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Antioxidant and toxicological effects of verbenone enhanced with cyclodextrin and lysine in diclofenac-induced oxidative stress mice

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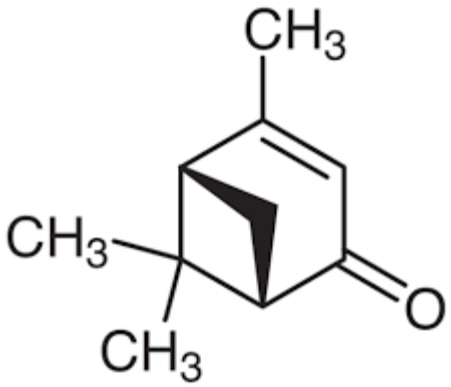
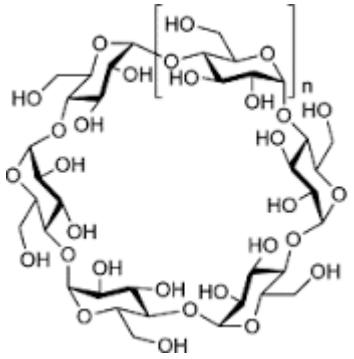
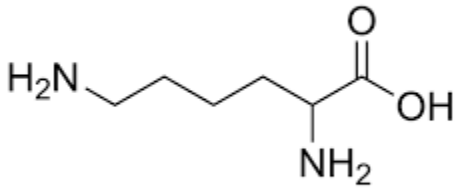
Graphical Abstract



Verbenone



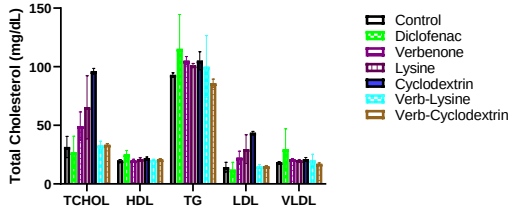
Cyclodextrin



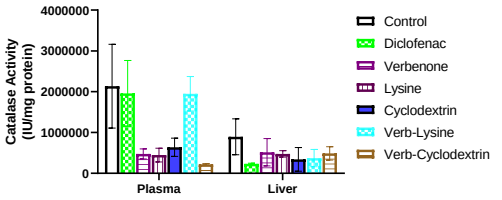
Lysine

Enhanced Activities

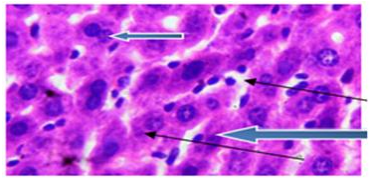
diclofenac-induced oxidative stress mice



Lipid profile



Catalase (CAT) activity



Liver and Kidney Photomicrograph

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Abstract:
Oxidative stress is a pathological condition that plays a crucial role in the pathogenesis of various diseases. This study evaluated the antioxidant and toxicological effects of verbenone enhanced with cyclodextrin and lysine in mice with diclofenac-induced oxidative stress. Adult Swiss mice (35) were randomly distributed into seven (7) groups, induced with oxidative stress, and orally administered verbenone, lysine, cyclodextrin, verbenone-lysine, and verbenone-cyclodextrin at 200 mg/kg body weight. Cyclodextrin treatment significantly increased ($p<0.05$) total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), and triglycerides compared with diclofenac control. No significant alterations ($p<0.05$) were observed in the atherogenic index, while cyclodextrin significantly increased the cardiac index and coronary artery index. Plasma protein and catalase activity decreased significantly ($p<0.05$) in all treatment groups. No significant alterations ($p<0.05$) were observed in malondialdehyde concentration and liver superoxide dismutase activity. Glutathione peroxidase activity decreased in plasma for verbenone, cyclodextrin, and verb-cyclodextrin, but increased in the liver with lysine and cyclodextrin treatments. Liver albumin and total bilirubin were elevated in treated groups, while gamma-glutamyl transferase activity significantly increased ($p<0.05$) across all groups except with verbenone treatment. Histopathology revealed periportal inflammation in verb-lysine, and while liver and kidney architecture in verb-cyclodextrin and verbenone groups was preserved. Verbenone enhanced with cyclodextrin and lysine mitigated oxidative damage, with cyclodextrin conjugation demonstrating a more favorable profile compared to lysine conjugation. The combination of verbenone and lysine or cyclodextrin may provide valuable insights into the modulation of renal and hepatic functions under oxidative stress conditions.

