Print ISSN : 0972-8813
e-ISSN : 2582-2780

[Vol. 24(1) January-April 2026]

Pantnagar Journal of Research

(Formerly International Journal of Basic and Applied Agricultural Research ISSN : 2349-8765)

G.B. Pant University of Agriculture & Technology
Pantnagar, U.S. Nagar; Uttarakhand, Website : gbpuat.res.in/PJR

PANTNAGAR JOURNAL OF RESEARCH

Vol. 24(1) January-April, 2026

CONTENTS

Histopathological and haematological evaluation of the ameliorative effect of piperine on quinalphos-induced subacute toxicity in Swiss Albino Mice

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ABSTRACT: Organophosphorus pesticides remain widely used in agriculture despite their documented toxic effects in non-target species. The present study investigated the modulatory effect of piperine on subacute quinalphos (QNP) toxicity in male Swiss albino mice. Mice were orally administered QNP at 2.5% (0.375 mg/kg) and 5% (0.75 mg/kg) of its maximum tolerated dose (MTD; 15 mg/kg) for 28 days, with or without piperine (10 mg/kg). Parameters evaluated included body weight, relative organ weight, haematological indices, and histopathology of liver, kidney, lung, and bone marrow. QNP exposure resulted in dose-dependent haematological suppression, including significant reductions in total erythrocyte count (TEC), haemoglobin (Hb), and total leukocyte count (TLC). Histopathological examination revealed hepatic congestion, focal necrosis, tubular degeneration in kidneys, and pulmonary inflammatory changes. Co-administration of piperine partially ameliorated hematological alterations and reduced the severity of histopathological lesions. These findings suggest that piperine exhibits protective effects against QNP-induced subacute toxicity, likely through modulation of oxidative and inflammatory pathways. Co-administration of piperine with QNP resulted in a statistically significant improvement in haemoglobin (Hb) and total leukocyte count (TLC) at the higher dose (0.75 mg/kg) compared to QNP II alone ($p \leq 0.05$), whereas no significant effect was observed on total erythrocyte count (TEC). No statistically significant changes were observed with piperine co-administration at the lower dose (0.375 mg/kg). Histopathological evaluation showed a reduction in lesion severity in the piperine co-treated group; however, this effect was not statistically quantified. These findings indicated that piperine exerts limited, parameter-specific effects against QNP-induced subacute toxicity rather than a consistent protective effect.

Key words: Haematology, Histopathology, Mice, Organophosphate toxicity, Piperine, Quinalphos

Organophosphorus (OP) pesticides are extensively used in agriculture because of their high insecticidal efficacy; however, their indiscriminate and prolonged application has raised serious concerns regarding environmental contamination and adverse effects in non-target organisms (Silva *et al*., 2014; Eddleston *et al*., 2020; Bagri and Kumar, 2020). Quinalphos (O, O-diethyl O-quinoxalinyl phosphorothioate; QNP), an OP insecticide widely applied in crop protection, has been reported to induce a spectrum of toxic manifestations following repeated exposure. Experimental investigations have demonstrated that quinalphos provokes oxidative stress, haematological disturbances, and structural damage in vital organs such as the liver, kidneys, lungs, and spleen (Subramaneyaan *et al*., 2012; Zapadia *et al*., 2014). Subacute exposure has been associated with hepatic congestion and necrosis, renal tubular degeneration, pulmonary inflammation, and significant alterations in erythrocytic and leukocytic parameters, indicating systemic toxicity and multi-organ involvement. Recent toxicological evaluations further suggest that OP pesticides, including quinalphos, can disrupt redox homeostasis, mitochondrial function, and apoptotic signaling pathways, thereby exacerbating tissue injury (Karami-Mohajeri and Abdollahi, 2013; Kalender *et al*., 2021).

The liver and kidneys are particularly vulnerable to pesticide-induced injury due to their central roles in xenobiotic metabolism and excretion. Bioactivation of OP compounds in hepatic tissues generates reactive oxygen species (ROS), leading to lipid peroxidation, protein oxidation, and DNA damage. Similarly, renal tissues are susceptible to oxidative and inflammatory insults during the elimination of toxic metabolites. Hematological alterations observed following OP exposure may reflect impaired hematopoiesis, haemolysis, or immune dysregulation (Galloway and Handy, 2020). Emerging evidence indicates that chronic or

subacute OP exposure may also interfere with immune competence and inflammatory responses, thereby contributing to systemic toxicity (Mostafalou and Abdollahi, 2017).

Natural phytochemicals with antioxidant potential have attracted attention as promising therapeutic agents against pesticide-induced toxicity. Piperine (PIP), the principal bioactive alkaloid of *Piper nigrum*, exhibits well-documented antioxidant, anti-inflammatory, immunomodulatory, and cytoprotective properties (Sudjarwo *et al*., 2017; Srinivasan, 2019). Piperine has been shown to mitigate chemical-induced organ damage by scavenging free radicals, enhancing endogenous antioxidant defences (e.g., SOD, CAT, GPx), and modulating pro-inflammatory cytokines and apoptotic mediators. Recent experimental studies have demonstrated its protective effects against various xenobiotic-induced hepatic and renal injuries, primarily through attenuation of oxidative stress and preservation of tissue architecture (Coelho *et al*., 2024; Abdel Moneim, 2022).

