Arch. Bas. App. Med.13 (2025) 99-106
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Research Article

Protective Role of Quercetin Against Aluminium Phosphide-Induced Gastric Toxicity in Wistar Rats

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Accepted: October 11, 2025

Abstract

Oral exposure to aluminium phosphide (ALP), an extensively used pesticide, has been reported to cause multiorgan and systemic toxicity, including significant gastrointestinal damage. Quercetin (QUE) is widely recognized for its ability to protect the gastrointestinal tract against various insults and toxicities. However, its likely protective effects against ALP-induced gastric toxicity is largely undocumented. Hence, this study was designed to evaluate the protective role of quercetin against aluminium phosphide induced-gastric toxicity in Wistar rats. Male Wistar rats were divided into seven groups: Groups I and II served as control and vehicle control, while Groups III-VII received for 28 days, ALP (2mg/kg) alone, QUE (25mg/kg) alone, QUE cotreatment+ALP, QUE pretreated+ALP and ALP+QUE posttreatment, respectively. Blood and gastric juice samples were collected under anaesthesia for haematological and biochemical analyses. The stomach tissues were excised and analysed for gastric mucin content, malondialdehyde (MDA), superoxide dismutase (SOD), nitric oxide (NO), reduced glutathione (GSH) and histology Data were analysed using one-way ANOVA and Newman-Keuls' post-hoc test ($p<0.05$). Quercetin significantly mitigated ALP-induced gastric toxicity ($p<0.05$) with co-treatment and pretreatment groups showing enhanced SOD and GSH levels, reduced MDA and NO, increased mucous and parietal cell counts and preserved mucosal integrity, compared with the ALP-only group (Group III, $p<0.05$). Post-treatment (Group VII) provided moderate recovery but was less effective in reversing ALP-induced gastric damage. Except for WBC count, haematological parameters (PCV, haemoglobin, and RBC count) showed no significant changes across groups ($p>0.05$). Quercetin treatment mitigated ALP-induced gastric toxicity, with co-treatment and pre-treatment showing superior protective effects.

Key Words: *Aluminium Phosphide, Quercetin, Oxidative Stress, Gastric Toxicity, Antioxidants*

INTRODUCTION

It is not an unusual agricultural practice worldwide to protect food and commercial produce using pesticides. The most commonly used pesticides in agriculture include organophosphates, organochlorines, and phosphides, especially aluminium phosphide (Mehrpour *et al*., 2012). However, pesticide poisoning has become not only a major environmental challenge but also a significant public health concern, with numerous unintended cases of poisoning resulting in fatalities (Abdollahi *et al*., 2004).

One such pesticide, aluminium phosphide, has been reported to be highly toxic, liberating phosphine as its active pesticidal component (Sudakin, 2005). In humans, its toxicity is acute and occurs due to the toxic effects of phosphine, which is released in the stomach after ingestion and is widely absorbed from the gastrointestinal tract (Mehrpour *et al*., 2012). Aluminium phosphide induces its toxicity by inhibiting mitochondrial cytochrome C oxidase, leading to cellular hypoxia and stimulating the formation of highly reactive hydroxyl radicals (Dua and Gill, 2001). It exerts its toxic effects on multiple organs, particularly targeting cardiac and vascular tissues, which manifest as profound and refractory hypotension, congestive heart failure, and electrocardiographic abnormalities (Soltaninejad *et al*., 2012). In the gastrointestinal tract, it has also been reported to cause severe haemorrhage and ulceration (Mojzis *et al*., 2001).

It has been reported that aluminium phosphide poisoning does not have a specific antidote (Karimani *et al*., 2018). Treatment protocols with some reported benefits include early gastric lavage with potassium permanganate, administration of activated charcoal, and palliative care (Mehrpour *et al*., 2012). In developing countries, there is no active legislation against its use as a pesticide. Due to its affordability, its use remains frequent, increasing the likelihood of unintentional poisoning in these regions. Therefore, while awaiting legislative action against its use, it is essential to investigate substances that can mitigate the hazardous effects of aluminium phosphide poisoning.

Quercetin, a common flavonoid found in plants, is widely reported to have beneficial effects on human health. It is abundantly found in fruits and vegetables such as citrus, onions, and apples (Qi *et al*., 2022). Quercetin has been observed to exhibit antioxidant, anti-inflammatory, anti-atherogenic, anti-carcinogenic, antiviral, and anti-allergic properties (Serafim *et al*., 2020, Aghababaei and Hadidi, 2023). In the gastrointestinal tract, quercetin has been shown to attenuate reactive oxygen species accumulation in damaged gastric mucosa, protect against inflammation, enhance intestinal barrier function, and modulate gut microbiota

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composition (Jia *et al*., 2021). However, whether quercetin can protect against aluminium phosphide-induced gastric toxicity remains largely undocumented.