Keywords: Antioxidant; Cyclodextrin; Lysine; Oxidative Stress; Toxicological Effect; Verbenone

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Introduction

- ✓ Oxidative stress arises from an imbalance between reactive oxygen species (ROS) production and antioxidant defense, contributing to diseases such as neurodegenerative disorders, cardiovascular diseases, and cancer (Halliwell and Gutteridge, 2015).
- ✓ Although diclofenac is an effective NSAID, it can cause oxidative stress, hepatotoxicity, and lipid peroxidation, necessitating adjunct therapies to mitigate these effects.
- ✓ Verbenone, a plant-derived monoterpenoid, exhibits strong antioxidant, anti-inflammatory, and antimicrobial properties and could serve as a natural adjunct to reduce oxidative damage (Alonso *et al*., 2019; Tijjani *et al*., 2022; Ado *et al*., 2024; Saliu *et al*., 2025).
- ✓ Cyclodextrin and lysine may improve verbenone's solubility and bioavailability through complex formation, and may enhance antioxidant defenses and stabilizes cellular proteins under oxidative stress.

Results and discussion

Table 1: Body weight changes of experimental mice after treatment with verbenone enhanced with cyclodextrin, and lysine in diclofenac induced oxidative stress mice

Groups	Day 1 (g)	Day 3 (g)	Day 6 (g)
Control	34.43±1.77	36.07±1.54	38.03±1.60
Diclofenac	35.97±4.62	36.87±4.49	24.63±7.00
Verbenone	35.90±2.91	33.43±3.21	34.70±3.70
Lysine	39.23±4.57	37.03±3.82	37.57±2.80
Cyclodextrin	32.97±7.17	32.43±6.72	36.77±1.32
Verb-Lysine	35.70±3.40	34.07±3.15	32.60±2.42
Verb-Cyclodextrin	32.07±5.15	30.80±4.66	32.50±5.90

Values are mean ± standard deviation (SD), n=5

Results and discussion (Continue)

