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Histopathological and Biochemical Assessment of Morin Hydrate's Protective Role against Cyclophosphamide-Induced Multi Organ Toxicity

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Abstract

Cyclophosphamide, an extensively used antineoplastic drug, exhibits therapeutic efficacy. However, it is associated with a significant number of side effects, with reproductive toxicity being the most severe side effect. In this study, we examined the potential therapeutic effects of morin hydrate, a bioactive flavonoid with multiple pharmacological properties, on organ damage caused by cyclophosphamide in male rats. The rats were divided into four groups: Sham, CYP control, MH per se, and CYP+MH. Cyclophosphamide was administered intraperitoneally at a dose of 40 mg/kg on days 0, 7, 14, 21, and 28 and morin hydrate (100 mg/kg body weight, PO route daily for 28 days in groups 3 and 4). On the 29th day, the rats were euthanized, and liver, lung, and intestinal samples were collected for evaluation. Parameters such as relative organ weight, body weight, serum markers, haematological parameters, antioxidant levels, and histopathological examination were used to evaluate organ damage. The CYP control group showed a significant decrease in body weight, relative liver weight, Total Erythrocyte Count (TEC), Total Leukocyte Count (TLC), Haemoglobin (Hb), Packed Cell Volume (PCV), and lymphocytes, while exhibiting increased relative lung weight, neutrophils, monocytes, eosinophils, Aspartate Transaminase (AST), Alanine Transaminase (ALT), and Alkaline Phosphatase (ALP) levels. Oxidative stress markers, such as Malondialdehyde (MDA), were elevated, while Superoxide Dismutase (SOD) activity and reduced glutathione (GSH) concentration were decreased in the liver, lungs, and intestines of the CYP control group. Histopathological examination revealed marked congestion, infiltration of mononuclear cells, alveolar damage, and hyperplasia of Type II pneumocytes in the lungs; pyknotic nuclei, vacuolar degeneration, and necrosis in the liver; and mucosal ulceration, degenerated villi, and epithelial degeneration in the intestine. In contrast, the CYP+MH group showed significant improvements in body weight, relative organ weights, haematological parameters, serum enzymes, oxidative stress markers, and histopathology compared to the CYP control group. These findings suggest that MH effectively counteracts CYP-induced organ damage in rats, possibly due to its antioxidant and free radical scavenging properties.

Major Findings: The study found that morin hydrate effectively counteracts cyclophosphamide-induced organ damage in rats. Specifically, morin hydrate treatment improved body weight, relative organ weights, hematological parameters, serum enzymes, oxidative stress markers, and tissue histopathology compared to cyclophosphamide alone. These protective effects are likely due to morin hydrate's antioxidant and free radical scavenging properties.

Keywords: Cyclophosphamide, Histopathology, Morin Hydrate, Oxidative Stress

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1. Introduction

Chemotherapy toxicity poses a significant clinical challenge, affecting patients quality of life, prolonging treatment duration, and exacerbating negative emotions associated with therapy. Concerns about potential new toxicities and side effects often lead cancer patients to decline further chemotherapy or to discontinue altogether[1]. Since its introduction in 1960, Cyclophosphamide (CYP) has been extensively used as an antineoplastic drug. It demonstrates efficacy against a broad spectrum of human cancers, including benign conditions, chronic and acute leukaemia, systemic lupus erythematosus, lymphomas, multiple sclerosis, multiple myeloma, rheumatoid arthritis, certain types of leukaemia, and solid tumours. This alkylating agent is often regarded as one of the most potent drugs and is commonly prescribed by rheumatologists[2]. Moreover, repeated use of Cyclophosphamide (CYP) increases susceptibility to bone marrow suppression[3]. Clinically notable side effects associated with CYP include nausea, vomiting, anorexia, haemorrhagic cystitis, lymphopenia, neutropenia, anaemia, thrombocytopenia, haematological malignancies, and increased risk of infection, fibrosis, interstitial pneumonitis, and gonadal insufficiency[4].

The use of cyclophosphamide and doxorubicin in chemotherapy often leads to haematological and gastrointestinal toxicities. The potent proliferative effects of chemotherapy specifically affect the haematological system. Among the myelotoxic side effects associated with breast cancer treatment, anaemia is of particular concern. In addition, the kidneys play a crucial role in drug excretion. However, these organs operate in an environment characterized by high blood pressure, low oxygen levels, and exposure to chemotherapeutic medications[1]. Cyclophosphamide is limited in its use due to its adverse impact on kidney function, liver health, cardiac function, and the immune system[5]. Through its metabolic process, cyclophosphamide generates active metabolites such as phosphorylamide and acrolein, which lead to DNA alkylation. Immediate repair mechanisms are initiated when DNA alkylation occurs. However, if repair is not feasible, the tumour suppressor protein p53 is activated. This activation halts the cell cycle, providing adequate time for DNA repair to occur[6]. Phosphoramide mustard, a critical component of cytotoxicity, alkylates DNA and disrupts replication through the formation of crosslinks. This process halts the cell cycle progression and inhibits cell proliferation. While the primary active metabolites are alkylating agents, acrolein serves as a by-product that exacerbates the severe side effects. Consequently, neutralizing acrolein could potentially reduce toxicity and enhance overall efficiency. Cyclophosphamide (CYP), a non-specific cell cycle inhibitor, predominantly acts during the S phase, preventing cell division before reaching the G2 phase. Although it had a minimal impact on resting cells, CYP significantly affected cell proliferation. Additionally, phosphoramide mustard can promote cell apoptosis by upregulating pro-apoptotic mRNA expression and downregulating anti-apoptotic mRNA expression[7].

Recently, there has been a noticeable upsurge in the use of herbal remedies in the healing sector. Plants contain approximately 4000 flavonoids, many of which have medicinal attributes[8]. Flavonoids are polyphenolic compounds that offer a variety of health benefits[9]. Among the bioactive flavonoids, Morin Hydrate (3,5,7,2',4'-pentahydroxyflavone) (MH) is notably abundant in plants that belong to the *Moraceae* family[10]. Morin exhibits a wide range of biological functions through the modulation of various antioxidant enzymes. These functions encompass antidiabetic, anti-inflammatory, antihypertensive, antitumor, antibacterial, and neuroprotective properties. Additionally, Morin acts as an inhibitor of xanthine oxidase, protecting DNA from free-radical damage, scavenging free-radicals, and impeding cell proliferation. Its antioxidant properties contribute to hepatoprotective, hypolipidemic, antidiabetic, and neuroprotective effects[11]. The objective of this study was to evaluate the pharmacological effectiveness of morin hydrate in preventing cyclophosphamide induced organ damage.

This study aims to assess the pharmacological efficacy of morin hydrate in ameliorating CYP-induced damage to the liver, lungs, intestines and hematological system through modulation of oxidative stress pathways. By examining multiple organ systems and biomarkers, this research provides novel insights into the protective mechanisms of morin hydrate against cyclophosphamide-induced toxicity, which could inform strategies to improve chemotherapy tolerability and outcomes.

2. Materials and Methods

2.1 Drugs and Chemicals

Endoxan-N, a brand of cyclophosphamide, was sourced from Cadila Health Care Ltd., Hyderabad, whereas morin hydrate was obtained from Hi Media Laboratories Pvt.

Ltd., Mumbai. Bradford Reagent and DTNB [5,5'-dithio-bis-(2-nitrobenzoic acid)] were purchased from M/s. Sigma-Aldrich Pvt. Ltd., St. Louis, MO, USA. Ellman's reagent, 2-Thiobarbituric Acid (TBA), eosin 2%, and other chemicals were procured from M/s. Hi MEDIA Lab. Pvt. Ltd., Mumbai, India.

