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Tebuconazole induced oxidative stress and histopathological alterations in muscle of *Cyprinus carpio* L.: Protective efficacy of propolis as a natural antioxidant

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ABSTRACT

This study investigated tebuconazole-induced oxidative stress and muscle toxicity in Cyprinus carpio, assessing biochemical, enzymatic, and histopathological parameters. Fish exposed to sublethal TBZ concentrations (6.47 µl/l and 8.09 µl/l) for 30 days showed significant reductions in protein, lipid, SOD, GSH, GPx, LDH, and a biphasic CAT response, alongside elevated free amino acids, GR, and AChE activity, indicating redox imbalance and neuromuscular disruption. Muscle histology revealed progressive degeneration. Propolis supplementation markedly reversed these alterations, restoring biochemical and enzymatic balance and preserving muscle architecture. Findings highlight propolis as a promising intervention against pesticide-induced aquatic toxicity.

Keywords: *Tebuconazole, oxidative stress, propolis, antioxidant.*

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Introduction

With the global population rising rapidly, our food systems are facing mounting pressure. By 2050, agricultural production must increase substantially to meet the growing demand for food [1]. Agriculture, which remains the backbone of food security, now struggles under a host of challenges: shrinking arable land, degrading soil quality, rising pest resistance, labour shortages, and unpredictable climate patterns [2]. In response, modern farming practices have leaned heavily on synthetic agrochemicals, especially pesticides, to sustain crop yields [3]. While these chemicals have proven effective in boosting productivity, their extensive use over the past two decades has triggered serious concerns regarding environmental safety and human health. Alarmingly, nearly 64% of global agricultural land, about 24.5 million km^2 is now contaminated with pesticide residues [1]. At the same time, aquatic ecosystems in regions like South Africa, China, India, Australia, and Argentina are reporting elevated levels of pesticide contamination [4].

Although pesticides play a key role in safeguarding crops [5], they are also increasingly implicated in widespread environmental degradation. Their chemical resilience allows them to persist in both land and water environments, where they may disrupt non-target species [6]. Surface runoff is one of the main ways these substances enter freshwater systems, disturbing aquatic life and threatening biodiversity [7].

One such pesticide is tebuconazole (TBZ), a widely used triazole fungicide known for its effectiveness against fungal infections in crops such as cereals, vegetables, and fruits [8,9]. TBZ is particularly concerning due to its long environmental half-life, ranging from 300 to 600 days in soil, and its high solubility in water, which facilitates its movement into nearby aquatic systems via agricultural runoff. Consequently, TBZ has been detected in surface waters at concentrations between 0.6 and 200 µg/L [10]. Growing evidence indicates that TBZ is toxic to non-target aquatic organisms. Studies have shown that it can disrupt thyroid function [11], delay development [12], cause genetic damage [13], impair neurological health [14], and negatively affect reproduction [8]. However, despite this body of research, there remains limited understanding of how TBZ impacts fish muscle tissue, a vital system essential for locomotion, respiration, and osmoregulation [15].

Muscle tissue is highly sensitive to environmental pollutants, particularly through oxidative stress, a key mechanism in TBZ-induced toxicity. This occurs when the overproduction of reactive oxygen species (ROS) overwhelms the body's natural antioxidant defences. Normally, enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione S-transferase (GST) work together to neutralize ROS and protect cells from damage [8]. When these defences falter under chemical stress, it can lead to lipid peroxidation, protein carbonylation, and deterioration of muscle integrity [16].

Because of their ecological significance and sensitivity to waterborne toxins, fish are commonly used as model organisms in environmental toxicology [17]. In the present study, *Cyprinus carpio* (common carp) was selected due to its ecological and economic value, widespread distribution, and vulnerability to sediment- and water-associated contaminants. As a bottom-dwelling species, it is particularly prone to absorbing pollutants such as TBZ. In recent years, there has been growing interest in the use of natural substances to mitigate the toxic effects of synthetic chemicals. Among these, propolis—a resinous substance collected by honeybees from plant exudates—has gained attention for its strong antioxidant, anti-inflammatory, and tissue-healing properties [18]. Rich in flavonoids and phenolic acids, propolis can help neutralise free radicals, enhance the activity of antioxidant enzymes, and protect tissues from oxidative injury [19]. Previous studies have shown that propolis can reduce pesticide-induced organ damage in fish, although its specific protective effects against TBZ-induced muscle toxicity have not yet been fully elucidated [20,21,22]. This study, therefore, aims to evaluate the protective effects of propolis against tebuconazole-induced muscle damage in *Cyprinus carpio* through detailed biochemical and histological assessments. By exploring both the extent of TBZ toxicity and the modulatory role of propolis, this research seeks to

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contribute to the development of eco-friendly strategies for mitigating pesticide impacts in aquatic systems.