This study was therefore designed to investigate the potential of quercetin in mitigating the harmful and toxic effects of aluminium phosphide. The study explores quercetin co-treatment with aluminium phosphide, pretreatment prior to aluminium phosphide exposure, and post-treatment following aluminium phosphide exposure as treatment protocols for evaluating its mitigative and / or ameliorative potentials. Aluminium phosphide will be administered to experimental animals at a dose of 2mg/kg body weight which is considered a sub-lethal, sub-chronic dose in Wistar rats (Assima *et al*, 2024) and is used in experimental studies to evaluate its long-term effects.

MATERIALS AND METHODS

Animals, Grouping, and Experimental Protocol: Ninety-eight (98) male Wistar rats weighing between 140–180 g was used for this study. The animals were housed in well-ventilated cages under standard laboratory conditions, including natural alternating light and dark cycles, room temperature, and *ad libitum* access to standard rat chow and drinking water. The rats were acclimatized for 14 days prior to the experimental procedures. Animal care complied with the guidelines of the University of Ibadan Animal Care and Use Research Ethics Committee and the Guide for the Care and Use of Laboratory Animals (National Research Council, 2011).

Experimental Design: The animals were randomly divided into seven groups and treated as follows;

Group I (control): Distilled water (0.1 mL/100g b.w) for 28 days
Group II (vehicle control): Corn oil (0.1mL/100g b.w.) for 28 days
Group III: Aluminium phosphide (2 mg/kg) for 28 days (Ghasemi *et al*, 2024)
Group IV: Quercetin (25 mg/kg body weight) for 28 days (Bule *et al*., 2019)
Group V: Aluminium phosphide (2 mg/kg) + Quercetin (25 mg/kg) concurrently for 28 days.
Group VI: Pretreated with Quercetin (25 mg/kg) 14 days, followed by aluminium phosphide (2 mg/kg) for another 14 days
Group VII: Pretreated with Aluminium phosphide for 14 days and then Quercetin for another 14 days.

All treatment were administered by oral gavage using a cannula.

Haematological assessment and evaluation of Gastric Mucin: Blood samples (n=5/group) were obtained after the various treatments from the orbital sinus, under light anaesthesia (sodium thiopental, 50mg/kg) (Ahmadi-Noorbakhsh *et al*., 2022), using non heparinized capillary tubes, into clean EDTA-containing sample bottles and analysed for haematological (red blood cell (RBC) count, packed cell volume (PCV), haemoglobin, total and differential white blood cell (WBC) counts, platelets) parameters using standard laboratory procedures. The stomachs of these animals were thereafter harvested for evaluation of gastric barrier mucus using the Alcian blue method as described by Corne *et al*., (1974). Briefly, excised stomachs were soaked in 0.1% Alcian blue dissolved in a buffer solution (0.1 M sucrose and 0.05 M sodium acetate; pH 5.8) for 2 hours. The dye bound to mucin was eluted using 0.5 M $MgCl_2$ and quantified spectrophotometrically at 605 nm.

Evaluation of Gastric antioxidant status: Stomach tissues from another set of five animals per group were excised, weighed, and homogenized in 0.1M phosphate buffer (5:1 w/v; pH 7.4) (Olaleye *et al*., 2007). Homogenates were centrifuged at 10,000 rpm for 15 minutes at 4°C, and the supernatant was stored at −20°C for gastric superoxide dismutase (SOD) activity (Misra and Fridovich,1972), reduced glutathione (GSH) (Ellman,1959), malondialdehyde (MDA) (Varshney and Kale, 1990) and nitric oxide (NO) (Griess reaction as described by Green *et al*. 1982) levels, respectively.

Evaluation of gastric secretion pH, electrolyte composition and gastric histology: Another set of experimental animals (n=4/group) were anaesthetized (sodium thiopental, 50mg/kg) and gastric effluents were collected using the pyloric ligation method (Shay *et al*., 1954) and evaluated for the pH of gastric secretion and its electrolyte composition. Briefly, after anaesthesia, a midline abdominal incision was made in the abdominal cavity to expose the stomach. The pyloric sphincter was located and ligated (surgical suture) to completely obstruct the passage of food from the stomach. The abdominal incision was closed and fluid was allowed to accumulate for two hours while the animal was still under anaesthesia. Thereafter, animals were euthanized, the incision was reopened, stomachs were carefully harvested and gastric effluents were collected into sample bottles and the pH of the effluent was taken using pH meter. The stomachs were then infused with 5mL distilled water and effluents added to corresponding sample bottles. The collected gastric effluents were centrifuged at 3,000 rpm for 10 minutes and analysed for Na^+, K^+, and Cl^- using a semi-automated electrolyte analyser. Gastric bicarbonate ions were also measured using standard titration techniques.