2.2 Experimental Design

Twenty-four adult male Wistar rats, with an approximate weight range of 170 -220 g, aged between 8 and 12 weeks, were procured from M/s. Jeeva Life Sciences in Hyderabad (registration number: 1757/PO/ReBiBt/S/14 CPCSEA, Hyderabad). The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC) of the College of Veterinary Science, Rajendranagar, Hyderabad (approval reference: 1/25/C.V.Sc, Hyd. IAEC). A total of 4 groups, each comprising six rats, were evenly allocated for the 28-day experiment. All groups underwent distinct treatments (Figure 1).

G-1: Sham (normal saline for 28 days).

G-2: Cyclophosphamide control (CYP, 40 mg/kg body weight) I/P on 0, 7, 14, 21 and 28 days.

G-3: Morin hydrate per se (100 mg/kg body weight, PO route daily for 28 days).

G-4: Cyclophosphamide (40 mg/kg body weight) IP route on 0, 7, 14, 21 and 28 days + Morin hydrate (100 mg/kg) P/O for 28 days.

2.3 Relative Organ Weight

At the end of the study, the animals were euthanized on day 29 using a CO_2 chamber. Liver and lung samples were promptly collected and weighed relative to the body weights of rats in the different groups. Organ weight was expressed as a percentage of body weight relative to a standard or reference value.

2.4 Blood Collection

Following a 12-hour fast, blood samples were obtained from the retro-orbital plexus of the rats on the 29th day of the experiment. These samples were divided into EDTA vacutainers for haematological investigations and serum vacutainers. Serum was isolated after centrifugation at 3000 RPM for 15 minutes and preserved at -80°C for subsequent analysis of Aspartate Transaminase (AST), Alanine Transaminase (ALT), and Alkaline Phosphatase (ALP). After blood collection, the rats were humanely euthanized using a CO_2 chamber, and their lung, liver, and intestinal

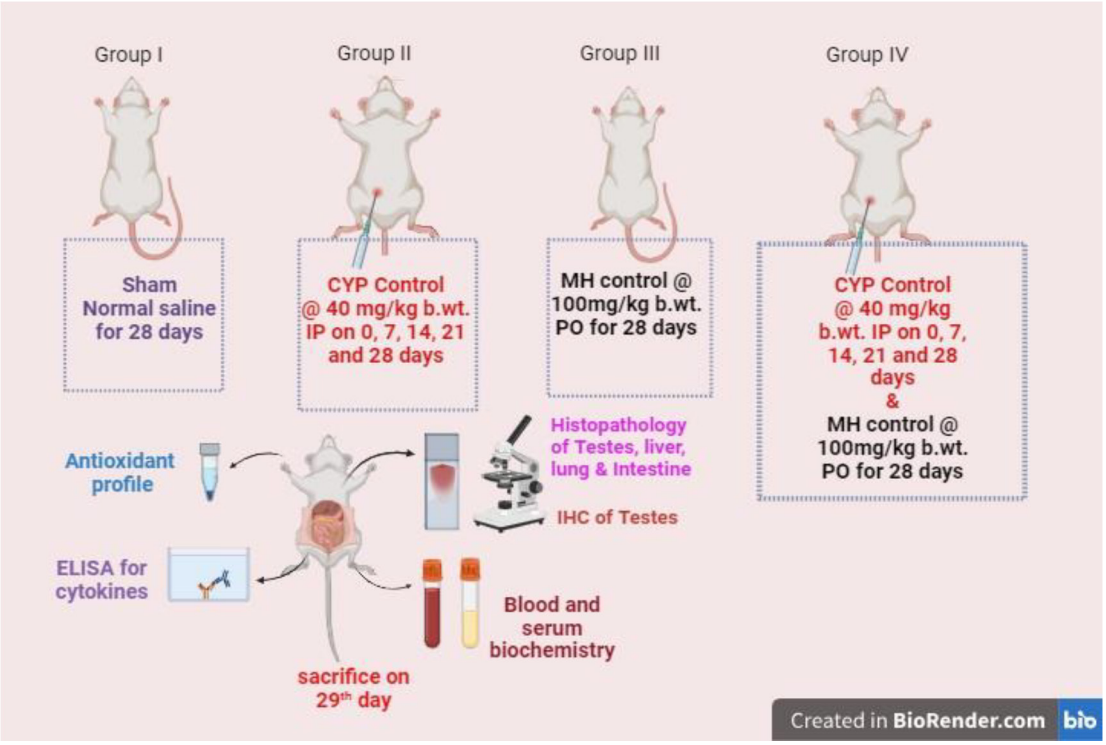


Figure 1. Experimental design (This image was created with Biorender.com).

tissues were collected, weighed, homogenized, and stored at -80°C for further analysis.

2.5 Histopathology

Tissue samples were preserved in 10% Neutral Buffered Formalin (NBF) solution for histopathological analysis. To prepare the samples for observation, a small representative portion of the fixed tissue was cut and cleaned by washing in running water. The tissue was dehydrated using increasingly concentrated alcohol solutions, followed by cleaning with xylene. Finally, tissue samples were embedded in paraffin at a temperature range of 55 -56°C. Using a microtome, the paraffin blocks were cut into slices approximately five microns thick. These sliced sections were then transferred onto grease-free glass slides that had been coated with Mayer's egg albumin and dried overnight at 37°C in an incubator. The fixed tissues were further processed and stained with Hematoxylin and Eosin (H and E) stains[12].

2.6 Estimation of Thiobarbituric Acid Reactive Substances (TBARS)

In a tissue homogenizer cup, 100 mg of a tissue sample with PBS buffer (pH 7.4) was taken and homogenized. In a 2 mL eppendorf tube, taken 100 µL of supernatants of homogenized samples and added 100 µL of 8.1% Sodium dodecyl sulfate, 100 µL of 20% Glacial acetic acid (GAA) and 750 µL of 0.8% Thiobarbituric acid. Distilled water was used to make up the volume to 2 mL. Then placed the eppendorf in a water bath and heated for 60 minutes at 96°C. After cooling, the samples were subjected for centrifugation at 10,000 rpm for 10 minutes after cooling beneath running water. Then, 200 µL of supernatants were added to 96-well ELISA plate and read at a wavelength of 532 nm. The values were analyzed with standard values.

Units of activity:

Units of activity = n moles/mg protein

2.7 Estimation of Glutathione (GSH)

Taken 20 g of potassium phosphate and dissolved it in 40 mL of distilled water to make the GSH buffer (pH 8.4). In a 96 well ELISA plate added 50 µL of tissue homogenate and 100 µL of GSH buffer to each well. Then each well in the plate was filled with Ellman's reagent and kept in the dark for 10 min at room temperature. The plate was read at a wavelength of 412 nm and observed values were calculated with the standard.

Units of activity:

Units of activity = n moles/mg protein

2.8 Estimation of Super Oxide Dismutase (SOD)

In each well of 96-well plate added 13 µL of PBS, followed by 6 µL of MTT reagent, 2 µL of homogenized samples and 15 µL of pyrogallol. Incubated the plate at room temperature for 5 minutes. Then filled each well with 15 µL of DMSO and the plate was read in a microplate reader at a wavelength of 570 nm. Obtained values were calculated with standard values.

Units of activity:

Units of activity = U/mg protein

2.9 Statistical Analysis

The mean values of all variables were expressed as mean± SE (n=6). To analyse the data, SPSS version 20 software was used, which involved conducting a one-way Analysis of Variance (ANOVA) followed by Duncan's post-hoc test. Statistical significance was set at $P<0.05$.