Furthermore, the broader ecological implications of pesticide contamination cannot be overlooked. Recent findings have shown that fungicides like TBZ can cause irreversible harm to marine organisms such as *Heterostegina depressa* and their algal symbionts, reflecting the far-reaching consequences of agrochemical runoff [23]. Such evidence reinforces the urgent need for sustainable pest management and the exploration of natural alternatives like propolis to safeguard environmental and aquatic health.

2. Materials and Methods

2.1 Chemicals and Materials

A commercial-grade tebuconazole (25.9% EC) formulation was used for toxicity testing. Working concentrations were prepared using distilled water. All other chemicals were of analytical grade and sourced from Merck (India).

2.2 Propolis Extraction

Propolis extraction was conducted following the procedure described by Mani *et al.* (2006) [24]. Briefly, 30 g of propolis was finely ground and mixed with 70% ethanol to a final volume of 100 ml to prepare a 30% ethanolic extract of propolis (EEP). The extraction was carried out at room temperature, shielded from direct light, with continuous moderate shaking. Subsequently, the solvents were evaporated, and the dry weights of the extracts were determined, yielding concentrations of approximately 126 mg/ml for the EEP.

2.3 Fish collection and maintenance

Healthy *Cyprinus carpio* (20 ± 2 cm; 180–250 g) were obtained from a hatchery in Bilaspur, Himachal Pradesh. Fish were transported in aerated bags and disinfected with 0.2% potassium permanganate for 2–4 minutes. They were acclimatised for 12-15 days in 80 L glass aquaria with filtered and aerated water, partially changed (40%) daily. Fish were fed twice daily, and water quality was maintained at: temperature 22 ± 1.4°C, pH 7.5 ± 0.2, DO 8 ± 1 mg/L, TDS 155 ± 5 ppm, alkalinity 165 ± 8 mg/L, and hardness 120 ± 4 mg/L.

2.4 Sublethal exposure study

Fish were divided into five groups: control (Group 1), 6.47 µl/l TBZ (Group 2), 8.09 µl/l TBZ (Group 3), Propolis only (Group 4) and 8.09 µl/l TBZ +propolis (Group 5). Exposure lasted 60 days, with daily renewal of toxicant solutions. Samples from groups 1,2, and 3 were collected at 10, 20, and 30-day intervals, while samples from groups 4 and 5 were collected at intervals of 20-40 and 60 days. No mortality occurred during the experiment.

2.5 Biochemical determinations

Biochemical parameters like total protein were measured by the method of Bradford (1976) [25], total amino acids by Moore and Stein (1954) [26] and total lipid content by the method of Folch et al. (1957) [27].

2.6 Bioenzyme assay

All bioenzyme assessments were carried out using the subcellular fraction extracted from the muscle tissue of *C. carpio*. The activities of key antioxidant enzymes—catalase (CAT) and superoxide dismutase (SOD)—along with lipid peroxidation (LPO) levels and lactate dehydrogenase (LDH) activity were evaluated based on the protocols outlined by Aebi, (1984) [28], Misra and Fridovich, (1972) [29]. Dhindsa *et al.* (1981) [30] and Borgmann *et al.,* (1974) [31]. Measurements of glutathione (GSH) content, glutathione reductase (GR) and glutathione peroxidase (Gpx) activity followed the methodology described by Moron *et al.,* (1979) [32], Rotruck *et al.,* (1973) [33] and Racker (1955) [34]. Acetylcholinesterase enzyme assay in muscle tissue was specifically measured with the method of Ellman *et al.* (1961) [35].

2.7 Histopathology

A standardised protocol for tissue handling, processing, and histological examination was carried out for tissue sampling of fish muscle. A mid-portion of the muscle was carefully excised and fixed in 10% neutral buffered formalin for 48 hours. Following fixation, the tissues were washed thoroughly with tap water, then gradually dehydrated through a graded ethanol series. The samples were subsequently processed using routine histological procedures and stained with hematoxylin and eosin for examination under a light microscope.