Despite accumulating evidence regarding the toxic potential of quinalphos and the pharmacological benefits of piperine, limited data are available concerning the protective efficacy of piperine against quinalphos-induced systemic toxicity under subacute exposure conditions. Therefore, the present study was designed to evaluate the modulatory role of piperine in mitigating subacute quinalphos-induced alterations in body weight, relative organ weight, haematological indices, and histopathological parameters in male Swiss albino mice.

MATERIALS AND METHODS

Chemicals

Quinalphos (VAZARA 25®, Cheminova India Ltd.) was diluted in distilled water. Piperine (Sigma Chemical Co., USA) was suspended in 2% gum acacia.

Experimental Animals

Healthy male Swiss albino mice (20–24 g) were procured from the Disease-Free Small Animal House, LUVAS, Hisar, Haryana. Animals were housed under standard laboratory conditions (22–27°C; 12 h light/dark cycle) with ad libitum access to feed and water. The study was approved by the Institutional Animal Ethics Committee (Approval No. VCC/IAEC/1630-58 dated 26-07-2018).

Experimental Design

The maximum tolerated dose (MTD) of quinalphos was found to be 15 mg/kg (Singh *et al*., 2023). Animals were divided into six groups (n = 5 per group):

1. Vehicle control (2% gum acacia i.e. 200 mg/ kg b.wt.), 2. QNP I (0.375 mg/kg; 2.5% MTD), 3. QNP II (0.75 mg/kg; 5% MTD), 4. Piperine (10 mg/kg), 5.QNP I + Piperine, QNP II + Piperine

All treatments were administered orally for 28 consecutive days with a 12-h interval between QNP and piperine dosing in combination groups.

Evaluated Parameters

Body weight

The body weight of mice from each of six groups was recorded weekly during 28 days of exposure period.

Relative body weight gain

Relative body weight gain of each male mouse was determined by following formula and was expressed in g/100 g b.wt. of male mice.

$$\text{Relative body weight gain} = \frac{\text{Final body weight (g)} - \text{Initial body weight (g)}}{\text{Initial body weight (g)}} \times 100$$

Relative organ weight

The relative organ weights of heart, liver, kidneys, testis and epididymis were expressed as g/100 g b.wt. of male mice.

$$\text{Relative organ weight} = \frac{\text{Organ weight (g)}}{\text{Body weight (g)}} \times 100$$

Haematological parameters

Adult male mice were sacrificed under thiopentone anaesthesia and necropsy was performed. Blood was collected through cardiac puncture in heparinized test tubes. Haematological parameters viz. haemoglobin (Hb) (Oser, 1976), total erythrocyte

count (TEC), total leukocyte count (TLC) were assessed.

Histopathological examination

Vital organs were examined for gross toxicopathological changes, if any. Small pieces of liver, kidney, lungs and bone marrow samples of mice from all the groups were fixed in 10% buffered formalin, dehydrated in ascending alcohol grades and embedded in paraffin wax. Approximately 5 µm thick sections were prepared and stained with haematoxylin and eosin (H&E) for assessment of histopathological changes under light microscopy. This effect was not statistically quantified, only reduction in lesion severity were observed after co-administration with piperine with QNP I and QNP II in comparison to other groups.

Statistical analysis

Data were analyzed using Graph Pad Prism version 5.03. Results were expressed as mean ± SEM with 'n' equal to number of animals. Differences among the groups were compared by one-way analysis of variance (One-Way ANOVA) with Tukey post-hoc test. In all tests, p values less than or equal to 0.05 were considered statistically significant.

RESULTS AND DISCUSSION

Clinical Observations and Body Weight Changes

The mean body weight (g) in control, QNP I-treated, QNP II-treated, PIP-treated, QNP I + PIP-treated and QNP II + PIP-treated groups are shown in Table 1 and 2. No mortality or overt clinical signs of toxicity such as tremors, salivation, diarrhoea, lethargy, or abnormal posture were observed in any of the treatment groups during the 28-day exposure period. All animals remained active and maintained normal feeding and drinking behaviour throughout the study. No statistically significant differences in mean body weight or relative body weight gains were observed among treated and control groups over 28 days of exposure.

Organ weights and relative organ weights

The effect of QNP, piperine and their combination on mean organ weight and relative organ weight gain of mice after 28 days exposure are presented in Table 3 and 4. Relative organ weights (expressed as g/100 g body weight) revealed more distinct alterations. A significant increase in relative weight of left kidney and right kidney was found in group treated with QNP II + PIP-treated group in comparison QNP II-treated group.