3. Results and Discussion

Chemotherapy leads to various severe side effects including early and late signs of chronic toxicity. The World Health Organization (WHO) has categorized these consequences into four categories: mild (Grade 1), moderate (Grade 2), severe (Grade 3), and life-threatening or incapacitating (Grade 4). All organs in the body, including vital organs, such as the heart, lungs, and brain, are susceptible. Additionally, chemotherapy can result in long-term effects, such as infertility, carcinogenicity, and drug resistance[13] including gastrointestinal mucositis, nausea and vomiting[14]. As many anticancer drugs target DNA in proliferating cells, their side effects, including gastrointestinal toxicity, myelosuppression, and immunosuppression, occur mostly in tissues with high levels of proliferative cells, such as the bone marrow and gastrointestinal tract, along with cardiotoxicity, nephrotoxicity, hepatotoxicity and pulmonary fibrosis[15].

Cyclophosphamide (CYP) is an immunosuppressive and cytotoxic alkylating agent. It is commonly used as a single medication or in conjunction with glucocorticoids or chemotherapy for the treatment of various inflammatory and malignant disorders[16]. CYP belongs to the oxazaphosphorine class of drugs and is a common

treatment choice for acute myeloid leukaemia, non-Hodgkin's lymphoma, acute lymphoblastic leukaemia, chronic myelogenous leukaemia, solid tumors, and breast cancer. Apart from its benefits, it also has disadvantages and side effects such as reproductive toxicity and leukopenia in both animals and humans. It also has cytotoxic effects on healthy cells and induces oxidative stress[17].

Owing to acrolein synthesis, CYP causes excess Reactive Oxygen Species (ROS), disrupts antioxidant mechanisms, and causes lipid peroxidation and a severe inflammatory response during drug metabolism. CYP-induced oxidative damage plays a significant role in the pathophysiology of injury to many tissues[18].

3.1 Body Weights and Relative Weights

In the current investigation, body weights and relative weights of the liver in the group receiving CYP decreased significantly on day 29 compared to the control group. In the treatment group, body weights and relative weights were improved compared to those in the CYP-intoxicated group, and both body and relative weights of the MH-treated group were the same as those of Group 1. This significant decline in body weight and organ index (liver) in Group 2 may be due to disturbances in appetite, imbalance of redox in the tissue and increased generation of free radicals and oxidative stress factors. Ultimately, the accumulation of these substances results in membrane deterioration, mitochondrial peroxidative damage and DNA fragmentation[19,20]. However, the relative weight of the lungs in Group 2 was significantly higher than that in the control group, which may be due to oedema, inflammation, and collagen over production[21]. Morin hydrate restored the absolute body weight and relative weights of the liver and lungs in the treatment groups. This may be due to the reduction in inflammation and the antioxidant properties of MH by preventing atrophy, necrosis, and tissue degeneration (Table 1; Figure 2) (Table 2; Figure 3A) (Table 2; Figure 3B).

Table 1. Effect of CYP and MH on average body weights (g) of different rat groups

Group	Day 1	Day 29
1.Sham	186.33±1.78	274.33±2.96^{a}
2.CYP control (CYP)	191.50±2.13	230.83±2.12^{c}
3. Morin hydrate control (MH)	187.50±1.71	277.33±2.45^{a}
4. CYP + MH	188.50±1.65	260.83±1.56^{b}

Values are expressed as mean ± SE (n=6); one-way analysis ANOVA with Duncan's post hoc test (SPSS). Means with different letters as superscripts differ significantly (P< 0.05).

3.2 Haematology

CYP treatment decreased PCV, TEC, TLC, haemoglobin, and lymphocyte counts, while increasing monocyte, eosinophil, and neutrophil counts in rats, consistent with previous studies[22,23]. The treatment group showed a significant increase in PCV, TEC, TLC, and haemoglobin levels compared to the CYP group (Table 3; Figure 4A-D) (Table 4; Figure 5A, B, C, D). Cyclophosphamide targets rapidly dividing cells[24], causing myelosuppression and reduced haematological parameters in Group 2. Myelotoxicity and oxidative damage by CYP in the bone marrow lower PCV, TEC, haemoglobin, and TLC[25]. In treatment Group 4, TEC, TLC, PCV, DLC, and haemoglobin levels normalized, likely due to MH's inhibition of free radical-induced haemolysis[26].

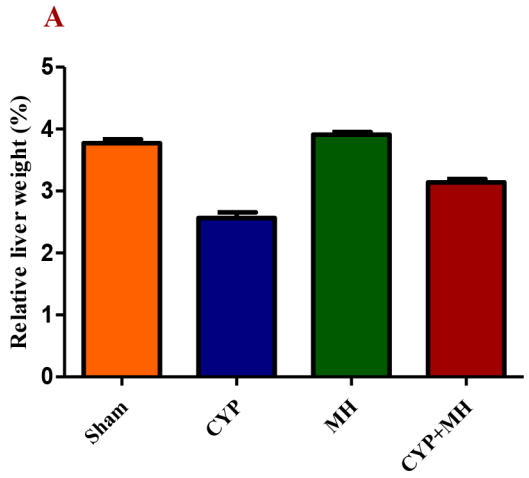


Figure 2. Effect of CYP and MH on Average body weights (g) of different rat groups.

Table 2. Effect of CYP and MH on relative weights (%) of liver and lung of different rat groups

Group	liver	lung
1. Sham	3.77±0.06^{c}	0.80±0.02^{a}
2. CYP Control (CYP)	2.57±0.08^{a}	1.26±0.04^{c}
3. Morin hydrate (MH)	3.91±0.04^{c}	0.81±0.02^{a}
4. CYP + MH	3.14±0.05^{b}	1.06±0.03^{b}

Values are expressed as mean ± SE (n=6); one-way analysis ANOVA with Duncan's post hoc test (SPSS). Means with different letters as superscripts differ significantly (P< 0.05).

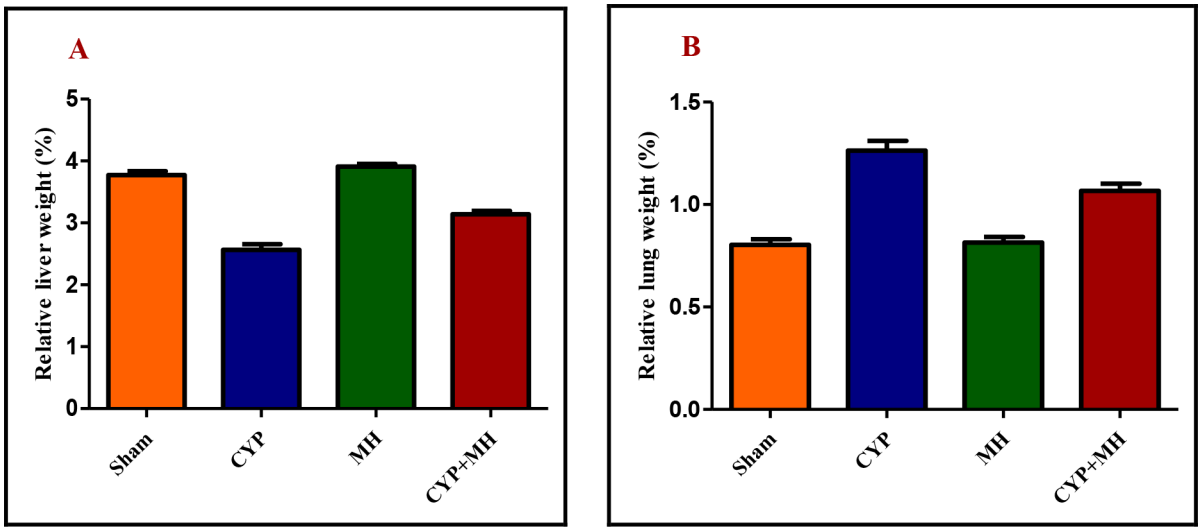


Figure 3. Effect of CYP and MH on relative weights (%) of liver and lung of different rat groups. **(A)** Relative weights of liver in different groups. **(B)** Relative weights of lung in different groups.

Table 3. Effect of CYP and MH on Total Erythrocyte Count, Total Leukocyte Count, Haemoglobin and Packed Cell Volume.