2.8 Statistical analysis

The results were expressed as mean ± SE. Statistical analysis was conducted using SPSS 20.0 software. Two-way ANOVA was used to assess the effects of treatments and exposure periods, with statistical significance set at $p < 0.05$. Tukey's post hoc test was applied to identify differences among group means. Capital letters indicated significant differences within groups across durations, while lowercase letters represented differences between treatments at the same time point; 'a' denoted the lowest difference, with ascending letters indicating progressively higher deviation from the normal value.

Results and Discussion

Tebuconazole induced notable biochemical alterations in the muscle tissue of the treated fish, which are summarised in Fig. A (1-3). A significant reduction in protein and total lipid contents was observed, along with a pronounced elevation in total free amino acids, indicating disrupted macromolecular metabolism and stress response. This reduction in protein and total lipid content was significantly lower ($P<0.05$) in experimental groups compared to the control fish. However, supplementation with propolis markedly reversed these changes, with all parameters showing a trend toward normalisation, closely resembling control values. This highlights the restorative effect of propolis in maintaining biochemical homeostasis under fungicide-induced stress.

Tebuconazole exposure also significantly impaired antioxidant and enzymatic activities, are presented in Fig. B (1-8). There was a decline in SOD, GSH, GPx, and LDH levels, suggesting oxidative stress and compromised cellular integrity. This decline in all the antioxidant enzymes' activity was significantly lower ($P<0.05$) in TBZ-treated fish in comparison to the control fish. These findings align with previous studies reporting that TBZ induces oxidative imbalance, DNA damage, and cellular apoptosis through ROS generation and disruption of redox mechanisms in mammalian and aquatic models [36,37]. Such enzymatic suppression reflects the oxidative burden imposed by fungicides on vital organs, as similarly evidenced in pesticide-induced hepatotoxicity and metabolic dysfunction [38]. Collectively, these alterations highlight the systemic oxidative threat posed by TBZ exposure.

Interestingly, CAT activity exhibited a biphasic response—initial elevation followed by a sharp decline—indicating an early

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compensatory mechanism overwhelmed by prolonged exposure. This pattern aligns with the notion that catalase, while crucial in decomposing hydrogen peroxide during early oxidative stress, can become functionally impaired or downregulated upon prolonged toxicant exposure, leading to cellular vulnerability [39,40]. In contrast, GR and AChE activities were significantly upregulated ($P<0.05$), reflecting disrupted redox balance and neuromuscular function. Such elevations may reflect compensatory responses to oxidative overload and disturbed mitochondrial homeostasis, as seen in pesticide-exposed aquatic models and oxidative injury-induced neuromuscular dysfunction [41,42]. Notably, co-administration of propolis effectively mitigated these disruptions, restoring all altered enzymatic markers toward normal physiological levels, likely due to its rich antioxidant profile and modulatory effects on cellular redox signalling and metabolic pathways, Fig. B (1-8). [43,44,45]. Collectively, these findings provide strong evidence for the protective role of propolis in counteracting tebuconazole-induced oxidative and metabolic toxicity.

Muscle histopathology revealed significant pathological alterations upon TBZ exposure, including fibre fragmentation, vacuolisation, nuclear malplacement, haemorrhage, fibrosis, and myotomal disintegration, with severity increasing dose- and time-dependently, demonstrated in Fig. C (1-11). Our findings are consistent with established drug-induced muscle toxicity patterns reported in both aquatic and mammalian models [46,47,48]. These changes indicated profound cytoskeletal damage and oxidative stress, aligning with prior studies that demonstrate how oxidative insults disrupt actin filament organisation and compromise muscle cell integrity under toxic or mechanical stress conditions [49,50]. However, co-treatment with propolis markedly ameliorated these effects. Fig. C (8-11), showing progressive structural recovery, reduced vacuolisation, minimised haemorrhage, and restored myofiber organisation, consistent with emerging evidence supporting the role of natural bee-derived antioxidants like propolis in preserving muscle architecture and counteracting toxin-induced myopathy [51,52,53].