Haematological Findings

The effect of QNP, piperine and their combination on haematological parameters of mice after 28 days exposure are presented in Table 5. Subacute exposure to quinalphos produced dose-dependent haematological alterations. QNP exposure caused dose-dependent reductions in TEC, Hb, and TLC, with significant decreases at 0.75 mg/kg of QNP only (Group III). A significant reduction in TEC was observed in the QNP II group compared to control ($p \leq 0.05$). Piperine co-administration with the lower QNP dose showed partial restoration, whereas at the higher dose the improvement was modest. The effect of QNP, piperine, and their combination on haematological parameters of mice after 28 days of exposure is presented in Table 5. Subacute exposure to QNP at 0.75 mg/kg (QNP II) resulted in significant reductions in total erythrocyte count (TEC), haemoglobin (Hb), and total leukocyte count (TLC) compared to the control group ($p \leq 0.05$). No significant alterations were observed at the lower dose of 0.375 mg/kg (QNP I). Piperine alone did not produce any significant changes in the measured parameters. Co-administration of piperine with QNP I (0.375 mg/kg) showed no significant changes. In the higher dose group (QNP II + piperine), a significant restoration in Hb and TLC levels was observed compared to QNP II alone ($p \leq 0.05$), although TEC remained significantly reduced compared to all groups except QNP I. Overall, significant haematological alterations were evident only at the higher dose of QNP, and piperine co-administration improved Hb and TLC but did not normalize TEC.

Histopathological Findings

Histopathological lesions in liver of control and treatment group after subacute exposure are presented in fig. 1. Control and PIP-alone groups showed

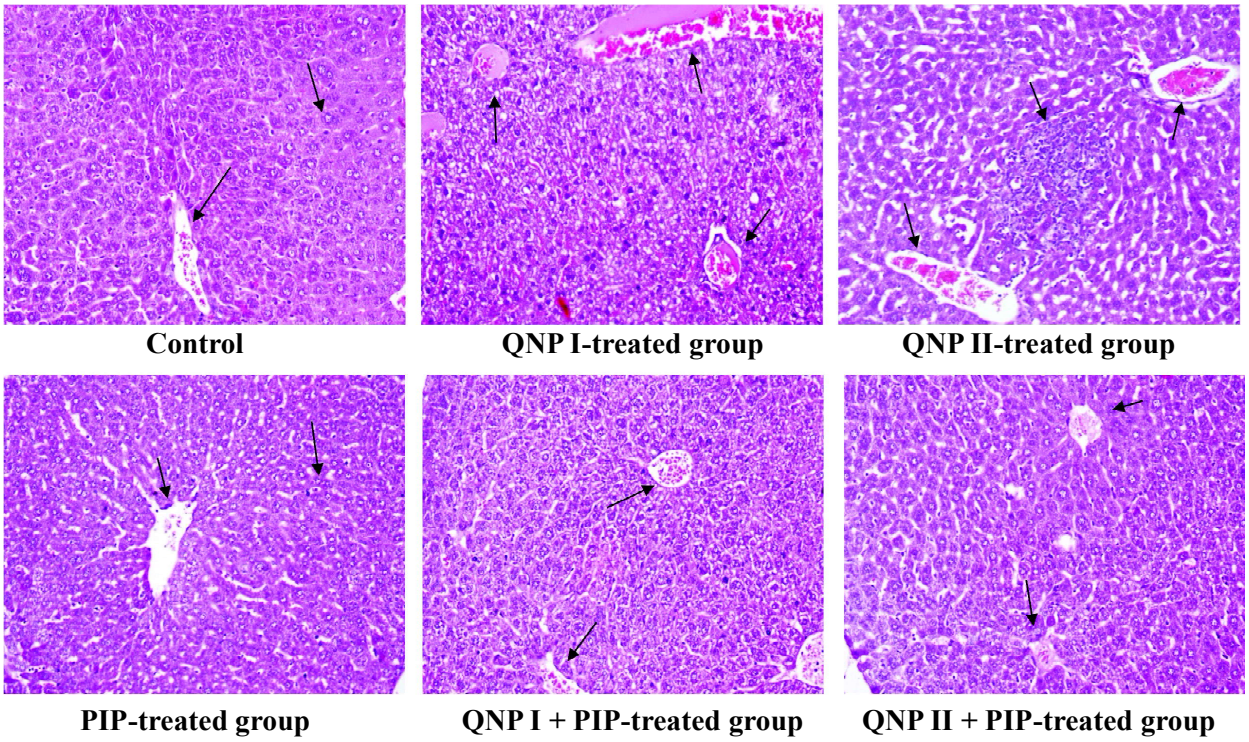

Fig. 1: Representative images (H&E stain 200x magnification) showing effects of subacute oral exposure of QNP, piperine and their combination in liver