Group	TEC (10^6/µL)	TLC (10^3/µL)	Hb (g/dL)	PCV (%)
1. Sham	10.06±0.55^c	9.56±0.52^a	14.11±0.43^c	46.40±0.87^a
2. CYP Control (CYP)	3.53±0.46^a	4.19±0.51^c	9.09±0.50^a	32.77±1.38^c
3. Morin hydrate (MH)	9.96±0.34^c	9.69±0.40^a	14.91±0.51^c	45.89±1.22^a
4. CYP + MH	8.10±0.45^b	6.92±0.38^b	11.73±0.67^b	38.11±1.12^b

Values are expressed as mean ± SE (n=6); one-way analysis ANOVA with Duncan's post hoc test (SPSS). Means with different letters as superscripts differ significantly (P< 0.05).

3.3 Serum Parameters

According to the current study, the administration of CYP damages the liver because ROS promotes oxidative damage to other important organs (Table 5; Figure 6A-C). Excessive ROS production can lead to apoptosis or programmed cell death[27]. The generation of Reactive Oxygen Species (ROS) contributes significantly to the progression of liver damage. ROS are short-lived, highly reactive molecules with low molecular weights. As a result, the administration of CYP damaged the liver, as evidenced by increased levels of ALT, AST and ALP. These enzymes are crucial indicators of the liver function[28]. In the present study, CYP administration resulted in elevated AST, ALT and ALP levels indicating hepatic injury in the CYP group compared with the control group, which agrees with previous findings[29,30]. Administration of MH resulted in reduced levels of AST, ALT, and ALP in the CYP + MH group. These outcomes align with previous research suggesting that MH has the potential to ameliorate liver damage by modulating the PI3K/Akt/mTOR signalling pathway, enhancing antioxidant defences, inhibiting lipid peroxidation, and reversing aberrations related to apoptosis, autophagy, and inflammation[10,31].

Serum total protein was also assessed in the present study and the results revealed that CYP treatment caused a significant reduction in serum total protein in Group 2 due to liver damage[32]. However, treatment with MH increased the total protein levels in the CYP+MH group compared with those in the CYP-treated group (Table 5; Figure 6D).

Rats receiving CYP+MH showed significantly decreased AST, ALT, ALP levels and elevated TP levels compared to CYP injected rats.

3.4 Oxidative Stress Parameters

Oxidative stress and lipid peroxidation have been shown to be important in the pathophysiology of CYP-induced toxicity. Conversion of CYP to its hazardous metabolite, acrolein causes over production of NO and lipid peroxidation, which leads to oxidative cell

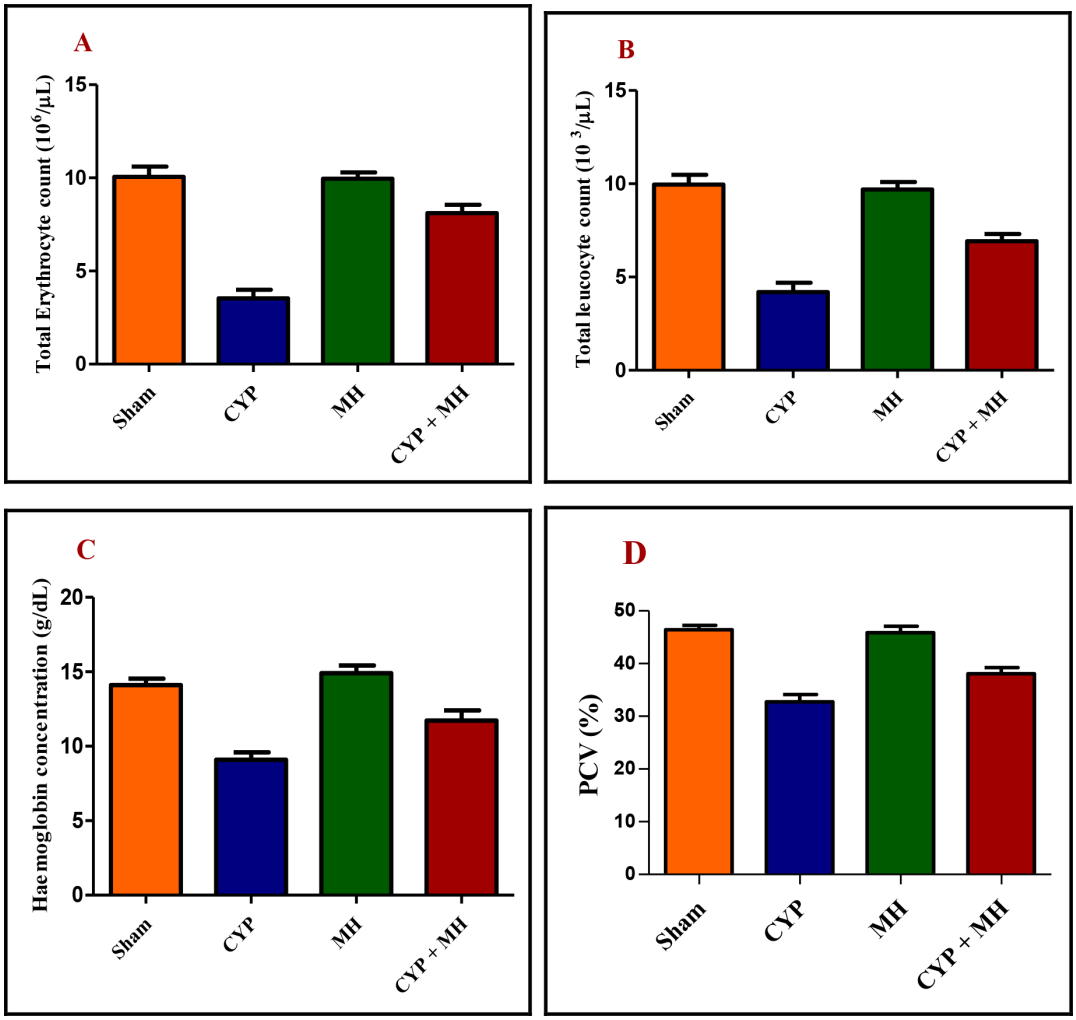


Figure 4. Effect of CYP and MH on Total Erythrocyte Count, Total Leukocyte Count, Haemoglobin and Packed Cell Volume. **(A)** Total erythrocyte count (10^6/**µL**) in different rat groups, **(B)** Total leukocyte count (10^3/**µL**) in different rat groups, **(C)** Haemoglobin concentration (g/dL) in different rat groups and (D) Packed cell volume (%) in different rat groups. Rats co-administered with CYP + MH restored TEC, TLC, Hb and PCV levels to normal.