Conclusion

The present findings underscore the profound biochemical and structural toxicity of tebuconazole on fish muscle, evidenced by oxidative stress, disrupted macromolecular metabolism, and severe histopathological damage. Alterations in enzymatic activity further highlight the systemic oxidative burden imposed by prolonged fungicide exposure. Notably, propolis supplementation demonstrated significant restorative effects, normalising biochemical markers and preserving muscle integrity. This suggests its therapeutic potential as a natural antioxidant intervention. Overall, propolis offers a promising strategy to mitigate pesticide-induced toxicity in aquatic organisms.

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Result

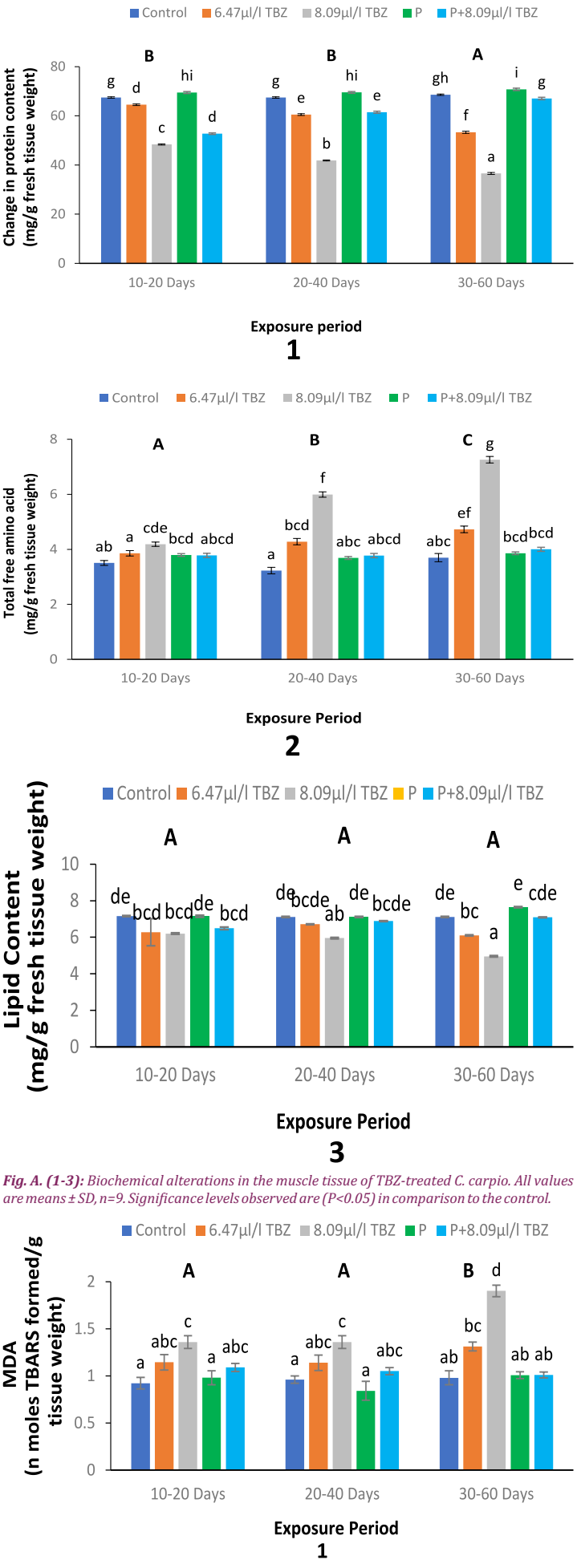

Fig. A. (1-3): Biochemical alterations in the muscle tissue of TBZ-treated C. carpio. All values are means ± SD, n=9. Significance levels observed are (P<0.05) in comparison to the control.

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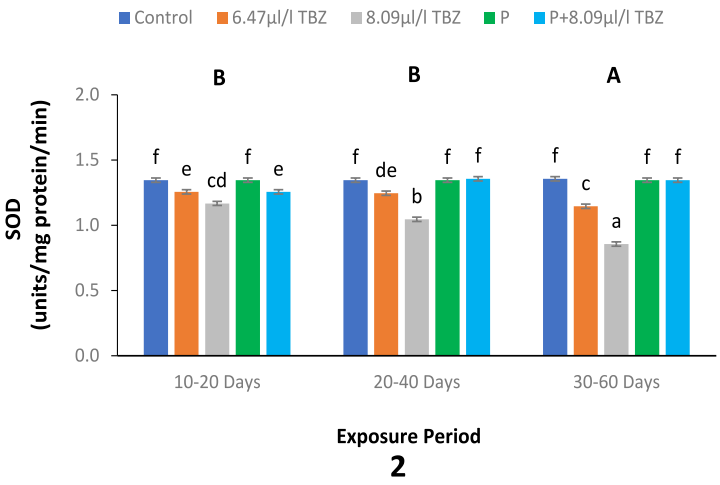