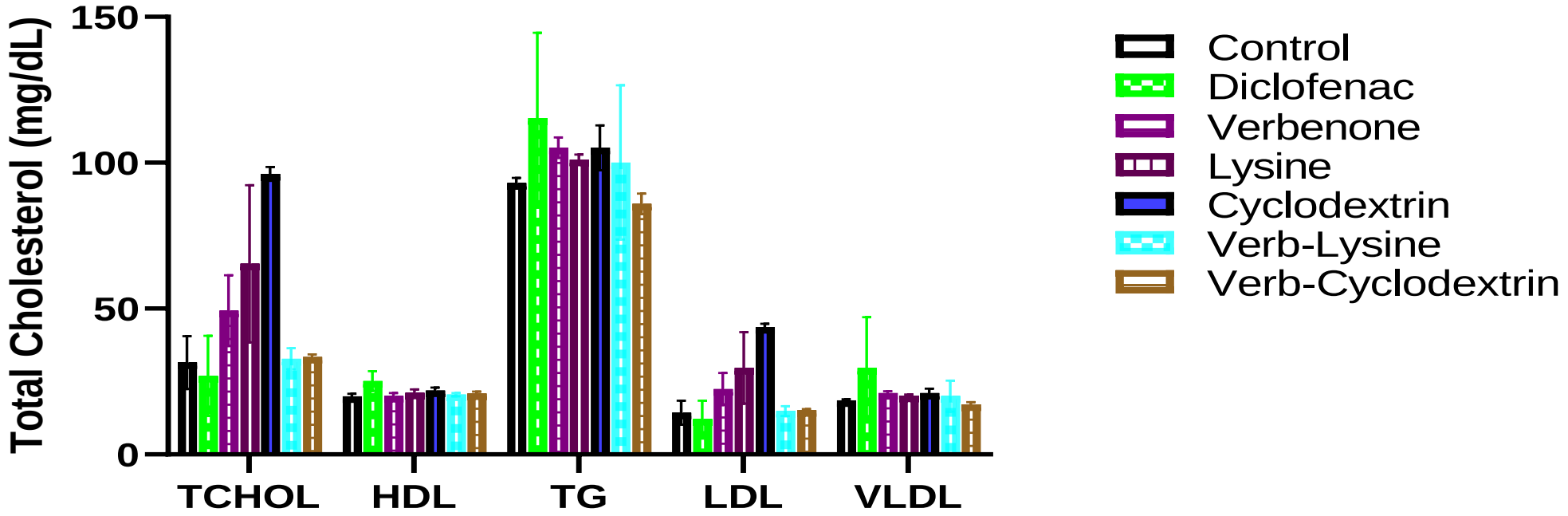

Figure 1: Lipid profile of experimental mice after treatment with verbenone enhanced with cyclodextrin, and lysine in diclofenac induced oxidative stress mice.

Values are mean ± SD (n=5)

Results and discussion (Continue)

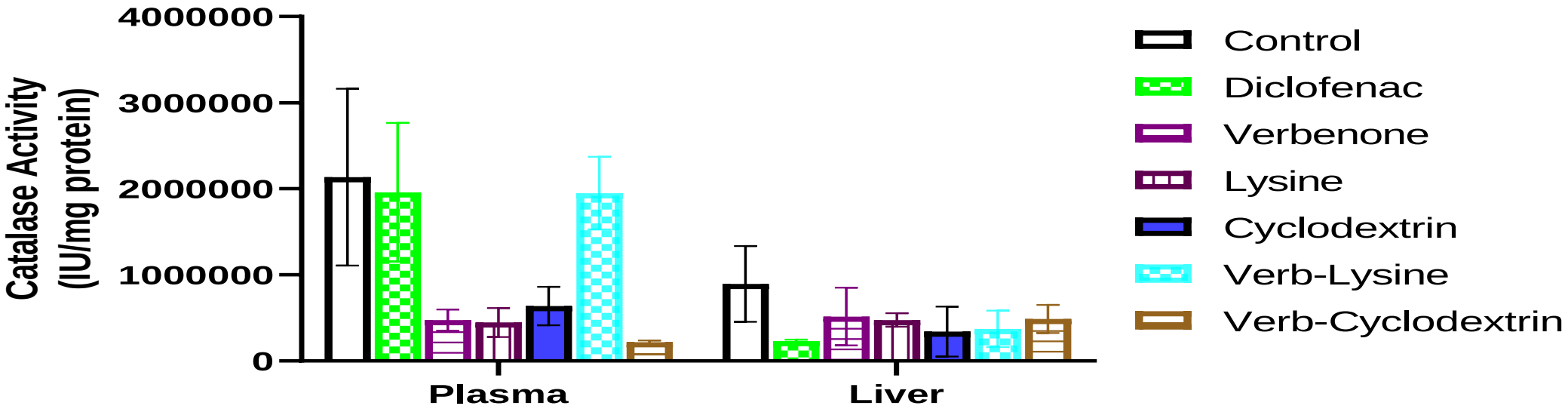

Figure 4: Catalase (CAT) activity of experimental mice after treatment with verbenone enhanced with cyclodextrin, and lysine in diclofenac induced oxidative stress mice. Values are mean ± SD (n=5).