Table 4. Effect of CYP and MH on Differential Leukocyte Count (DLC)

Group	Lymphocytes count (%)	Neutrophils count (%)	Monocytes count (%)	Eosinophils count (%)
1. Sham	78.85±1.05^c	15.38±0.34^a	1.70±0.07^c	1.22±0.08^a
2. CYP Control (CYP)	68.50±0.82^a	22.65±0.59^c	2.53±0.04^a	1.83±0.06^c
3. Morin hydrate (MH)	78.11±0.85^c	16.90±0.62^a	1.72±0.05^c	1.23±0.05^a
4. CYP + MH	74.27±0.89^b	20.38±0.57^b	2.21±0.09^b	1.49±0.02^b

Values are expressed as mean ± SE (n=6); one-way analysis ANOVA with Duncan's post hoc test (SPSS). Means with different letters as superscripts differ significantly (P< 0.05).

damage[33]. In the present study, we assessed the antioxidant profiles (GSH, SOD, and MDA) in the liver, lungs, and intestine. Rats exposed to CYP exhibited elevated MDA levels and lower levels of GSH and SOD than to the other groups. However, treatment with MH mitigated MDA levels and enhanced antioxidant levels (GSH and SOD) (Table 6-8; Figure 7-9). These alterations in the antioxidant profile within the liver,

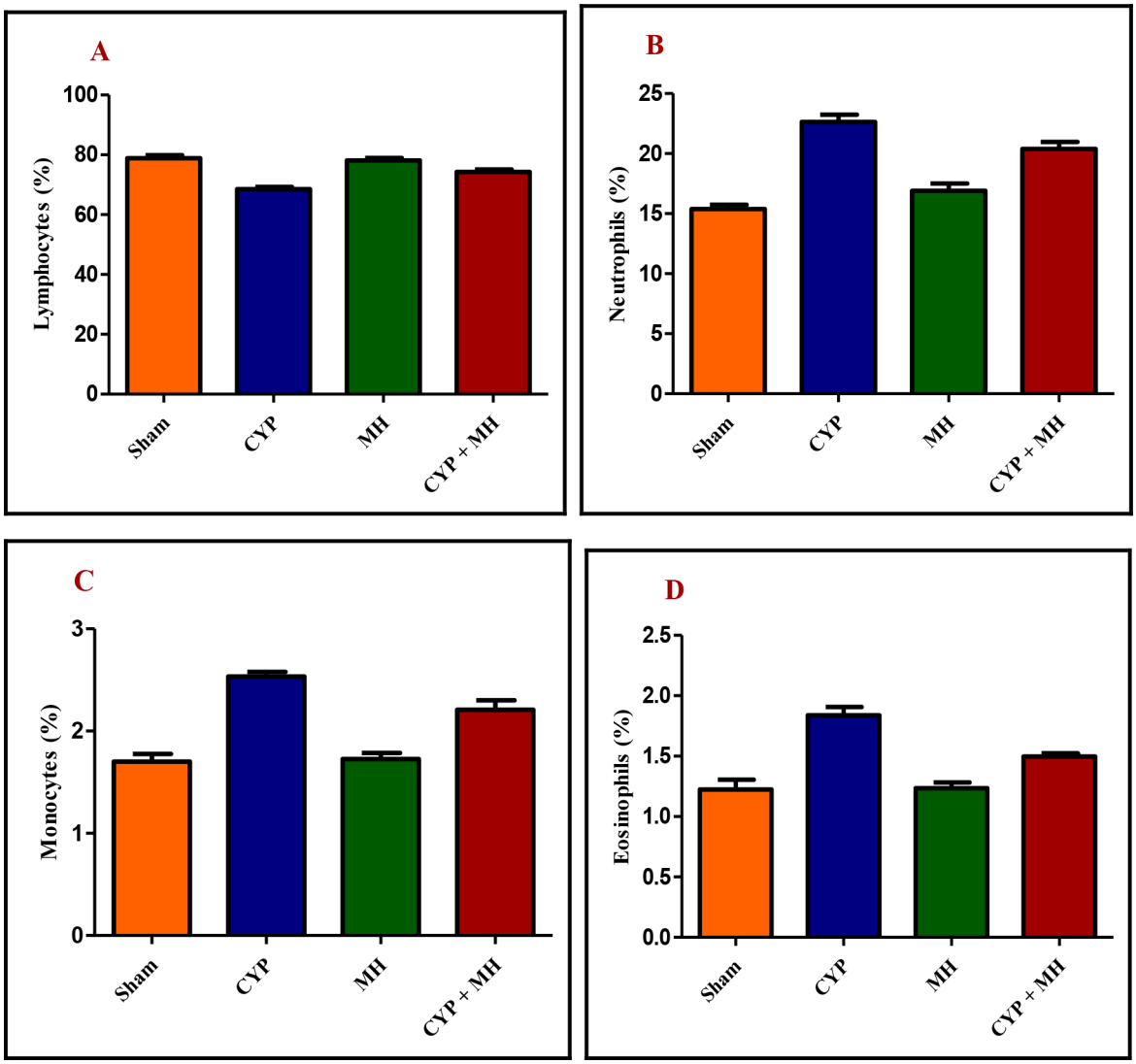


Figure 5. Effect of CYP and MH on Differential Leukocyte Count (DLC). **(A)** Lymphocytes count (%) in different groups, **(B)** Neutrophils count (%) in different groups, **(C)** Monocytes count (%) in different groups, **(D)** Eosinophils count (%) in different groups.

Table 5. Effect of MH on liver function markers in CYP intoxicated rats.

Group	AST (IU/L)	ALT(IU/L)	ALP(IU/L)	TP(g/dL)
1. Sham	39.37±1.90^{c}	34.51±1.37^{c}	52.37±1.88^{a}	6.55±**0.35**^{c}
2. CYP Control (CYP)	90.91±1.43^{a}	72.58±1.45^{a}	115.5±1.49^{c}	4.01 ± 0.29^{a}
3. Morin hydrate (MH)	41.47±2.39^{c}	36.15±1.50^{c}	54.03±2.36^{a}	6.97±0.26^{c}
4. CYP + MH	78.38±2.11^{b}	57.63±1.72^{b}	99.74±2.69^{b}	5.30±**0.23**^{b}

Values are expressed as mean ± SE (n=6); one-way analysis ANOVA with Duncan's post hoc test (SPSS). Means with different letters as superscripts differ significantly (P< 0.05).

lung and intestine of Group 2 align with previous findings, indicating suppression of antioxidant enzyme activity and lipid peroxidation[28,34,35]. In the CYP + MH treatment group, there was reduction in oxidative stress and enhancement of antioxidant defences because MH treatment decreases oxidative stress by increasing endogenous antioxidant enzymes such as SOD and GSH and lowering MDA levels[26,36,37].