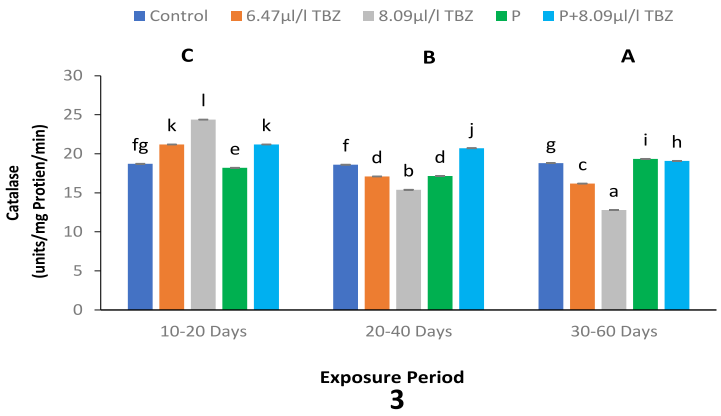

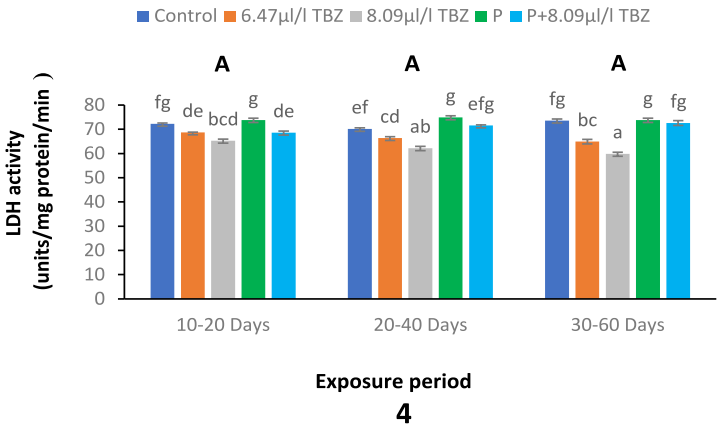

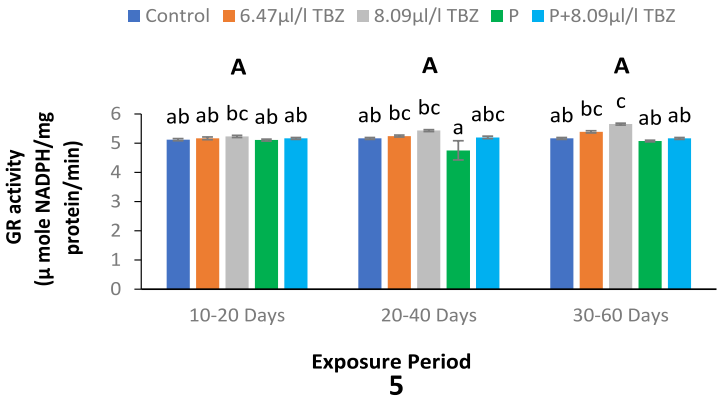

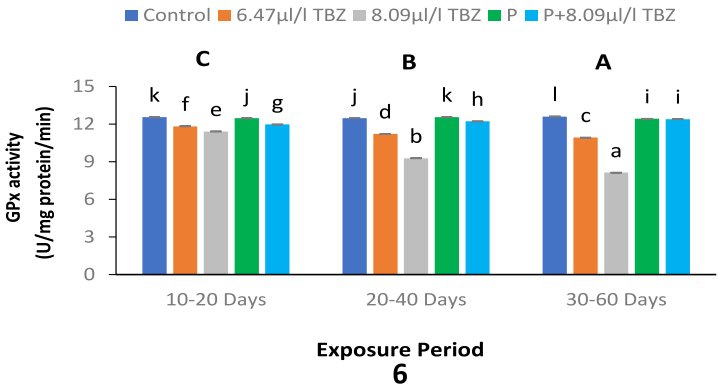

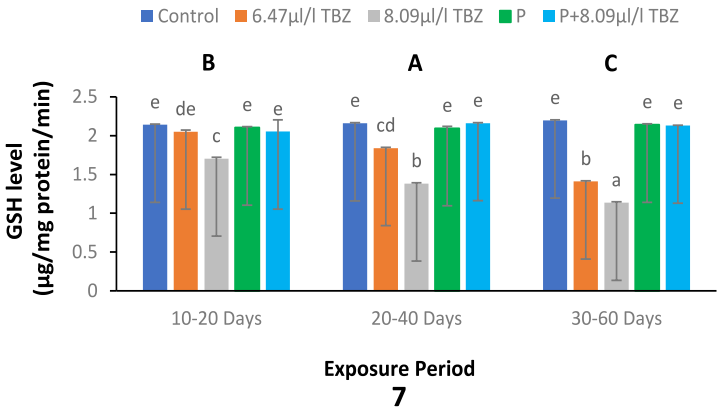

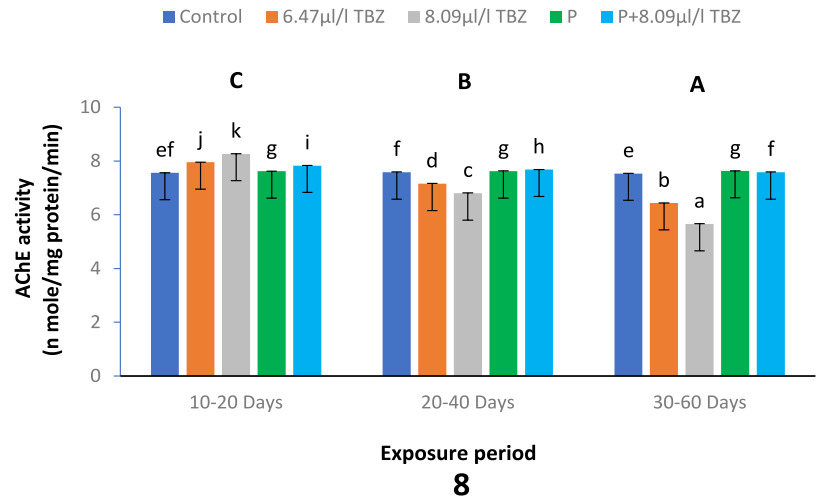

Fig. B (1-8): *Change in level of MDA and activity of antioxidant enzymes; SOD, CAT, LDH, GR, GPx, GSH level and AchE. All values are means ± SD, n=9. Significance levels observed are (P<0.05) in comparison to the control.*