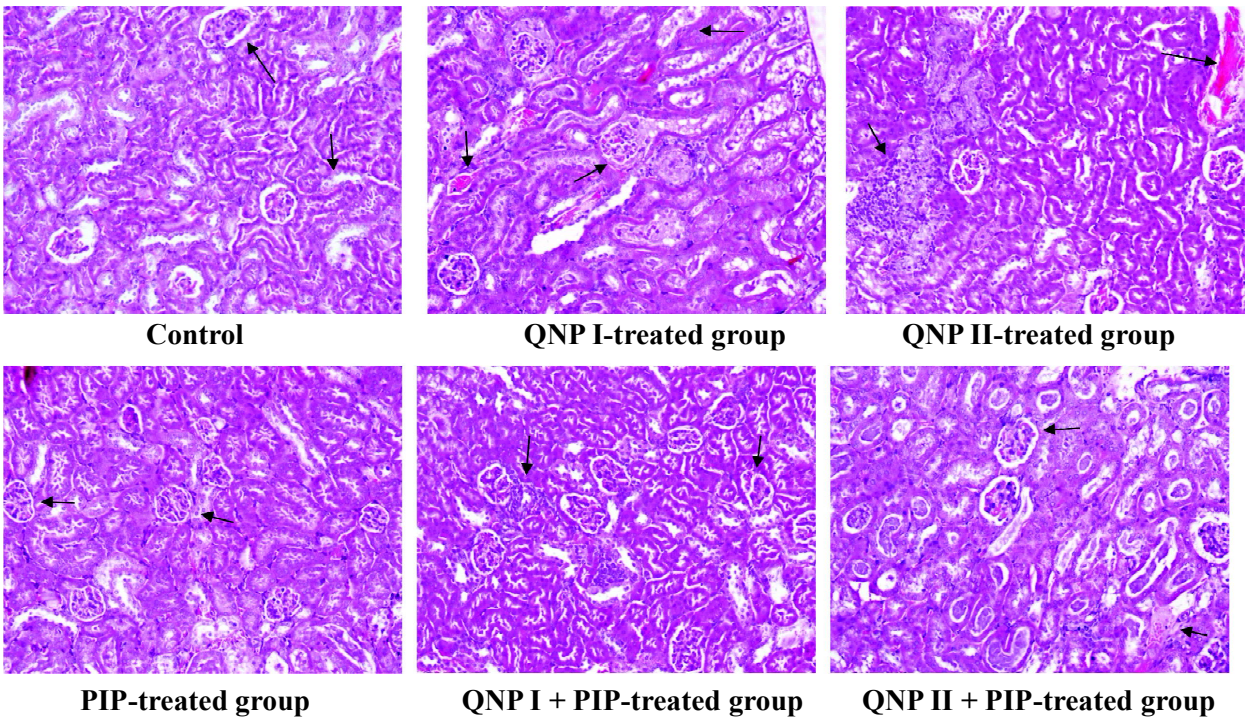

Fig. 2: Representative images (H&E stain 200x magnification) showing effects of subacute oral exposure of QNP, piperine and their combination in kidney