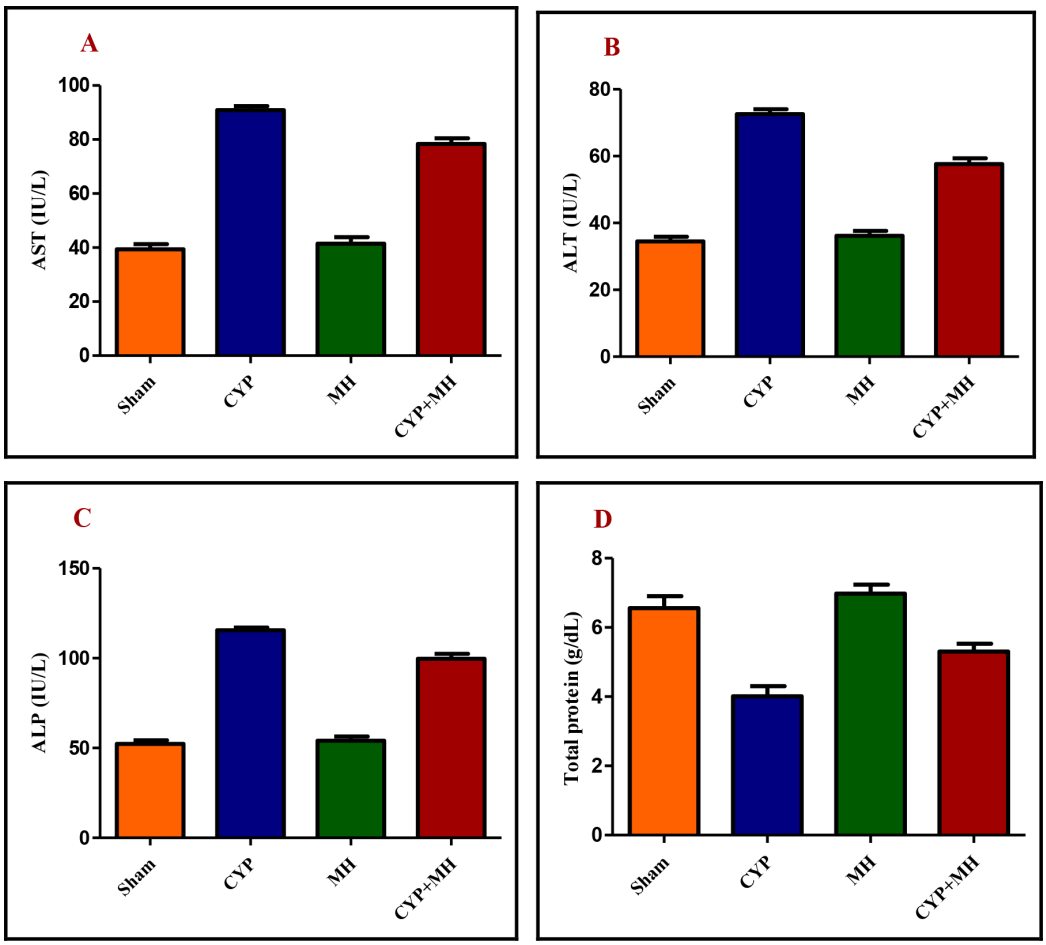


Figure 6. Effect of MH on liver function markers in CYP intoxicated rats. **(A)** Serum Aspartate transaminase (AST) activity (IU/L) in different groups, **(B)** Serum Alanine transaminase (ALT) activity (IU/L) in the different rat groups, **(C)** Serum Alkaline phosphatase (ALP) activity (IU/L) in the different rat groups, **(D)** Serum Total Protein (TP) concentration (g/dL) in the different rat groups.

Table 6. Effect of MH on Liver antioxidant parameters in CYP-intoxicated rats

Groups	SOD activity (U/mg protein)	GSH concentration (n moles/mg protein))	TBARS concentration (n moles/mg protein
1. Sham	11.68±**0.44**^{c}	11.35±**0.30**^{c}	3.88±**0.20**^{a}
2. CYP Control (CYP)	8.26±0.36^{a}	7.99±0.26^{a}	7.97±0.22^{c}
3. Morin hydrate (MH)	12.09±0.41^{c}	12.23±0.24^{c}	4.09±0.12^{a}
4. CYP + MH	10.02±0.12^{b}	9.31±0.15^{b}	6.71±0.16^{b}

Values are expressed as mean ± SE (n=6); one-way analysis ANOVA with Duncan's post hoc test (SPSS). Means with different letters as superscripts differ significantly (P< 0.05).

3.5 Histopathology

Examination of H and E-stained sections of the liver (Figure 10) showed normal architecture with normal hepatocytes, central vein, radiating hepatic cords, and uniform sinusoids in the control (Figure 10A) and MH supplemented rats (Figure 10B). The CYP intoxicated group showed pyknotic nuclei, marked central vein congestion, vacuolar degeneration, degenerated hepatocytes, marked MNC infiltration, congestion at sinusoidal spaces, and moderate hepatocyte necrosis (Figure 10C-E). In contrast, rats co-administered CYP

Table 7. Effect of MH on Lung antioxidant parameters in CYP-intoxicated rats

Groups	SOD activity (U/mg protein)	GSH concentration (n moles/mg protein))	TBARS concentration (n moles/mg protein
1. Sham	13.43±**0.52**^{a}	7.98±**0.25**^{a}	4.46±**0.14**^{a}
2. CYP Control (CYP)	6.51±0.34^{c}	4.63±0.31^{c}	7.04±0.17^{c}
3. Morin hydrate (MH)	13.04±0.36^{a}	8.16±0.17^{a}	4.65±0.16^{a}
4. CYP + MH	8.79±0.40^{b}	6.32±0.22^{b}	5.93±0.19^{b}

Values are expressed as mean ± SE (n=6); one-way analysis ANOVA with Duncan's post hoc test (SPSS). Means with different letters as superscripts differ significantly (P< 0.05).

Table 8. Effect of MH on intestinal antioxidant parameters in CYP-intoxicated rats

Groups	SOD activity (U/mg protein)	GSH concentration (n moles/mg protein))	TBARS concentration (n moles/mg protein
1. Sham	12.97±**0.45**^{a}	8.44±**0.32**^{a}	6.17±**0.21**^{a}
2. CYP Control (CYP)	8.12±0.41^{c}	3.86±0.28^{c}	11.13±0.29^{c}
3. Morin hydrate (MH)	13.18±0.33^{a}	9.18±0.25^{a}	6.32±0.16^{a}
4. CYP + MH	9.91 ±0.31^{b}	5.68±0.21^{b}	9.74±0.17^{b}

Values are expressed as mean ± SE (n=6); one-way analysis ANOVA with Duncan's post hoc test (SPSS). Means with different letters as superscripts differ significantly (P< 0.05).

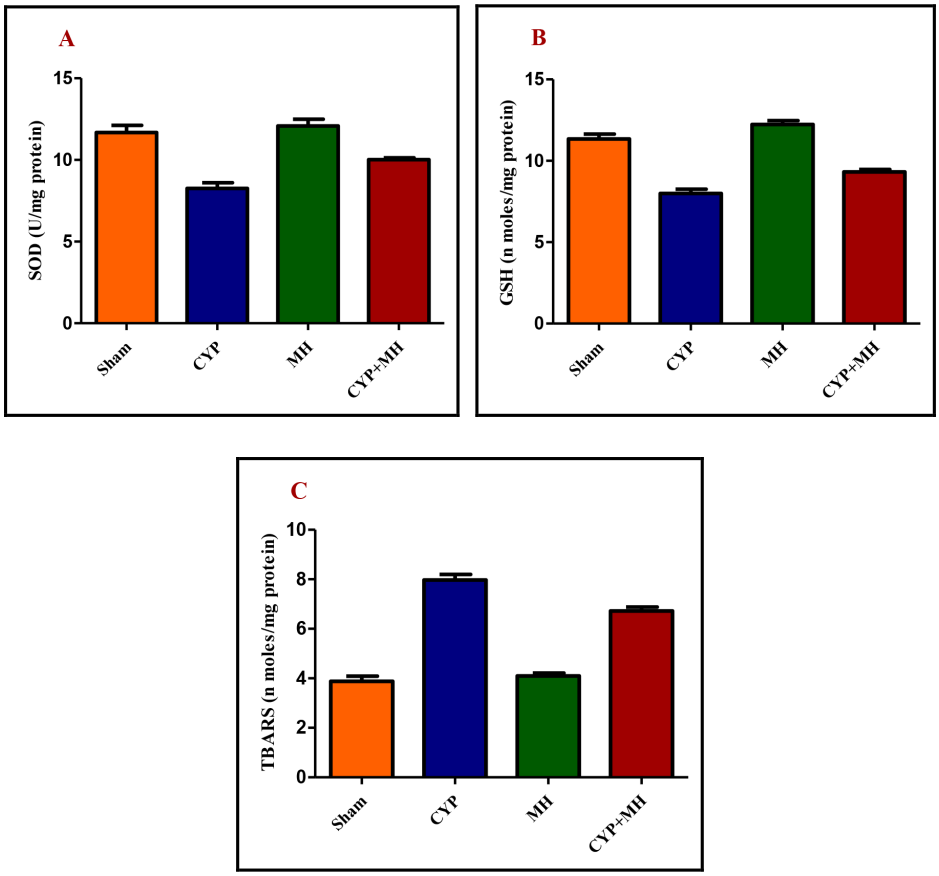


Figure 7. Effect of MH on Liver antioxidant parameters in CYP intoxicated rats. **(A)** SOD activity (U/mg protein) of liver, **(B)** GSH concentration in different groups of rats and **(C)** TBARS concentration in different groups of rats. Pre-treatment with MH significantly reduced TBARS level and increased SOD activity and GSH concentration compared to CYP treated group.