Results and discussion (Continue)

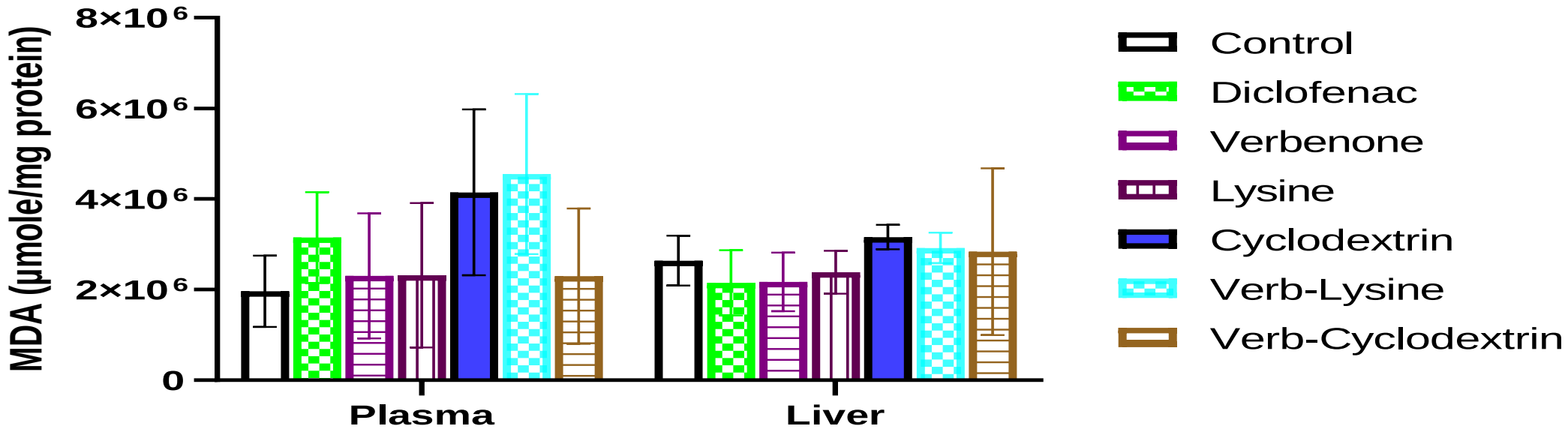

Figure 5: Malondialdehyde (MDA) level of experimental mice after treatment with verbenone enhanced with cyclodextrin, and lysine in diclofenac induced oxidative stress mice. Values are mean ± SD (n=5).

Results and discussion (Continue)