The stomachs were then fixed in 10% neutral buffered formalin, dehydrated through graded alcohols, embedded in paraffin, and sectioned at 5 µm thickness. Sections were stained with Haematoxylin and Eosin (H&E) and Period Acid-Schiff (PAS) and examined under a light microscope for histological evaluation of epithelial integrity, mucous cell density, parietal and mucous cell count and signs of inflammation or ulceration.

Statistical Analysis: Data obtained are expressed as mean ± standard error of the mean (SEM). Statistical comparisons between groups were performed using one-way analysis of variance (ANOVA) followed by Newman-Keuls post-hoc test. Differences were considered significant at $p<0.05$.

RESULTS

Effect of quercetin on red cell indices in control and aluminium phosphide-exposed animals: Red blood cell count (RBC), packed cell volume (PCV), and haemoglobin concentration (Hb) values in all experimental groups were not significantly different (p>0.05) when compared with control values (Table 1).

Table 1:
Red cell indices in control and experimental groups

Groups	Red blood cell count (x10^{3}mm^{-3})	Packed cell volume (%)	Haemoglobin (g/dL)
I	6.84±0.22	40.80±1.39	13.62±0.39
II	7.62±0.21	46.40±1.08	15.16±0.29
III	7.29±0.56	45.00±3.18	14.64±0.98
IV	7.76±0.50	47.40±3.72	15.42±1.12
V	6.80±0.73	41.60±3.91	13.68±1.35
VI	7.25±0.03	44.20±0.74	14.92±0.21
VII	7.86±0.21	46.60±1.66	15.60±0.48

Values are expressed as mean ± SEM, *n* = *5*. I = control group, II = Vehicle control, III = Aluminium phosphide only treatment group, IV = Quercetin only treatment group, V = Aluminium phosphide+Quercetin cotreatment group, VI = Quercetin pretreatment+aluminium phosphide group, VII = Aluminium phosphide+Quercetin posttreatment group.

Effect of quercetin on white blood cell indices and platelet count in control and experimental groups: Total white blood cell count (cell/mm3) was increased (p<0.05) in groups III, V and VII when compared with groups I and II. However, values in groups IV and VI were significantly reduced (p<0.05) when compared with group III, but comparable to groups I and II, respectively. Neutrophils (%) were significantly elevated (p<0.05) in groups III (34.50±3.30), V (32.50±0.50) and VI (36.00±0.82) compared to groups I (27.25±0.48) and II (27.75±1.25). However, values obtained in group VII (20.50±1.19) were reduced when compared with groups I and II, respectively. Compared to groups I and II, lymphocytes in group VI were significantly reduced (p<0.05). Values in group VII were significantly increased when compared with group III. No significant difference was observed for monocytes counts across all groups while for platelets, significant difference was only observed in group VII when compared with groups I-III, respectively (Table 2).

Table 2:
White blood cell indices and platelet count in control and experimental groups

Groups	Total WBC (cell/mm^3)	Neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Platelet Count x10^4 (cell/mm^3
I	5745.0±108.5	27.25±0.48	68.20±1.36	1.60±0.24	12.30±1.73
II	5425.0±131.5	27.75±1.25	68.20±1.32	1.60±0.40	14.88±1.41
III	7500.0±212.5$^{*\#}$	34.50±3.30$^{*\#}$	63.80±2.80	1.60±0.37	13.38±0.82
IV	5945.0±315.3^{a}	30.25±1.89	67.00±1.70	2.20±0.37	12.98±1.73
V	6388.0±243.9^{*a}	32.50±0.50$^{*\#}$	65.80±1.39	1.60±0.24	11.38±0.69
VI	5900.0±306.2^{a}	36.00±0.82$^{*\#}$	61.80±1.16$^{*\#}$	1.20±0.20	12.6±2.85
VII	7363.0±431.7$^{*\#}$	20.50±1.19$^{*\#a}$	74.20±1.93^{a}	1.80±0.37	20.64±1.11$^{*\#a}$

Values are mean ± SEM; n=5; P<0.05. *, $^{\#}$, ^{a} indicates values that are significantly different (p<0.05) from control, vehicle and aluminium phosphide only treatment groups, respectively. I = control group, II = Vehicle control, III = Aluminium phosphide only treatment group, IV = Quercetin only treatment group, V = Aluminium phosphide+Quercetin cotreatment group, VI = Quercetin pretreatment+aluminium phosphide group, VII = Aluminium phosphide+Quercetin posttreatment group.