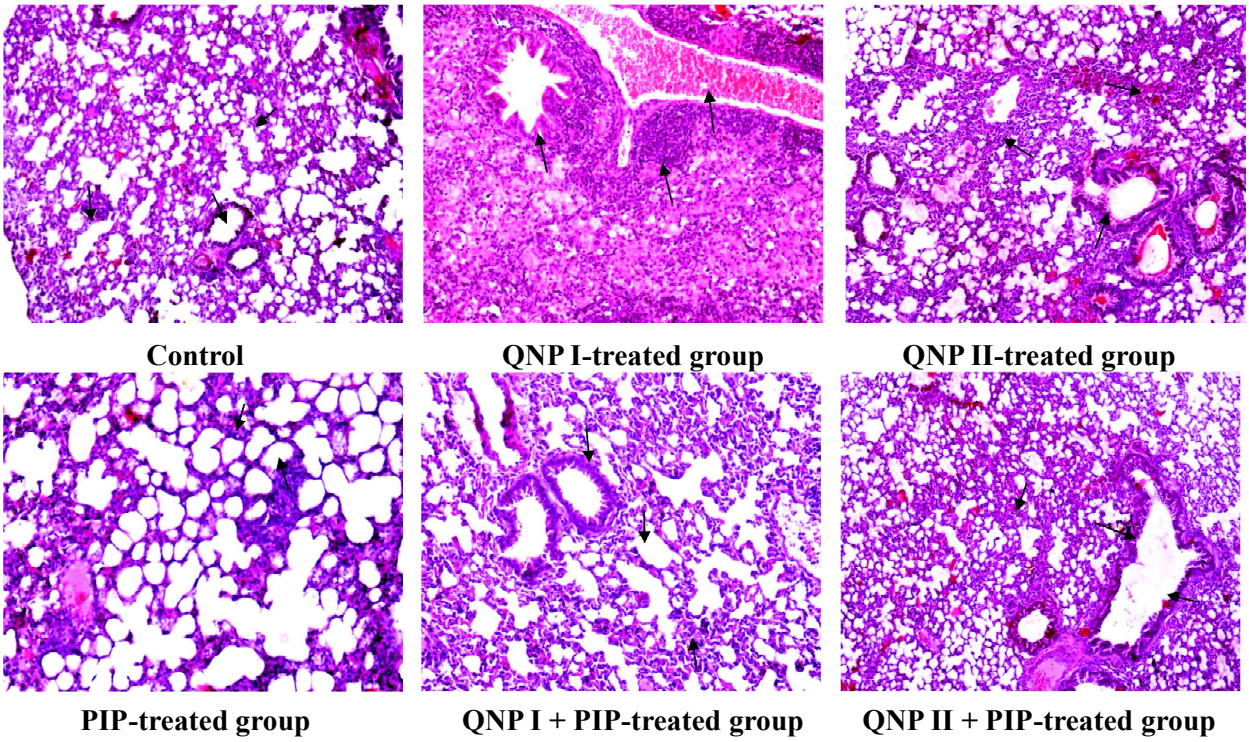

Fig. 3: Representative images (H&E stain 200x magnification) showing effects of subacute oral exposure of QNP, piperine and their combination in lung

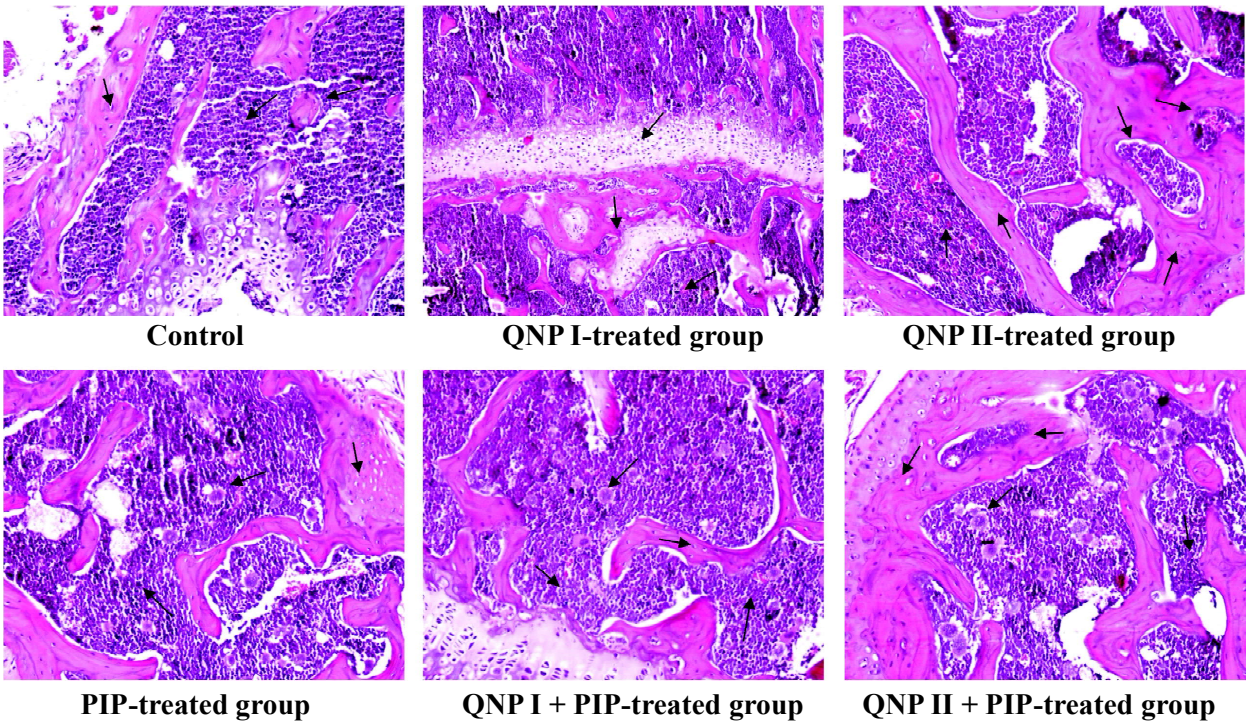

Fig. 4: Representative images (H&E stain 200x magnification) showing effects of subacute oral exposure of QNP, piperine and their combination in bone marrow

Table 1:Effects of subacute oral exposure of mice to QNP, piperine and their combination on body weight

Treatment(mg/kg b.wt.)	Body weight (g)				
	weeks				
	0th	1st	2nd	3rd	4th
Control (200)	22.1 ±0.71	23.10 ± 0.73	24.10 ± 0.33	24.90 ± 0.19	25.20 ± 0.20
QNP I (0.375)	23.70 ± 1.04	25.50 ± 1.05	26.20 ± 1.03	26.10 ± 1.32	26.60 ± 1.41
QNP II (0.75)	25.80 ± 1.10	25.00 ± 1.21	26.00 ± 1.05	27.40 ± 0.83	27.20 ± 0.84
PIP (10)	23.40 ± 0.99	24.10 ±1.03	24.60 ± 1.02	25.00 ± 1.01	25.80 ± 0.86
QNP I (0.375) + PIP (10)	24.60 ± 0.91	26.00 ± 1.46	26.90 ± 1.09	28.00 ± 1.21	27.30 ± 1.08
QNP I ((0.75) + PIP (10)	23.40 ± 1.25	26.00 ± 0.79	26.50 ± 0.91	23.20 ± 4.12	27.40 ± 0.70

Data are presented as mean ± SEM (n= 5 mice/group). QNP: quinalphos; PIP: piperine. The mean values were compared using one-way ANOVA followed by Tukey post-hoc test.