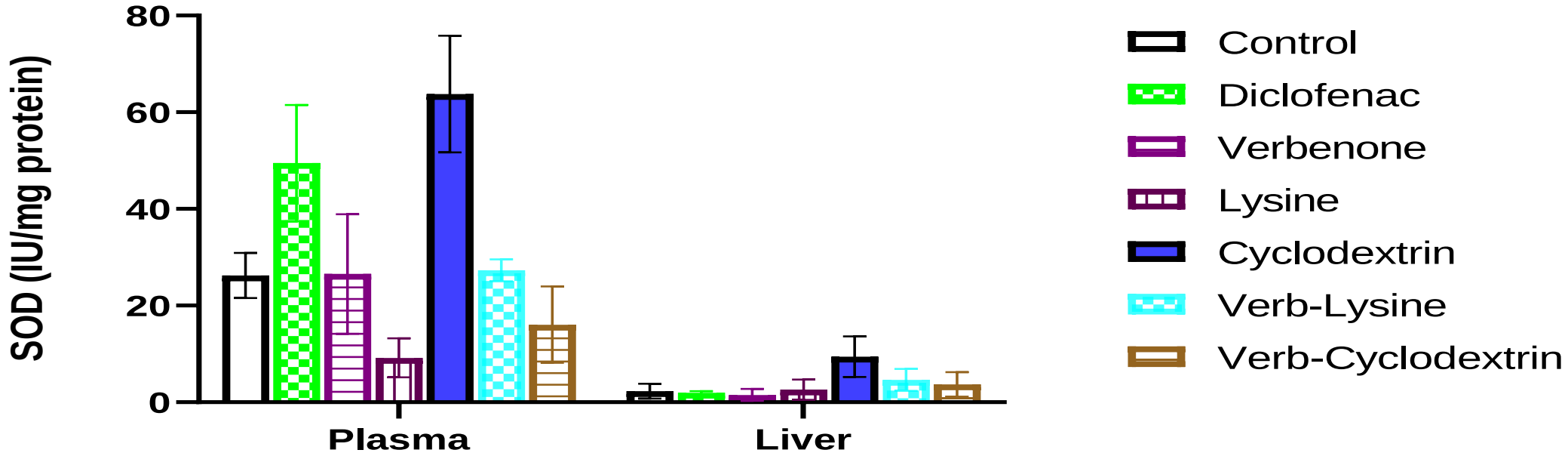

Figure 7: Glutathione peroxidase (GPx) activities of experimental mice after treatment with verbenone enhanced with cyclodextrin, and lysine in diclofenac induced oxidative stress mice

Values are mean ± SD (n=5).

Results and discussion (Continue)

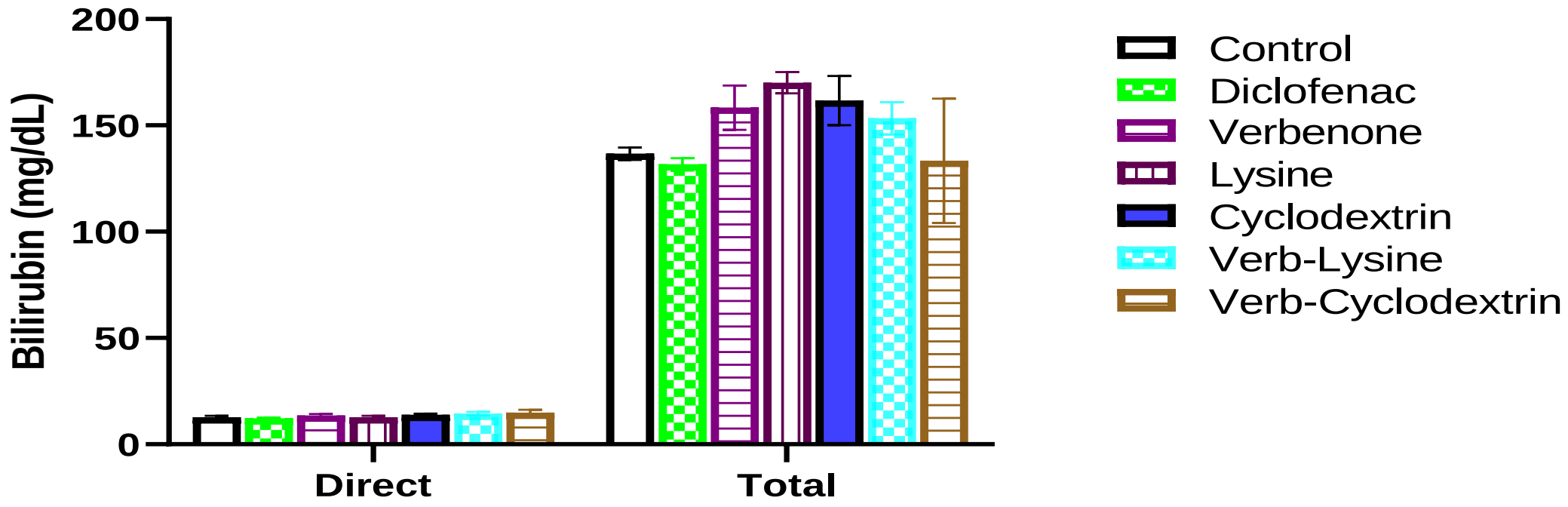

Figure 8: Total and direct bilirubin concentrations of experimental mice after treatment with verbenone enhanced with cyclodextrin, and lysine in diclofenac induced oxidative stress mice Values are mean ± SD (n=5).