Gastric antioxidant-oxidative balance in control and experimental groups: Gastric malondialdehyde (MDA) levels in group III (693.80±52.22) increased by 75.4% and 49.3% when compared with control (395.30 ±1.44) and vehicle (429.80±20.68) groups, respectively. Compared to group III (693.80±52.22), MDA values in groups IV (401.80±43.71), V (421.50±50.27) and VI (342.00±22.62) were significantly reduced (P<0.05) while values in group VII (618.80±56.15) were comparable (P>0.05). Superoxide dismutase (SOD) and reduced glutathione (GSH) in group III was significantly reduced when compared with groups I and II, respectively. However, values for these antioxidant markers in groups IV - VII were significantly increased when compared with group III (Table 3). Nitric oxide (NO) was significantly increased in group III (p<0.05) when compared with control. Values observed in groups IV-VII for NO were significantly reduced when compared with group III, respectively (Table 3).

Electrolyte Composition of Gastric Juice in control and experimental groups: The electrolyte composition of gastric juice in control and experimental groups is shown in Table 5. Sodium ion concentration (48.06 ± 14.8 mmol/L) in group III was significantly increased compared with groups I (38.05 ± 2.52 mmol/L) and II (37.30±8.94), respectively. Values in groups IV-VII were significantly reduced (p<0.05) compared with group III. Potassium and chloride ion levels in group III (Aluminium phosphide only) increased (p<0.05) by 96.3% and 121.4% when compared with the controls (Group I), respectively. Values for potassium and chloride ion levels observed in groups IV -VII were significantly reduced when compared group III, respectively Bicarbonate levels in group VI and VII were significantly decreased, while values in groups IV and VI were comparable with control and aluminium phosphide only treatment groups, respectively (Table 4).

Table 3:
Effect of Quercetin on gastric antioxidant-oxidative balance in control and experimental groups

Groups	MDA (Mu/mg)	SOD (U/mg protein)	GSH (mg/mL)	NO (mM)
I	395.30 ±1.44	0.049 ±0.001	55.31 ±3.132	0.150 ±0.014
II	429.80 ±20.68	0.042 ±0.003	51.51 ±2.14	0.144 ±0.005
III	693.80 ±52.22$^{*\#}$	0.025 ±0.001$^{*\#}$	36.08 ±2.29$^{*\#}$	0.224 ±0.012$^{*\#}$
IV	401.80 ±43.71 ^{a}	0.049 ±0.005^{a}	52.97 ±3.79^{a}	0.147 ±0.001 ^{a}
V	421.50 ±50.27 ^{a}	0.042 ±0.001^{a}	56.20 ±2.76^{a}	0.187 ±0.009 ^{a}
VI	342.00 ±22.62 ^{a}	0.050 ±0.003^{a}	61.36 ±4.27^{a}	0.085 ±0.006 ^{a}
VII	618.80 ±56.15$^{*\#}$	0.0375 ±0.002^{a}	46.35 ±1.27^{a}	0.116 ±0.010 ^{a}

Values expressed as mean± SEM; n=5, P<0.05. *, #, a indicates values that are significantly different (p<0.05) from control, vehicle control and aluminium phosphide only treatment groups, respectively. I = control group, II = Vehicle, III = Aluminium phosphide only treatment group, IV = Quercetin only treatment group, V = Aluminium phosphide+Quercetin cotreatment group, VI = Quercetin pretreatment+aluminium phosphide group, VII = Aluminium phosphide+Quercetin posttreatment group.

Table 4:
Electrolyte composition of gastric juice in rats treated with aluminium phosphide and quercetin

Groups	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Bicarbonate (mmol/L)
I	38.05 ±2.52	4.00 ±1.11	16.70 ±3.40	40.38 ±6.16
II	37.30 ±4.94	3.55 ±0.40	17.93 ±2.97	34.02 ±1.39
III	48.06 ±4.81*	7.85 ±2.69*#	36.98 ±4.59$^{*\#}$	30.08 ±1.13*
IV	27.19 ±1.52$^{*\#a}$	4.59 ±0.99	15.88 ±1.99^{a}	32.48 ±3.58
V	22.73 ±0.97$^{*\#a}$	2.87 ±0.22^{*a}	12.27 ±2.15^{a}	33.42 ±1.74
VI	30.82 ±1.25^{*a}	1.80 ±0.03$^{*\#a}$	11.19 ±1.27^{a}	08.14 ±2.48$^{*\#a}$
VII	30.78 ±0.59^{*a}	1.94 ±0.11$^{*\#a}$	15.24 ±3.30^{a}	21.84 ±5.22^{a}

Values expressed as mean± SEM; n=5, P<0.05. *, $^{\#}$, ^{a} indicates values that are significantly different (p<0.05) from control, vehicle and aluminium phosphide only treatment groups, respectively. I = control group, II = Vehicle control, III = Aluminium phosphide only treatment group, IV = Quercetin only treatment group, V = Aluminium phosphide+Quercetin cotreatment group, VI = Quercetin pretreatment+aluminium phosphide group, VII = Aluminium phosphide+Quercetin posttreatment group.