Table 2: Effects of subacute oral exposure of mice to QNP, piperine and their combination on relative body weight gain

Parameter	Treatment (mg/kg b.wt.)					
	Control (200)	QNP I (0.375)	QNP II (0.75)	PIP (10)	QNP I (0.375) + PIP (10)	QNP II (0.75) +PIP (10)
Relative body weight gain (g/100 g b.wt.)	14.45 ± 3.41	12.13 ±2.20	7.57 ±3.67	10.43 ± 1.17	11.11 ± 2.87	17.85 ± 4.01

Data are presented as mean ± SEM (n= 5 mice/group). QNP: quinalphos; PIP: piperine. The values were compared using one-way ANOVA followed by Tukey post-hoc test.

Table 3: Effects of subacute oral exposure of mice to QNP, piperine and their combination on organ weight

Treatment(mg/kg b.wt.)	Organ weight (g)				
	Spleen	Thymus	Liver	Left kidney	Right kidney
Control (200)	0.12 ± 0.01	0.05 ± 0.01	1.68 ± 0.17	0.22 ± 0.02	0.23 ± 0.02
QNP I (0.375)	0.11 ± 0.01	0.04 ± 0.01	1.54 ± 0.18	0.22 ± 0.02	0.23 ± 0.02
QNP II (0.75)	0.11 ± 0.00	0.04 ± 0.00	1.52 ± 0.15	0.21 ± 0.02	0.22 ± 0.01
PIP (10)	0.15 ± 0.01	0.06 ± 0.01	1.52 ± 0.06	0.21 ± 0.02	0.23± 0.02
QNP I (0.375) + PIP (10)	0.14 ± 0.03	0.06 ± 0.00	1.73 ± 0.10	0.24 ± 0.02	0.25 ± 0.03
QNP II (0.75) + PIP (10)	0.16 ± 0.01	0.06 ± 0.00	1.81 ± 0.06	0.29 ± 0.02	0.34 ± 0.03 abcd

Data are presented as mean ± SEM (n= 5 mice/group). QNP: quinalphos; PIP: piperine. The values were compared using one-way ANOVA followed by Tukey post-hoc test. Mean bearing a, b, c, and d superscript differ significantly (P<0.05) vs. control, QNP I, QNP II, and PIP, respectively.

Table 4: Effects of subacute oral exposure of mice to QNP, piperine and their combination on relative organ weight gain of mice

Treatment(mg/kg b.wt.)	Relative organ weight gain (g/100 g b.wt.)				
	Spleen	Thymus	Liver	Left kidney	Right kidney
Control (200)	0.36 ± 0.03	0.13 ± 0.01	4.73 ± 0.49	0.65 ± 0.05	0.69 ± 0.06
QNP I (0.375)	0.33 ± 0.02	0.09 ± 0.01	4.11 ± 0.22	0.70 ±0.04	0.75 ± 0.05
QNP II (0.75)	0.33 ± 0.02	0.10 ± 0.00	4.60 ± 0.39	0.64 ± 0.04	0.65 ± 0.01
PIP (10)	0.47 ± 0.04	0.19 ± 0.02b	4.81 ± 0.19	0.65 ± 0.06	0.72 ± 0.07
QNP I (0.375) + PIP (10)	0.43 ± 0.08	0.19 ± 0.03b	5.44 ± 0.27	0.76 ± 0.06	0.80 ± 0.07
QNP II (0.75) + PIP (10)	0.52 ± 0.01bc	0.19 ± 0.01b	5.82 ± 0.29b	0.92 ± 0.07ac	1.08 ± 0.08abcde

Data are presented as mean ± SEM (n= 5 mice/group). QNP: quinalphos; PIP: piperine. The values were compared using one-way ANOVA followed by Tukey post-hoc test. Mean bearing a, b, c, d, and e superscript differ significantly (P<0.05) vs. control, QNP I, QNP II, PIP, and QNP I + PIP, respectively.

normal hepatic architecture with intact central veins and well-arranged hepatocytes.QNP I-treated animals exhibited mild congestion of central veins, sinusoidal dilatation, hepatocellular vacuolar

Table 5: Effects of subacute oral exposure of mice to QNP, piperine and their combination on haematological parameters

