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Hepatoprotective effects of piperine on cypermethrin-induced oxidative stress in rats

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Abstract

This study investigated the protective effect of piperine against cypermethrin-induced hepatic oxidative stress in rats. Adult male Wistar rats were divided into five groups and treated orally for 28 days with normal saline, groundnut oil, cypermethrin, piperine, or cypermethrin plus piperine. Cypermethrin exposure significantly increased serum AST and ALT levels, indicating liver injury, and caused marked oxidative stress in liver tissue, as shown by elevated lipid peroxidation and reduced levels of glutathione, catalase, and glutathione peroxidase. Superoxide dismutase activity also increased in the cypermethrin group, suggesting a compensatory response to oxidative insult. Co-administration of piperine significantly reversed these alterations by reducing lipid peroxidation and restoring antioxidant enzyme activities and glutathione levels. The findings suggest that piperine offers significant hepatoprotective and antioxidant effects against cypermethrin-induced toxicity, likely through attenuation of reactive oxygen species and enhancement of endogenous defense mechanisms. These results support the potential use of piperine as a protective dietary phytochemical against pesticide-induced liver injury.

Keywords: Piperine, cypermethrin, oxidative stress, antioxidants, rats

Introduction

Cypermethrin, a broadly applied type II synthetic pyrethroid insecticide, is widely used in agriculture and public health for pest control due to its high insecticidal potency and relative mammalian safety at low doses. However, mounting experimental evidence indicates that cypermethrin can produce significant hepatotoxic effects in rodents, primarily mediated by oxidative stress mechanisms. Studies report that cypermethrin exposure increases reactive oxygen species (ROS) generation, elevates lipid peroxidation markers such as malondialdehyde (MDA), and impairs endogenous antioxidant defenses including superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH), culminating in biochemical and histopathological alterations in liver tissue (Gupta *et al.*, 2013; Kumar *et al.*, 2017) [3, 4]. Piperine, the major bioactive alkaloid of *Piper nigrum* (black pepper), has demonstrated antioxidant, anti-inflammatory, and hepatoprotective properties in multiple preclinical models. Mechanistically, piperine is reported to scavenge free radicals, enhance endogenous antioxidant enzyme activities, modulate phase I/II detoxification pathways and reduce inflammatory cytokine expression, thereby limiting tissue damage from diverse xenobiotics (Srinivasan, 2007; Bhat *et al.*, 2016) [9, 2]. Although isolated studies suggest that piperine can attenuate pesticide as well as drug-induced oxidative injury, comprehensive evaluation of its protective efficacy specifically against cypermethrin-induced hepatic oxidative stress and associated biochemical endpoints in rats remains insufficiently explored. Therefore, this study investigates whether piperine supplementation ameliorates cypermethrin-induced oxidative stress in rat liver by measuring serum biomarkers, hepatic MDA and antioxidant enzyme, to clarify its therapeutic potential and underlying mechanisms.

Materials and Methods

Adult male Wistar rats (6–8 weeks old, 100–120 g) were procured from the Laboratory Animal Resources Section of the Institute. Animals were housed under standard environmental

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conditions (temperature 22 ± 2 °C, relative humidity 50–60%, 12 h light/dark cycle) with free access to standard laboratory chow and water. Animals were acclimatized for at least 7 days prior to the experiment. All procedures were performed according to institutional animal ethics guidelines and national regulations for the care and use of laboratory animals.

Rats were randomly assigned to five groups (n = 6 per group):

- **Group I (Control):** received normal saline (vehicle for oral dosing).
- **Group II (Vehicle control):** received groundnut oil (1% v/v), the vehicle for cypermethrin.
- **Group III (CYP):** received cypermethrin 25 mg/kg body weight, orally, once daily for 28 days.
- **Group IV (Piperine):** received piperine 50 mg/kg body weight, orally, once daily for 28 days.
- **Group V (Piperine + CYP):** received piperine 50 mg/kg, orally, once daily and cypermethrin 25 mg/kg, orally, once daily for 28 days (piperine administered prior to cypermethrin each day).

The activity of alanine amino transferase (ALT), aspartate amino transferase (AST) was determined spectrophotometrically, according to the manufactures protocol (Span diagnostics Ltd; India).

Immediately after sacrifice, the liver was excised, rinsed in ice-cold normal saline, blotted, weighed, and processed for biochemical assays. For biochemical assays, liver samples (200 mg) were homogenized in 2.0 mL ice-cold phosphate-buffered saline (PBS, pH 7.4) to prepare 10% (w/v) homogenates using an IKA homogenizer under ice-cold conditions. For reduced glutathione (GSH) estimation, separate tissue samples (200 mg) were homogenized in 2.0 mL of 0.02 M EDTA. Homogenates were centrifuged at $3,000 \times g$ for 10 min at 4 °C and the supernatants were collected and stored at -20 °C until analysis.