The pH of gastric juice and mucin content in control and experimental groups: The pH values for gastric juice in group III (3.65±0.47) were significantly reduced when compared with groups I (5.57±0.22) and II (5.42±0.81), respectively. However, values obtained IV (5.72±0.46) and V (5.21±0.74) were increased compared with group III, and comparable to controls. The gastric pH values observed in groups VI (2.41±0.07) and VII (2.44±0.07) reduced compared with control, group III and all other experimental groups (Figure 1). The gastric mucin content in group III was significantly compared to control and all other experimental groups (Figure 2).

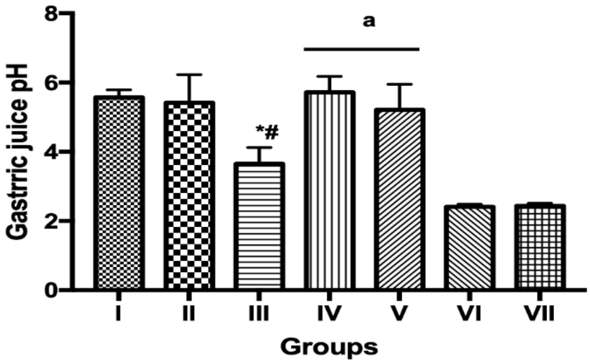

Figure 1:
Acidity of Gastric juice in control and experimental groups.
Values expressed as mean± SEM; n=5, P<0.05. *, #, a indicates values that are significantly different (p<0.05) from control, vehicle and aluminium phosphide only treatment groups, respectively. I = control group, II = Vehicle control, III = Aluminium phosphide only treatment group, IV = Quercetin only treatment group, V = Aluminium phosphide+Quercetin cotreatment group, VI = Quercetin pretreatment+aluminium phosphide group, VII = Aluminium phosphide+Quercetin posttreatment group.

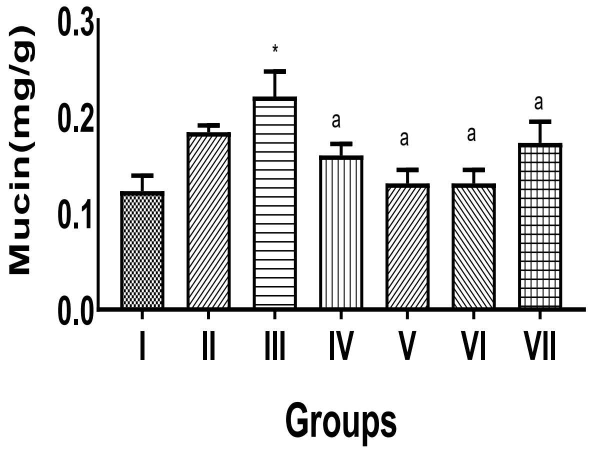

Figure 2:
Gastric Mucin content in Rats treated with aluminium phosphide and quercetin
Values expressed as mean± SEM; n=5, P<0.05. *, $^{\#}$, ^{a} indicates values that are significantly different (p<0.05) from control, vehicle and aluminium phosphide only treatment groups, respectively. I = control group, II = Vehicle control, III = Aluminium phosphide only treatment group, IV = Quercetin only treatment group, V = Aluminium phosphide+Quercetin cotreatment group, VI = Quercetin pretreatment+aluminium phosphide group, VII = Aluminium phosphide+Quercetin posttreatment group.

Parietal and mucous cell counts in control and experimental groups: Parietal cell count (cells/field) in Group III was increased (414.70±40.38) when compared with control (338.00±17.72). Values observed in groups IV (480.00±30.10) and V (400.00±30.21) were comparable to group III, while values in values in groups VI (638.00±29.40) and VII (592.00±24.83) were significantly increased when compared with control and all other experimental groups (Figure 3). The mucous cell count (cells/field) in group III (267.30±15.35) was significantly (p<0.05) reduced compared to control (529.30±24.83) and vehicle (564.00±18.61) groups, respectively. Values in groups IV-VII were significantly increased when compared with group III, respectively (Figure 4).