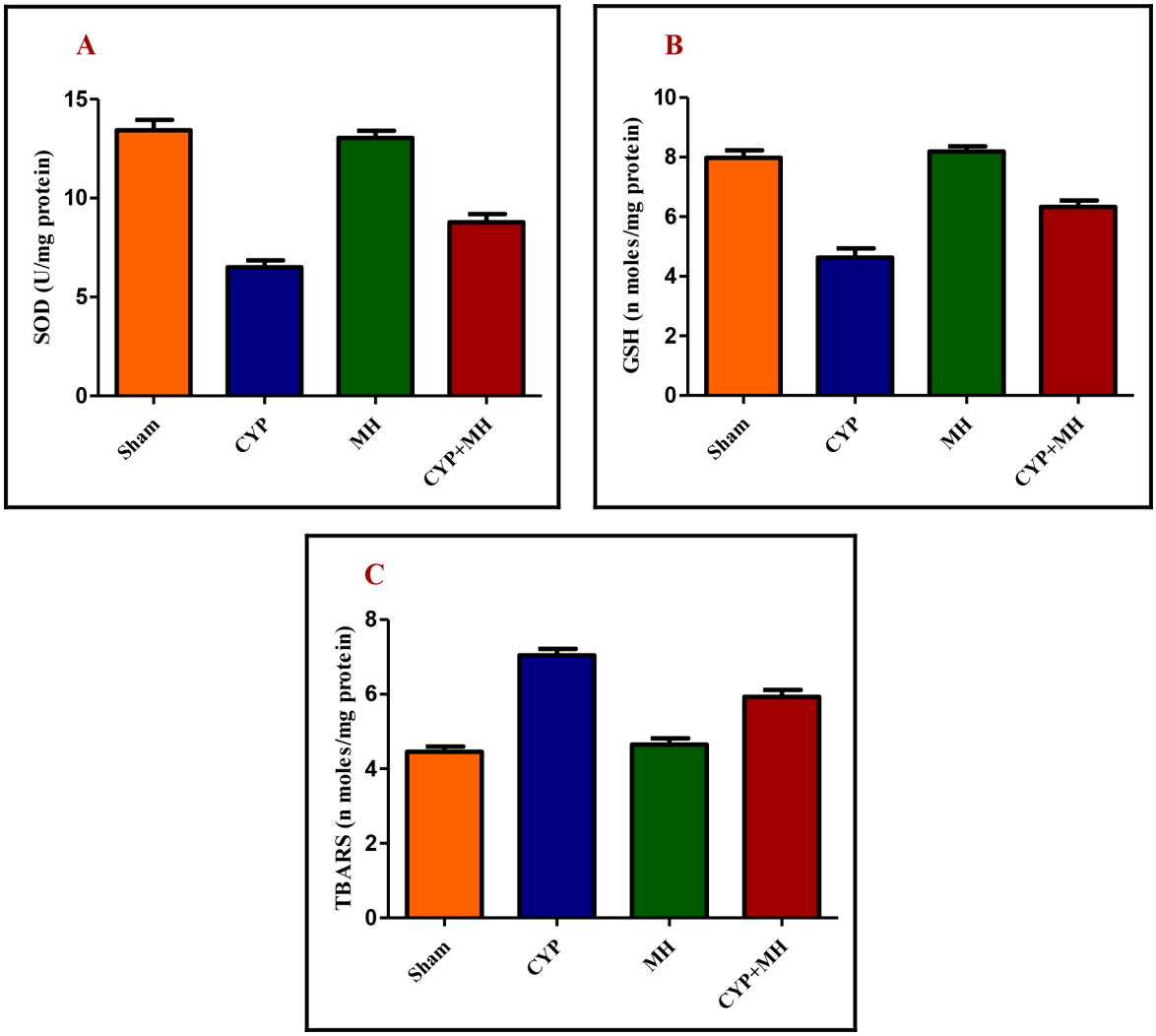


Figure 8. Effect of MH on Lung antioxidant parameters in CYP intoxicated rats. **(A)** SOD activity (U/mg protein) of lung, **(B)** GSH concentration in different groups of rats **(B)** and **(C)** TBARS concentration in different groups of rats. Pre-treatment with MH significantly reduced TBARS level and increased SOD activity and GSH concentration compared to CYP treated group.

+ MH exhibited remarkable amelioration of testis histology with mild central vein congestion, restored normal architecture of hepatocytes, mild sinusoidal dilatation, mild pyknotic nuclei, and few hepatocytes degeneration (Figure 10F). These alterations were in agreement with those reported in previous studies[26,38,39]. Treatment with MH in Group 4 restored the architecture of hepatocytes, mild congestion, reduced vacuolation and degeneration due to ROS-depleting capacity[40-42]. Liver sections from Groups 1 and 3 displayed normal hepatocyte architecture.

Lung sections (Figure 11) from the CYP-intoxicated group revealed marked congestion, infiltration of mononuclear cells, marked inflammation of alveoli, thickened interalveolar septa with alveolar damage, mild to moderate fibrous tissue proliferation and moderate hyperplasia of Type II pneumocytes (Figure 11C-E). In contrast, the CYP + MH treated group exhibited remarkable amelioration of lung histology with a reconstructive appearance of alveolar epithelium, normal alveolar septa, and mild MNC infiltration (Figure 11F). The histopathology of the lung tissue in the control group (Figure 11A) and MH-supplemented rats (Figure 11B) showed normal alveolar architecture and interalveolar septa. Histopathology of the lungs in Group 2 showed thickened interalveolar septa, marked thickening of alveolar septa, congestion, infiltration of mononuclear cells and moderate hyperplasia of Type II