Results and discussion (Continue)

Table 7: Plasma AST, ALT and ALP concentration (IU/L) of experimental mice after treatment with verbenone enhanced with cyclodextrin, and lysine in diclofenac induced oxidative stress mice

Groups	Serum AST	Serum ALT	Serum ALP
Control	991.74±165.26	306.54±37.24	341.00±147.66
Diclofenac	1604.82±391.13	270.48±86.24	397.83±130.22
Verbenone	1622.85±328.36	216.38±43.12	312.58±274.04
Lysine	324.57±93.70	162.29±87.39	312.58±98.44
Cyclodextrin	649.14±296.87	450.79±52.63	227.33±49.22
Verb-Lysine	324.57±162.29	270.48±56.38	198.92±49.22
Verb-Cyclodextrin	703.24±480.81	3480.11±584.75	312.58±160.44

Values are mean ± standard deviation (SD), n=5

Results and discussion (Continue)

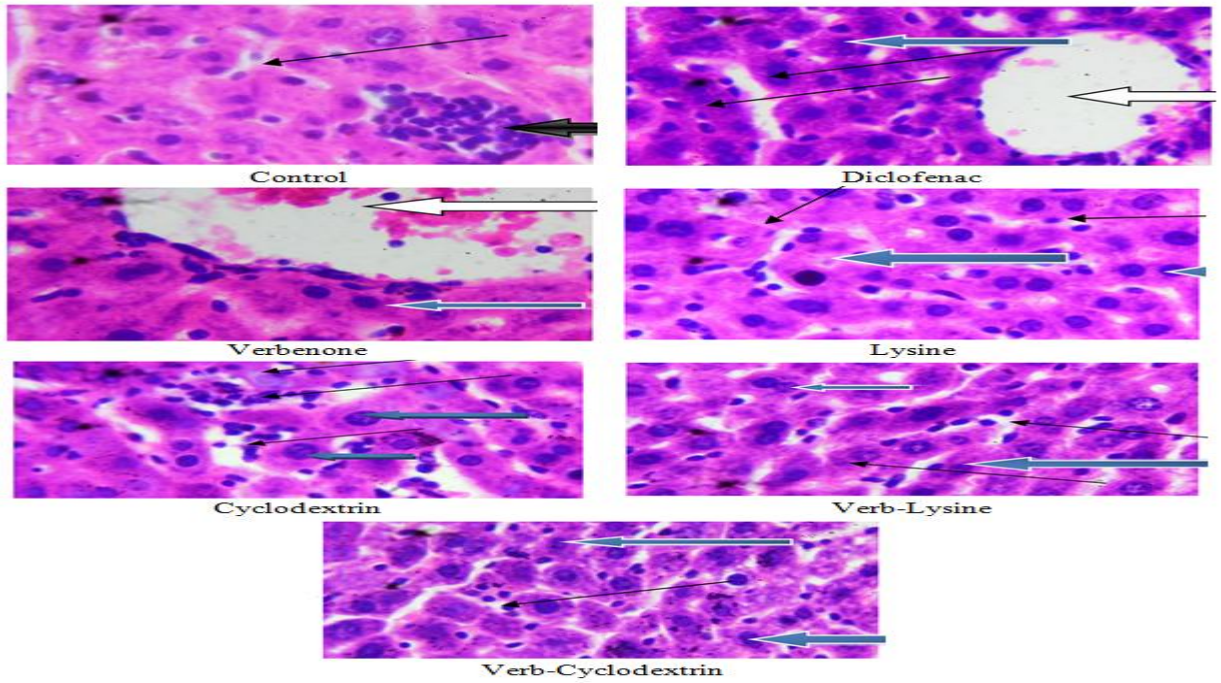

Figure 10: Liver photomicrograph of experimental mice after treatment with verbenone enhanced with cyclodextrin, and lysine in diclofenac induced oxidative stress mice (Haematoxylin and Eosin x400)

Conclusions

The study reveals complex interactions between diclofenac-induced oxidative stress and the modulatory effects of verbenone, lysine, and cyclodextrin against oxidative damage, with cyclodextrin conjugation presented more safety profile compared to lysine conjugation. The treatments demonstrated organ- and biomarker-specific effects in diclofenac-induced oxidative stress mice. The combination of verbenone and lysine or cyclodextrin may provide valuable insights into the modulation of renal and hepatic functions under oxidative stress conditions.

Acknowledgments

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