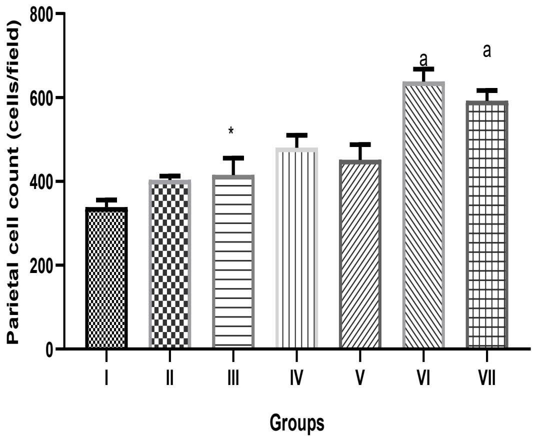

Figure 3:
Parietal cell counts in Rats treated with aluminium phosphide and quercetin
Values expressed as mean± SEM; n=5, P<0.05. [*], [#], [a] indicates values that are significantly different (p<0.05) from control, vehicle and aluminium phosphide only treatment groups, respectively. I = control group, II = Vehicle control, III = Aluminium phosphide only treatment group, IV = Quercetin only treatment group, V = Aluminium phosphide+Quercetin cotreatment group, VI = Quercetin pretreatment+aluminium phosphide group, VII = Aluminium phosphide+Quercetin posttreatment group.

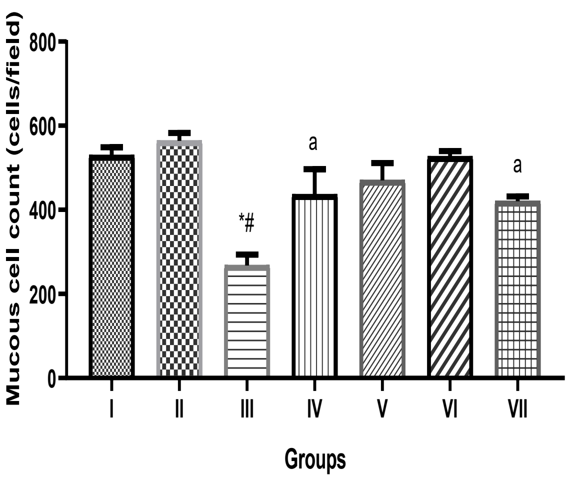

Figure 4:
Mucous cell counts in Rats treated with aluminium phosphide and quercetin
Values expressed as mean± SEM; n=5, P<0.05. *, #, a indicates values that are significantly different (p<0.05) from control, vehicle and aluminium phosphide only treatment groups, respectively. I = control group, II = Vehicle control, III = Aluminium phosphide only treatment group, IV = Quercetin only treatment group, V = Aluminium phosphide+Quercetin cotreatment group, VI = Quercetin pretreatment+aluminium phosphide group, VII = Aluminium phosphide+Quercetin posttreatment group.

Gross morphology of the gastric tissue in control and experimental groups: Evaluation of stomach samples in groups I and II show preserved mucosa epithelial cells layer (a), the submucosal layers appeared normal and were not infiltrated by inflammatory cells (b) (Figure 4 I-II). In Group III, the gastric architecture was moderately preserved, the mucosa epithelial cells layer showed moderate to severe erosion (a), the submucosal layers also had severe vascular congestion however, infiltration by inflammatory cells was not observed (b) (Figure 4-III). Gastric tissue from group IV showed normal architecture. However, the mucosa epithelial cell layer was poorly preserved (a) and the submucosal layers appeared mildly infiltrated by inflammatory cells (b) (Figure 4-IV). Group V also showed normal architecture, with mucosa epithelial cells layer being moderately preserved (a). The submucosal layers in this group appeared normal and were not infiltrated by any inflammatory cells (b) (Figure 4-V). Samples from group VI had gastric architecture and mucosa epithelial cells layer that was poorly preserved with focal areas of mild ulceration (a), the submucosal layers showed mild vascular congestion but were not infiltrated by any inflammatory cells (b) (Figure 4-VI). Gastric tissue in group VII had poor architecture, the mucosa epithelial cells layer was poorly preserved with severe ulceration (a), the submucosal layers also showed severe vascular dilation and congestion (b), and increased connective tissue deposition (Figure 4-VII). The mucosa layer (c) in control and all experimental groups showed no infiltration of the gastric glands and lamina propria and the circular muscle layer (d) in these groups all appeared normal.

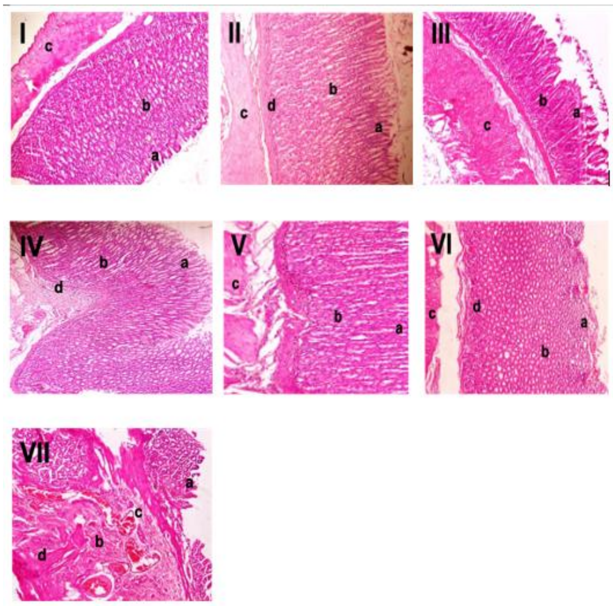

Figure 4:
I-VII Stomach sections in control and experimental groups (H and E, x100).