Hematological parameters	Treatment (mg/kg b.wt.)					
	Control (200)	QNP I (0.375)	QNP II (0.75)	PIP (10)	QNP I (0.375) + PIP (10)	QNP II (0.75)+ PIP (10)
TEC (x 10^6 mm^3)	8.08 ± 0.16	7.47 ± 0.22	6.91 ± 0.13[a]	7.98 ± 0.08[c]	7.65 ± 0.18	6.62 ± 0.21[abde]
Hb (g/dl)	12.72 ± 0.36	11.28 ± 0.27	10.24 ± 0.40[a]	11.96 ± 0.29[c]	11.68 ± 0.42	12.56 ± 0.53[c]
TLC (x 10^3 mm^3)	6.17 ± 0.30	5.26 ± 0.26	4.81 ± 0.16[a]	5.97 ± 0.17[c]	5.28 ± 0.11	5.78 ± 0.21[c]

Data are presented as mean ± SEM (n= 5 mice/group). QNP: quinalphos; PIP: piperine; TEC: total erythrocyte count; Hb: hemoglobin; TLC: total leukocyte count. The values were compared using one-way ANOVA followed by Tukey post-hoc test. Means bearing a, b, c, d, and e superscripts differ significantly ($P<0.05$) vs. control, QNP I, QNP II, PIP, and QNP I + PIP, respectively.

degeneration, and focal necrosis. QNP II-treated animals displayed more pronounced lesions, including moderate to severe congestion, focal necrotic hepatitis, and inflammatory cell infiltration. Combination groups (QNP I + PIP and QNP II + PIP) showed reduced severity of lesions, with mild congestion and limited degenerative changes compared to QNP-alone groups.

Histopathological lesions in kidneys of control and treatment group after subacute exposure are presented in Fig. 2. Control and PIP groups exhibited normal glomerular and tubular architecture.QNP I-treated mice showed congested glomerular capillaries, tubular epithelial degeneration, vacuolation, and presence of hyaline casts. QNP II-treated mice demonstrated more severe changes including medullary haemorrhages, pyknotic nuclei, interstitial inflammation, and mild fibrosis. Combination groups exhibited milder degenerative and inflammatory changes, suggesting partial protection by piperine.

Histopathological lesions in lung of control and treatment group after subacute exposure are presented in Fig. 3. Control and PIP groups showed normal alveolar architecture. QNP I-treated animals exhibited vascular congestion and serous pneumonia, whereas QNP II-treated mice showed severe emphysema and interstitial pneumonia. Co-administration with piperine reduced pulmonary congestion and inflammatory changes.

Histopathological lesions in bone marrow of control and treatment group after subacute exposure are presented in Fig.4. Histopathological examination of bone marrow did not reveal marked structural alterations in any group.

The present study evaluated the modulatory effect of piperine against subacute toxicity induced by quinalphos in male Swiss albino mice. Repeated oral exposure to quinalphos at 2.5% and 5% of its maximum tolerated dose for 28 days produced dose-dependent haematological alterations with significant changes observed only at the higher dose QNP II, whereas co-administration of piperine attenuated many of these changes, suggesting a protective role. whereas piperine co-administration resulted in a significant improvement in haemoglobin and total leukocyte count compared to quinalphos alone, indicating a parameter-specific ameliorative effect. Despite this improvement, total erythrocyte count remained significantly reduced, suggesting that piperine did not restore all altered haematological parameters. Histopathological findings were consistent with the observed haematological changes. Quinalphos exposure at the higher dose produced notable tissue alterations, including hepatic congestion and focal necrosis, renal tubular degeneration, and pulmonary inflammatory changes. In the piperine co-treated group, a reduction in the severity of these lesions was observed; however, these changes were not quantitatively assessed and therefore remain descriptive. No marked histopathological alterations were evident at the lower dose. These findings are consistent with growing evidence that organophosphate (OP) pesticides induce multi-organ toxicity primarily through oxidative stress and inflammatory mechanisms (Mostafalou and Abdollahi, 2017; Kalender *et al*., 2021).

For toxicological investigations, animal growth in terms of body weight, relative body weight gain, organ weight, and relative organ weight is crucial (Devi *et al*., 2024a; Singh *et al*., 2023). In the present study, no significant changes in body weight or relative body weight gain were observed in QNP-treated groups compared with controls, indicating that the selected subacute doses did not produce overt systemic metabolic impairment. Similar findings have been reported in sublethal exposure studies of organophosphates where moderate doses did not significantly affect growth parameters (Ngoula *et al*., 2007). However, other studies have documented reduced body weight gain following higher doses of quinalphos (Zapadia *et al*., 2014), suggesting that severity of toxicity is dose- and duration-dependent. Recent toxicological assessments also emphasize that subacute OP exposure may induce cellular and biochemical alterations even in the absence of gross changes in body weight (Galloway and Handy, 2020).

