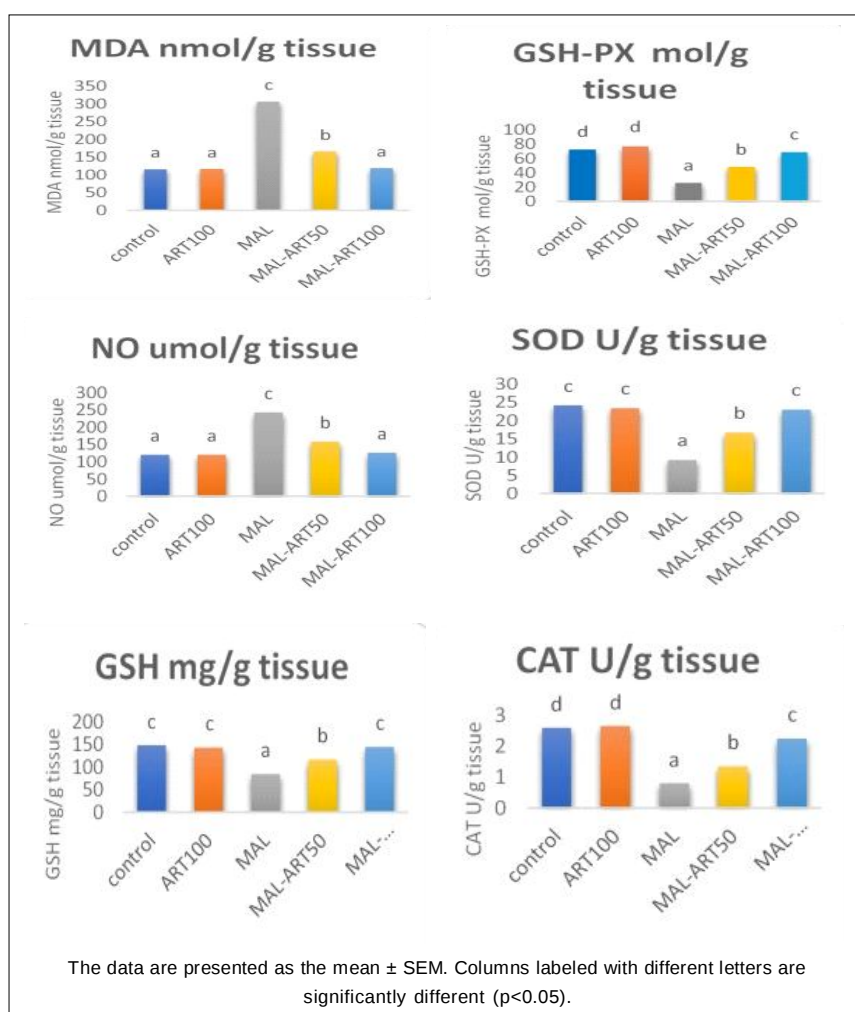


Fig 4: Illustrates the antioxidant effects of ART against MAL-induced nephrotoxicity.

that causes major changes in lipid peroxidation levels and essential antioxidant enzyme activities (Medithi *et al.*, 2021).

The main toxic effect of MAL occurs through oxidative stress, which produces excessive free radicals while depleting antioxidant defenses (Ince *et al.*, 2017). Free radicals produced by reactive oxygen species can cause damage to biomolecules, including lipids. This metabolic process includes lipid peroxidation as its most destructive chemical reaction, which produces permanent cell death. The lipophilic nature of MAL allows it to penetrate cell membranes, where it triggers lipid peroxidation reactions. The central nervous system becomes more vulnerable to oxidative stress damage because MAL interacts strongly with neuronal membrane components due to its lipophilic properties (Yousefsani *et al.*, 2024). The toxic effects of MAL can lead to the complete destruction of all nephron components (Alhilal *et al.*, 2025).

The excessive production of reactive oxygen species makes proteins, lipids and DNA vulnerable to oxidative

damage (Amini *et al.*, 2022). Zhang *et al.* (2024) reported that the appropriate dosage of ART protects cells from ROS and oxidative stress damage. One of the main cytoprotective effects of ART includes its ability to decrease ROS production (Fang *et al.*, 2019). The study by Qin *et al.* (2022) demonstrated that ART treatment leads to reduced ROS production, delayed fission, restored biosynthesis and maintained homeostasis in mitochondria. The treatment of PC12 cells with ART resulted in substantial protection against cell death and LDH release, while simultaneously increasing ROS production and causing potential mitochondrial membrane collapse and apoptosis (Li *et al.*, 2023). A study showed that ART protected rats from doxorubicin-induced heart and liver damage through its ability to decrease caspase-3, TNF- α , iNOS and NF- κ B expression (Aktaş *et al.*, 2020). The treatment of rat bone marrow-derived mesenchymal stem cells (BMSCs) exposed to hydrogen peroxide (H_2O_2) with ART led to improved survival rates and decreased ROS production and elevated antioxidant enzyme activities,