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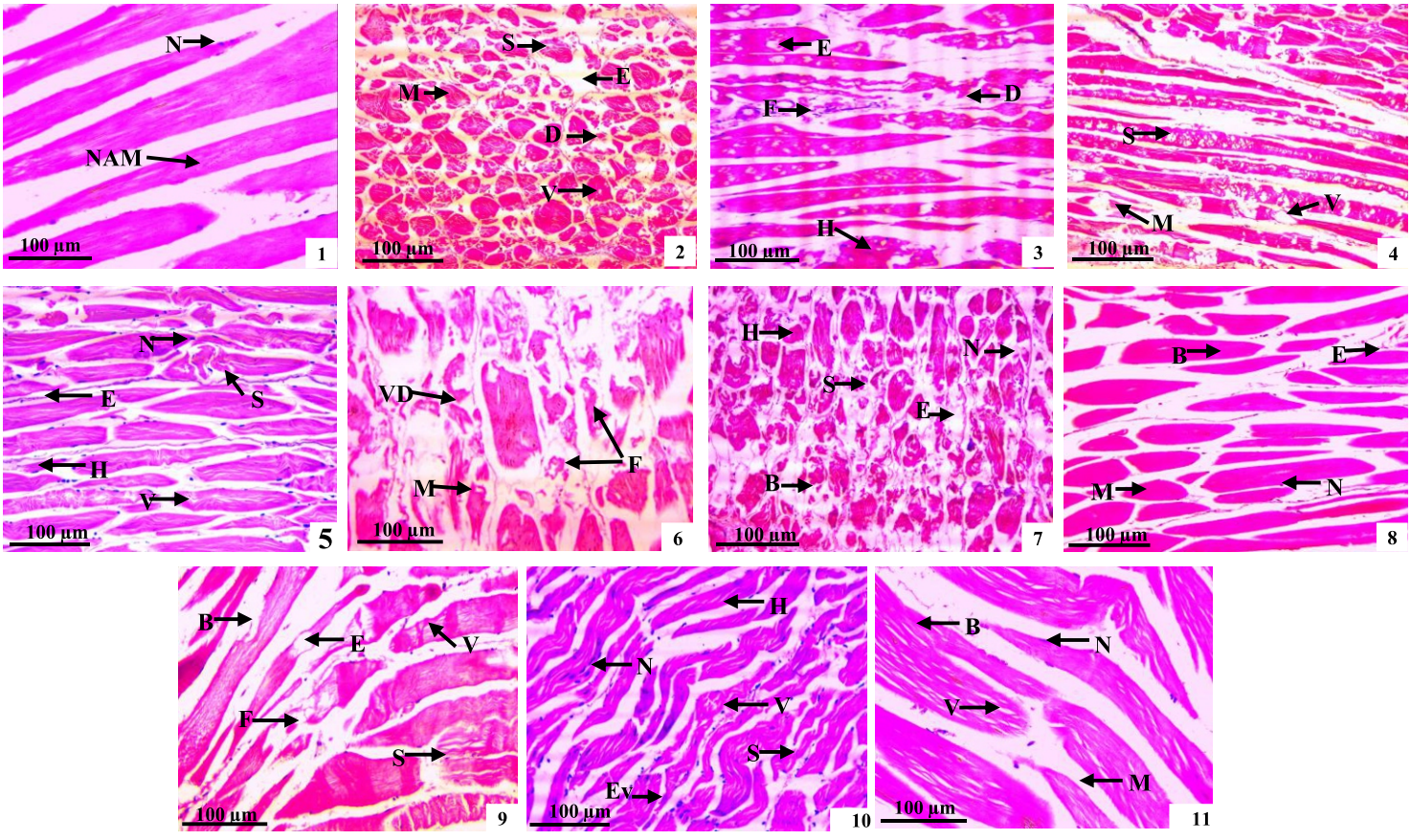

Fig. C (1-11)

(1) Control muscle with normal muscular architecture with well-organized fiber bundles (NAM) and a single nucleus positioned at the periphery (N). (**2-4): Muscle treated with 6.47 µl/l TBZ** showing **2);** structural abnormalities, including fragmentation of muscle fibers (S), swelling (E), tissue breakdown (MD), mild vacuolization within myotomes (V), and defective muscle segments (MT) at 10 days. **3);** Aggravated interstitial swelling (E), progressive tissue degradation (D), hemorrhagic regions (H), and fibrotic changes (F) at 20 days. **3);** Persistent degenerative effects, such as splitting of muscle fibres (S), vacuolised membrane (V), and multifocal deterioration of myotomes (M) at 30 days**. (5-7); Muscle treated with 8.09 µl/l TBZ** showing **5)**; Nuclear displacement and degeneration (N), epithelial breakdown (E), hemorrhagic regions (H), vacuolization within myotomes (V) and pronounced fibre splitting (S) at 10 days. **6);** Increased fibrosis (F), vacuolar degeneration (VD) and advanced vacuolization of myotomes (M) at 20 days. **7);** Severe hemorrhage (H), extensive myoepithelial disintegration (E), fragmented myotomes, necrotic nuclei (N) and disrupted muscle bundles (B) at 30 days. **(8); Only propolis treated muscle** with normal structure, displayed well-organized myotomes (M), intact muscle bundles (B), peripheral nuclei (N), and a healthy myoepithelium. (**9-11); Muscle with propolis+8.09 µl/l TBZ** depicting, **9);** regenerating bundles (B), reduced edema (E), fibrotic muscle fibers (F), and vacuolization (V). Split fibres (S) indicate ongoing muscle repair at 20 days. **10);** Progressive structural normalization, with decreasing hemorrhage (H), mild myotomal vacuolization (V), restored nuclear integrity (N), reduced fibre splitting (S), and diminished epithelial vacuolization (Ev)at 40 days. **11);** Well-formed muscle bundles (B), stable peripheral nuclei (N), and minimal vacuolization (V). Structural integrity is fully restored with normal myotomes (M) showing nearly complete muscle recovery at 60 days.

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