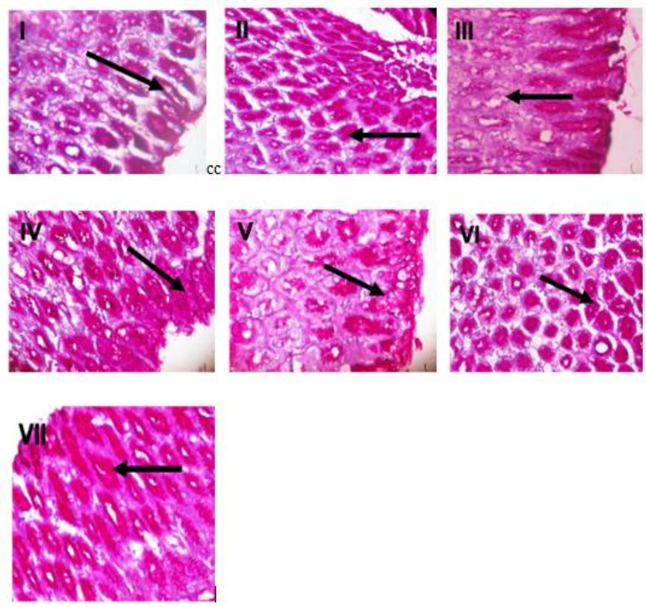

Figure 5:
I-VII) Mucin secretion in stomach sections for control and experimental groups (PAS, x400).

Histological evaluation for mucin secretion in control and experimental groups: Evaluation of the gastric samples in groups I, II, IV, and V showed normal surface epithelia mucin production and intracellular mucin production (slender arrow). Group III exhibited mild surface epithelia mucin production and no intracellular mucin production (slender arrow), group VI showed moderately increased surface epithelia mucin production and intracellular mucin production (slender arrow), while samples from group VII showed mild surface epithelia mucin production and no intracellular mucin production (slender arrow) (Figure 5: I-VII).

DISCUSSION

Environmental toxicants pose a great danger to man and his environment. The risk posed by these toxicants to human health depends on the concentration and duration of exposure (Sokan-Adeaga *et al*., 2023). Haematological profile, changes in organ weight and other pathological manifestations are used to assess exposure to toxicants with haematological assessments remaining the frontline indicator before other major injuries become obvious. In this study, PCV, Hb and RBC count were not significantly affected by exposure to aluminium phosphide. However, the observed increase in WBC counts in this group (aluminium phosphide only) may suggest possible reactions to the presence of infection or toxicants. Quercetin pre-treatment or co-treatment with aluminium phosphide resulted in reduced WBC count relative to aluminium phosphide only suggesting an improvement in the inflammation and immune mechanisms in the body. However, differential WBC in these groups showed elevated neutrophils (groups V and VI) and reduced lymphocytes (group VI only) suggesting that these animals might still be experiencing some level of infection or inflammatory reaction. White blood cell count, neutrophils and lymphocytes in group VII (ALP+Quercetin post-treated), were elevated suggesting the presence of inflammation and or activated immune mechanisms in this group. It is likely that Quercetin treatment (group V and VI) may by preventing leucocytosis and neutrophilia which have been associated with ALP exposure (Yuan *et al*., 2020).