Lipid peroxidation (LPO) was estimated by measuring malondialdehyde (MDA) formation according to Shafiq-u-Rehman *et al.* (1984). Reduced glutathione (GSH) content was determined by the method of Sedlak and Lindsay (1968) [8]. Catalase (CAT) activity was assayed following Aebi (1983) [1]. Superoxide dismutase (SOD) activity was measured according to Madesh and Balasubramanian (1998) [6]. Glutathione peroxidase (GPx) activity was determined by the method of Paglia and Valentine (1967) [7]. Total protein concentration in tissue homogenates was quantified by the Lowry method using bovine serum albumin as the standard (Lowry *et al.*, 1951) [5]. Statistical analyses were performed using GraphPad Prism.

Results and Discussion

Cypermethrin exposure for 28 days produced clear biochemical evidence of hepatic injury and oxidative stress. Rats treated with cypermethrin showed significant elevations

in serum transaminases (Table.1), indicating hepatocellular damage and increased membrane permeability. Co-administration of piperine significantly attenuated these increases. while groundnut-oil and piperine-alone groups did not differ from control.

Hepatic oxidative stress markers mirrored the serum enzyme changes. Cypermethrin markedly increased lipid peroxidation and depleted reduced glutathione (Table. 2). Antioxidant enzymes catalase and glutathione peroxidase were significantly decreased by cypermethrin ($p < 0.05$). Superoxide dismutase (SOD) activity, however, increased (8.93 ± 0.03 vs. control 7.08 ± 0.09 ; $p < 0.05$), suggesting a compensatory response to elevated superoxide generation. Together, these changes indicate excessive reactive oxygen species (ROS) production with overwhelmed downstream peroxide-detoxifying systems, promoting lipid peroxidation and cellular injury (Selvendiran and Sakthisekaran, 2004).

Piperine co-treatment substantially restored redox balance. In cypermethrin + piperine animals, LPO decreased to 43.02 ± 1.02 nmol/g and GSH recovered to 0.43 ± 0.01 mmol/g (both $p < 0.05$ vs. cypermethrin alone). CAT and GPx activities were also significantly elevated relative to the cypermethrin group (CAT: 183.32 ± 1.7 ; GPx: 229.48 ± 1.6 ; $p < 0.05$) and approximated or exceeded control values, while SOD activity was reduced toward baseline (7.53 ± 0.10). These results indicate that piperine mitigates cypermethrin-induced oxidative damage by lowering lipid peroxidation, replenishing intracellular GSH, and restoring peroxide-scavenging enzyme activities. Mechanistically, piperine's effects may arise from direct free-radical scavenging, induction of phase II detoxification and antioxidant enzymes, and modulation of inflammatory signaling that otherwise exacerbates ROS production (Srinivasan, 2007; Bhat *et al.*, 2016) [9, 2]. The normalization of serum AST and ALT with piperine further supports its hepatoprotective role, likely through preservation of membrane integrity via decreased lipid peroxidation and improved antioxidant defense. The paradoxical SOD increase after cypermethrin likely reflects an adaptive upregulation to superoxide overload; without concomitant CAT/GPx activity, hydrogen peroxide accumulation can follow and propagate oxidative injury. Piperine's restoration of CAT and GPx thus appears crucial to interrupting this cascade.

Table 1: Effect on serum biomarkers following 28-day exposure to cypermethrin and cypermethrin plus piperine in rats

Groups	AST (units/mL)	ALT (Units/mL)
Control	64.14±1.29	32.28±1.44
Ground nut oil	66.23±2.93	33.37±2.25
Piperine	63.9±1.65	30.07±2.28
Cypermethrin	92.19±3.14 ^a	73.19±3.12 ^a
Cypermethrin+Piperine	76.58±2.76 ^b	42.78±3.62 ^b

Values are mean $\pm$ SE. Superscript a significantly different from control group; superscript b significantly different from cypermethrin treated group.

Table 2: Effect of cypermethrin and piperine and their co-administration on oxidative stress parameters measured in liver of rats

Group/Parameters	Control	Groundnut oil	Cypermethrin	Piperine	Cypermethrin+ piperine
LPO (nmol MDA formed/g tissue)	37.77±0.48	31.68±0.99	85.83±1.02 ^a	29.65±0.27	43.02±1.02 ^b
GSH (mmol GSH/g tissue)	0.70±0.01	0.62±0.01	0.25±0.01 ^a	0.62±0.01	0.43±0.01 ^b
SOD (Units/mg protein)	7.08±0.09	6.96±0.09	8.93±0.03 ^a	7.08±0.04	7.53±0.1 ^b
CAT (mmol H2O2 utilized/ min/mgprotein)	165.60±2.7	160.85±1.84	99.46±0.88 ^a	168.50±1.9	183.32±1.7 ^b
GPx (mol NADPH oxidized to NADP/min/mg/protein)	236.33±1.3	227.89±1.06	151.02±2.9 ^a	235.46±1.7	229.48±1.6 ^b

Values given represent the mean $\pm$ S.E. Significant differences are indicated by ^a compare to control, ^b compare to cypermethrin in a given row.

Conclusion

In conclusion, 28-day cypermethrin exposure induces hepatic oxidative stress, depletes antioxidant defenses, and elevates serum transaminases; piperine co-administration significantly attenuates these effects, restoring antioxidant enzyme activities and reducing lipid peroxidation and transaminase release. Future studies should include histopathology, molecular pathway analysis, and dose-response evaluation to confirm mechanisms and therapeutic windows

Conflict of Interest

Not available

Financial Support

Not available

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