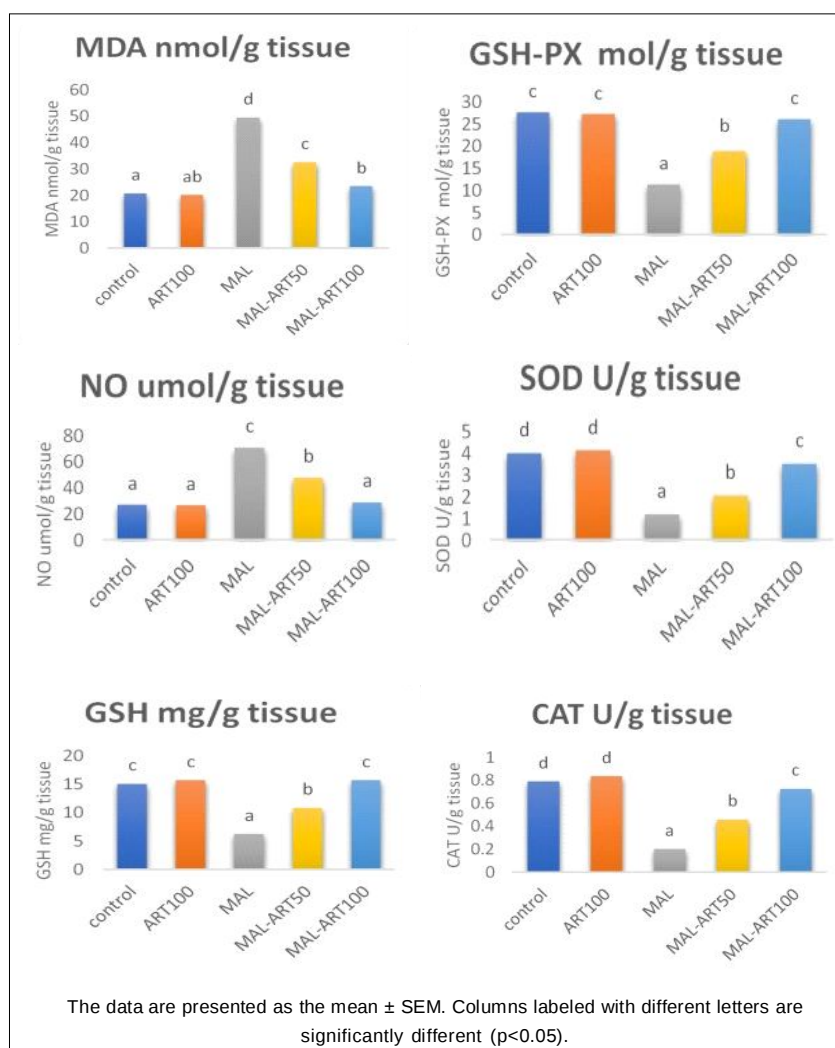


Fig 5: Illustrates the antioxidant effects of ART against MAL-induced neurotoxicity.

accompanied by lower caspase-3 activation, reduced LDH release and decreased apoptosis rates (Fang *et al.*, 2019). Recent research has demonstrated that ART treatment reduces diclofenac-induced kidney damage through SIRT3 modulation, which leads to better renal function, decreased oxidative stress, increased LC3-II expression, reduced caspase-3 activity and preserved mitochondrial stability (Hella *et al.*, 2025).

The anti-inflammatory properties of ART become evident through its ability to block pro-inflammatory signaling pathways, resulting in decreased IL-1 β , IL-6 and TNF- α expression (Li *et al.*, 2022). The immunomodulatory effects of ART in rat heart transplant models lead to reduced allograft rejection rates and tissue damage through its ability to control both cellular and humoral immune responses. Furthermore, ART reduced antibody-mediated rejection (ABMR) through its ability to block B cell activation and antibody production (Yang *et al.*, 2021).

The neuroprotective effects of ART include its ability to reduce oxidative stress, prevent neuronal death, decrease neuroinflammation and enhance synaptic connections. A wide range of neurological disorders, including stroke and Alzheimer's disease can be treated with ART due to its multiple therapeutic mechanisms (Yan *et al.*, 2021; Chen *et al.*, 2025). Furthermore, research has demonstrated that ART treatment leads to better thyroid function; reduced anxiety and depression symptoms; improved liver, kidney and cardiac health and decreased oxidative stress (Li *et al.*, 2024). These findings may have clinical consequences for people exposed to organophosphate pesticides in their occupations, such as agricultural laborers. Considering the safety profile of ART, it may be investigated as a dietary supplement or a preventive treatment to mitigate the chronic multi-organ damage linked to pesticide exposure to humans.

CONCLUSION

This study demonstrated that treatment with ART protected rat tissues from the MAL-induced DNA damage and oxidative stress that affected multiple organs and reduced pro-inflammatory cytokine levels in the serum. The protective effects of ART against MAL-induced blood biochemical indicator changes and organ damage were found to depend on the ART dosage. These results suggest that ART has potential as a therapeutic agent for individuals exposed to MAL.

ACKNOWLEDGEMENT

We thank all participants in this study.

Funding

The author declare that no financial support was received for the research, authorship and/or publication of this article.

Conflict of interest

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

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