Pesticides, like many other environmental toxins, are known to generate oxidative stress and data have suggested that reactive oxygen species (ROS) production plays a significant role in the toxicity of these compounds (Abdollahi *et al*., 2004). The stomach's antioxidant defence system is crucial for protecting the gastric mucosa from damage caused by reactive oxygen species (ROS) and free radicals (Kemmerly and Kaunitz, 2013). In line with other reports, this study shows elevated gastric malondialdehyde (a marker of lipid peroxidation) and nitric oxide levels as well as reduced antioxidant (GSH level and SOD) activity in the ALP only exposure groups (group III) which suggests an overwhelmed gastric antioxidant defence system, increase in lipid peroxidation and possibly, cellular damage (Kariman *et al*., 2012). Quercetin, a naturally occurring flavonoid has been reported to possess a wide array of effects including potent anti-inflammatory, antioxidant, antibacterial, antiviral, gastroprotective, and immune-modulatory properties (Vollmannová *et al*., 2024). In this study, treatment with quercetin was able to significantly ameliorate ALP-induced gastric oxidative damage in the pre-treated and co-treated groups, respectively. However, Quercetin was not able to reverse already existing oxidative damage to the gastric tissue in group VII, as MDA levels were still elevated despite slight increases in GSH and SOD as well as reductions in NO levels. This study also shows an increase in gastric mucin in the ALP only treated group suggesting a potentiation of mucin secretion in response to the assault of aluminium phosphide on the stomach. Furthermore, the reduced mucous cell counts in this group suggests likely overactivity resulting in exhaustion and mucous cell death. More so that the gastric tissue slices from this group showed mild surface epithelia mucin production and no intracellular mucin production (Figure 5:III). Parietal cell counts were also elevated in the ALP only treated group suggesting increase acid secretion and hence an increase in the amount of gastro-aggressive factors in the stomach. This increase in gastro-aggressive factors may account for the impaired gastric architecture, moderate to severe erosion of the mucosa epithelial cell layer and severe vascular congestion in the submucosal layers that was observed in the ALP only treated group (group III). Treatment with quercetin (concurrent and pretreatment) in the ALP exposure groups suggests a reversal of mucin secretion to normal levels as values for mucin and mucous cell count seen in these groups were found comparable to control. In addition to this, moderate to normal surface epithelia mucin production and intracellular mucin production were observed in these groups (V-VI) further reflecting a likely restoration of normal mucin and mucus cell function in these groups. In group VII (ALP+Quercetin), mucin levels were not only found to be elevated, mucous cell counts were not completely reversed to values similar to control suggesting that some level of ALP gastrotoxicity might still be present. Moreso that gastric tissues from this group showed mild surface epithelia mucin production and no intracellular mucin production (Figure 5:VII). Increased parietal cell counts was also observed in groups V-VII, with higher values seen in VI-VII, suggesting increased acid secretion and likely elevation of gastro-aggressive factors. This may account for the normal gastric architecture with moderately preserved mucosa epithelial cell layer seen in group V and the poorly preserved gastric architecture, mild to severe gastric ulceration and vascular congestion observed in the group VI and VII, respectively.

The gastric juice is a liquid produced by the gastric glands and plays essential roles in gastroprotection, digestion and nutrient absorption (Martinsen *et al*., 2019). It can be described as a liquid of variable composition consisting of water, hydrochloric acid, electrolytes (sodium, potassium, calcium, phosphate, sulphate, and bicarbonate), and organic substances (mucus, pepsins, and protein) (Martinsen *et al*., 2019). It provides an acidic medium that kills ingested bacteria and helps protein digestion. The electrolytes contained therein help to maintain the osmotic balance within the stomach which ensures proper fluid flow, facilitate enzyme action and prevent dehydration (Adewoye *et al*., 2007). The secretion of electrolytes into gastric juice is dependent on the constant exchange of electrolytes between the intracellular fluids (ICF) of gastric cells and the extracellular fluid (ECF) (Pitts, 1974). Hence alteration of electrolytes in the ECF will likely affect the ICF concentration of electrolytes of gastric cells which contribute to the electrolyte composition of gastric juice (Adewoye *et al*., 2007). This study shows a depletion in gastric juice Na^+, Cl^- and, to a lesser extent, HCO_3^- levels as well as reduced pH (increased acidity) in animals exposed to ALP only compared with control, suggesting a likely reduction in the ability of the juice to protect the gastric walls against its acidic content. Treatment of ALP exposed animals with quercetin (co-, pre- and post- treatment) did not appear to reverse the observed gastric juice electrolyte aberrations as Na^+, Cl^-, K^+, HCO_3^- and pH levels (except group V) were still reduced and compared with control. The alteration may be ascribed to the effects of ALP on the ECF which include hypokalaemia, metabolic acidosis or mixed metabolic acidosis, hypomagnesemia and hyponatraemia resulting in alterations in the ICF of gastric cells and hence gastric juice electrolyte composition (Saffaei *et al*., 2022)

In conclusion, this study shows that oral exposure to aluminium phosphide results in gastrotoxicity marked by increased oxidative stress markers, severe reductions in mucous cell count despite increased mucin secretion, increased parietal cell counts resulting in increased acidity (reduced pH) of gastric juice, and compromised gastric mucosal integrity. Quercetin treatment, particularly when administered as a pre-treatment before exposure to aluminium phosphide and co-treatment with aluminium phosphide, significantly mitigated these effects by reducing oxidative damage, preserving mucous secretion, and facilitating the integrity of the gastric mucosa. It is likely that pretreatment and co-treatment with quercetin may help prime the gastric mucosa and enhance its resistance to aluminium phosphide induced-oxidative damage. This study also suggests in conditions of where gastrotoxicity caused by aluminium phosphide already exists, treatment with quercetin may not mitigate already existing pathologies.

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