Despite stable body weight, significant haematological alterations were observed, particularly at the higher QNP II. Reductions in total erythrocyte count (TEC), haemoglobin (Hb), and total leukocyte count (TLC) indicate hematotoxicity and possible suppression of hematopoietic activity (Devi *et al*., 2024b). OP pesticides are known to enhance reactive oxygen species (ROS) generation, leading to membrane lipid peroxidation and increased fragility of erythrocytes (Karami-Mohajeri and Abdollahi, 2013). Oxidative injury may shorten erythrocyte lifespan and impair haemoglobin synthesis. Decreased leukocyte counts may reflect immunosuppressive effects and altered cytokine regulation associated with pesticide exposure (Mostafalou and Abdollahi, 2017; Galloway and Handy, 2020). The observed improvement in Hb and TLC values following piperine co-administration suggests mitigation of QNP-induced haematological suppression, likely attributable to its antioxidant and membrane-stabilizing properties (Sabina *et al*., 2010; Srinivasan, 2019).

Histopathological findings further substantiated systemic toxicity of quinalphos. Liver sections from QNP-treated mice exhibited congestion, sinusoidal dilatation, hepatocellular degeneration, and focal necrosis. The liver, being the primary site of xenobiotic metabolism, is particularly susceptible to pesticide-induced oxidative injury. Previous investigations have demonstrated that quinalphos exposure enhances lipid peroxidation, disrupts mitochondrial function, and alters hepatic antioxidant enzyme activity (Subramaneyaan *et al*., 2012; Zapadia *et al*., 2014). More recent studies also implicate mitochondrial dysfunction and activation of apoptotic pathways in OP-induced hepatotoxicity (Kalender *et al*., 2021). The attenuation of hepatic lesions in piperine-treated groups indicates preservation of hepatocellular architecture, in agreement with reports demonstrating the hepatoprotective efficacy of piperine against chemically induced liver injury through modulation of oxidative and inflammatory pathways (Abdel Moneim, 2022; Zhao *et al*., 2021).

Renal histopathology revealed glomerular congestion, tubular epithelial degeneration, haemorrhages, and cast formation in QNP-treated animals, indicating nephrotoxicity. The kidneys are highly vulnerable to toxicants because of their filtration and excretory functions. Oxidative stress-mediated tubular injury and inflammatory infiltration have been implicated in OP-induced renal damage (Karami-Mohajeri and Abdollahi, 2013). Experimental evidence suggests that OP metabolites may directly impair tubular epithelial cells, leading to compromised renal function (Kalender *et al*., 2021). Piperine co-treatment reduced tubular degeneration and inflammatory changes, corroborating earlier findings that piperine ameliorates toxin-induced renal injury by enhancing antioxidant defences and reducing pro-inflammatory mediators (Sudjarwo *et al*., 2017; Abdel Moneim, 2022).

Pulmonary lesions such as vascular congestion, emphysema, and interstitial pneumonia were also observed in QNP-treated groups. These findings align with previous reports describing inflammatory and vascular alterations in lung tissue following OP exposure (Chamarthi *et al*., 2014). Emerging

evidence indicates that oxidative stress and cytokine imbalance contribute significantly to OP-induced pulmonary pathology (Galloway and Handy, 2020). The reduction in severity of pulmonary lesions following piperine administration further supports its anti-inflammatory and cytoprotective potential.

Interestingly, no marked histopathological changes were observed in bone marrow sections despite peripheral haematological alterations. This suggests functional suppression of hematopoiesis rather than overt structural damage at the examined doses and duration. Similar observations have been reported in subacute pesticide exposure studies where peripheral blood indices were altered without pronounced marrow architectural disruption (Silva *et al*., 2014; Mostafalou and Abdollahi, 2017).

Collectively, the protective effects of piperine observed in this study may be attributed to its antioxidant, free radical scavenging, anti-inflammatory, and immunomodulatory properties. Piperine has been shown to upregulate endogenous antioxidant enzymes (SOD, CAT, GPx), inhibit lipid peroxidation, and modulate NF-κB–mediated inflammatory signaling pathways (Srinivasan, 2019; Abdel Moneim, 2022). By mitigating oxidative stress, preserving membrane integrity, and reducing inflammatory responses, piperine likely attenuates tissue injury induced by quinalphos. These findings support the potential therapeutic application of piperine as a natural protective agent against subacute organophosphate-induced systemic toxicity.

CONCLUSION

Subacute exposure to quinalphos induces hematotoxicity and multi-organ histopathological damage in male Swiss albino mice. Piperine co-administration significantly mitigates these toxic effects. Overall, these findings suggested that piperine exhibits limited modulatory activity against quinalphos-induced subacute toxicity, with its effects being selective rather than broadly protective. The findings further indicate that higher doses of piperine may enhance its modulatory potential. The observed effects may be attributed to its antioxidant and anti-inflammatory properties. However, further mechanistic studies at the molecular level are warranted to substantiate these effects. The protective action may involve antioxidant and anti-inflammatory mechanisms. Further mechanistic studies at molecular level are warranted.

ACKNOWLEDGEMENTS

We are thankful to Department of Veterinary Pharmacology and Toxicology, College of Veterinary Sciences, Hisar for providing infrastructural facilities.

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Received: April 16, 2026
Accepted: April 24, 2026