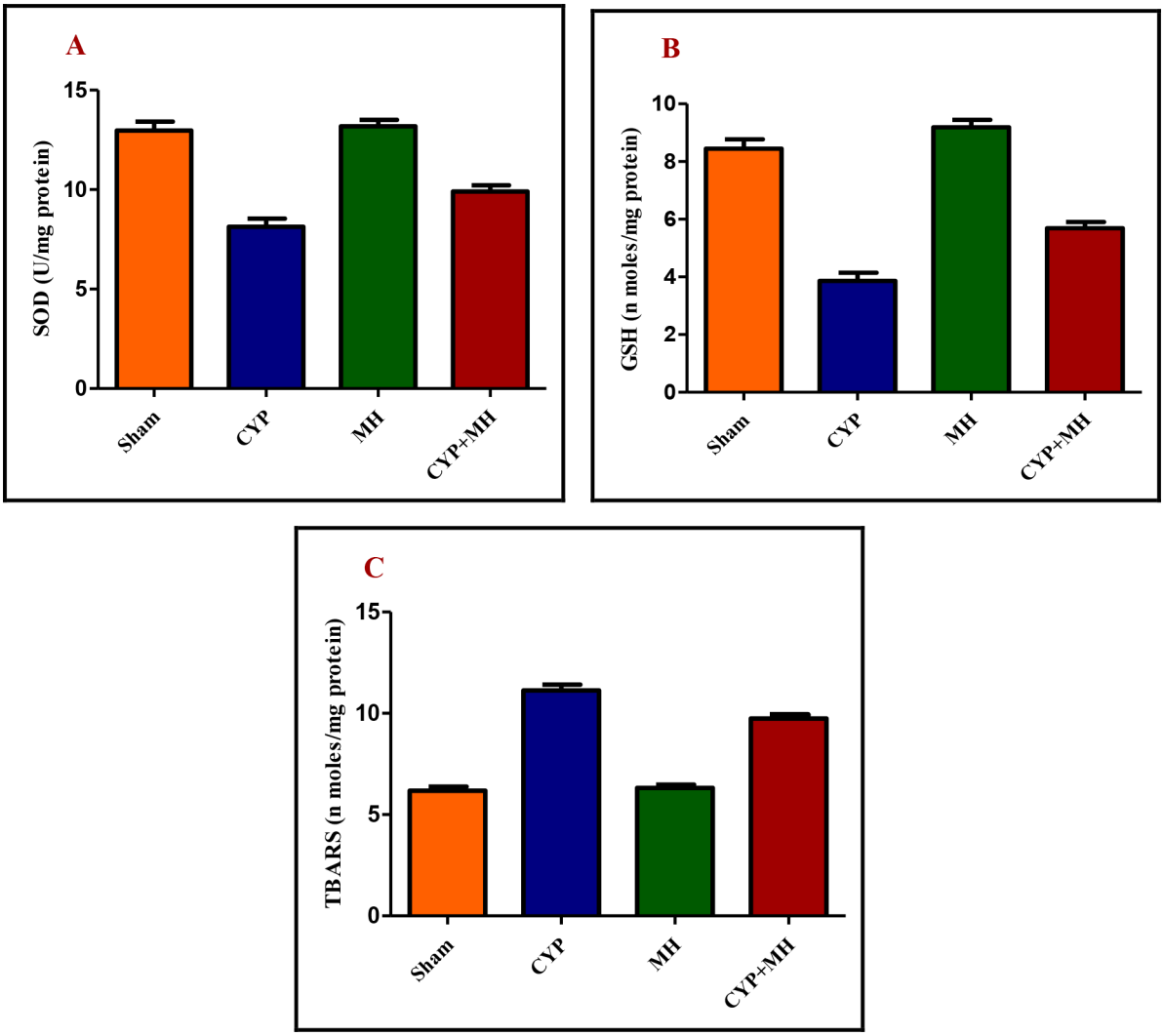


Figure 9. Effect of MH on Intestinal antioxidant parameters in CYP intoxicated rats. **(A)** SOD activity (U/mg protein) of intestine, **(B)** GSH concentration in different groups of rats and **(C)** TBARS concentration in different groups of rats. Pre-treatment with MH significantly reduced TBARS level and increased SOD activity and GSH concentration compared to CYP treated group.

pneumocytes[34,43,44]. These alterations in Group 4 may be due to reduced inflammation and suppression of oxidative damage in the lungs by MH[45].

Examination of H and E-stained sections of the intestine (Figure 12) revealed normal intestinal villi and epithelium in the control group (Figure 12A), and MH pre-treated group (Figure 12B). Histopathology of the intestine in the CYP-treated group showed loss of intestinal lining, marked mucosal ulceration, degenerated villi, blunt crypts, marked epithelial degeneration at the villi, and mononuclear cell infiltration with vacuolar degeneration (Figure 12C-E) compared to that in the control group. Intestine sections from the CYP+MH treatment group displayed restored intestinal morphology, mild vacuolar degeneration, and mild MNC infiltration (Figure 12F) compared with the CYP-intoxicated group. Pathological evaluation of the intestinal tissue in Group 2 showed that CYP led to severe mucosal ulceration, blunt crypts with mononuclear cell infiltration, thinning of the intestinal wall and damaged villi[46,47]. Intestine sections of MH-treated Group 4 revealed intact villi and crypts, restored epithelium, and reduced cellular infiltration. This explains the anti-inflammatory effects of MH on the intestine[48].

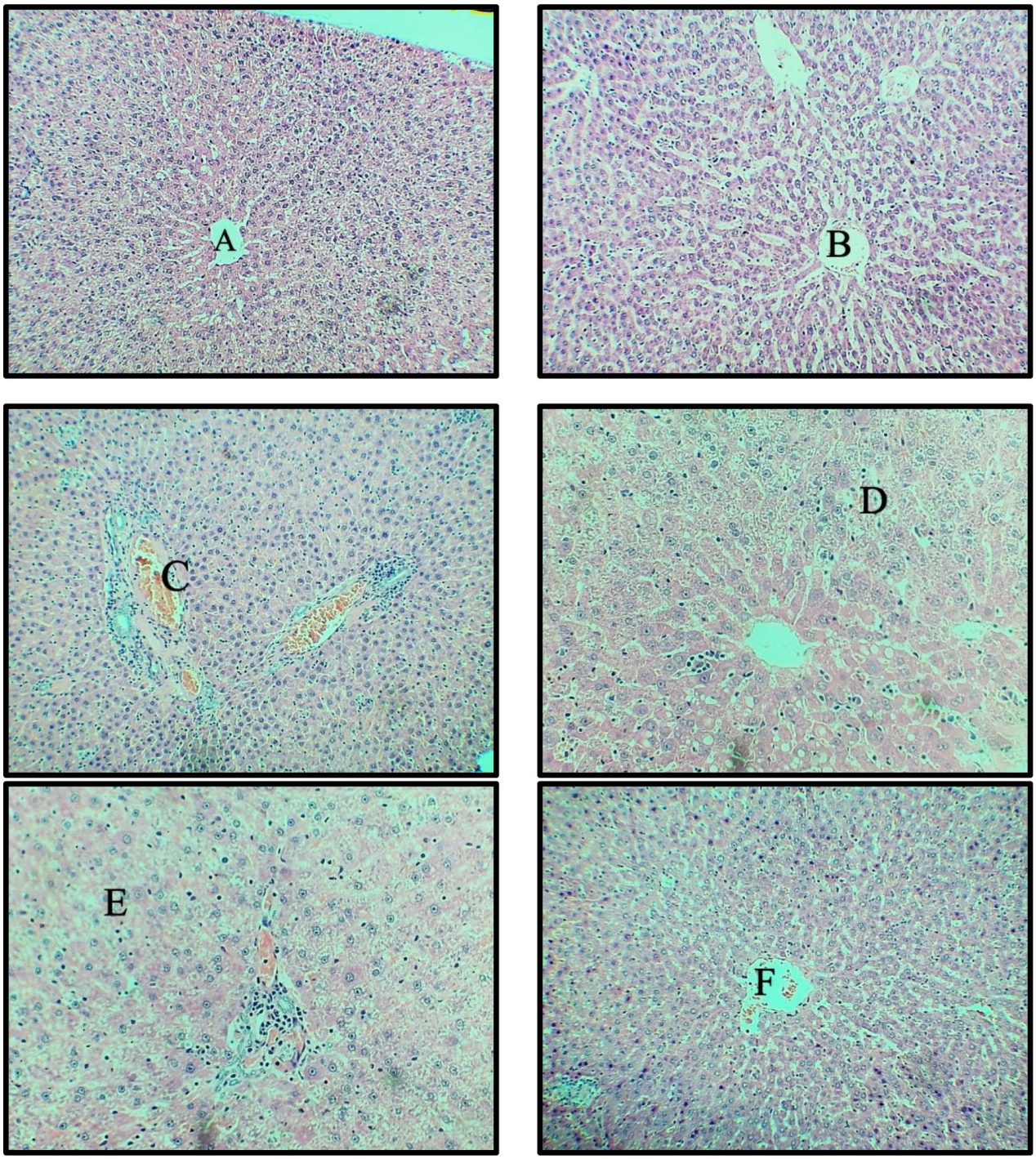


Figure 10. Histopathology of liver sections (H&E staining 100X). **(A)** Photomicrograph of liver showing normal architecture with normal hepatocytes, central vein, radiating hepatic cords, and uniform sinusoids in the control group, **(B)** MH receiving group showing normal architecture with radiating hepatic cords, **(C)** CYP receiving group showing moderate central vein congestion, pyknotic changes in hepatic nuclei and mononuclear cell infiltration, **(D)** marked hepatocyte degeneration, vacuolar degeneration, moderate central vein congestion, **(E)** marked MNC infiltration, pyknotic nuclei, congestion at sinusoidal spaces and moderate hepatocyte necrosis, and **(F)** the treatment group receiving CYP+MH showing restored normal architecture of hepatocytes, mild pyknotic nuclei and few hepatocyte degenerations.

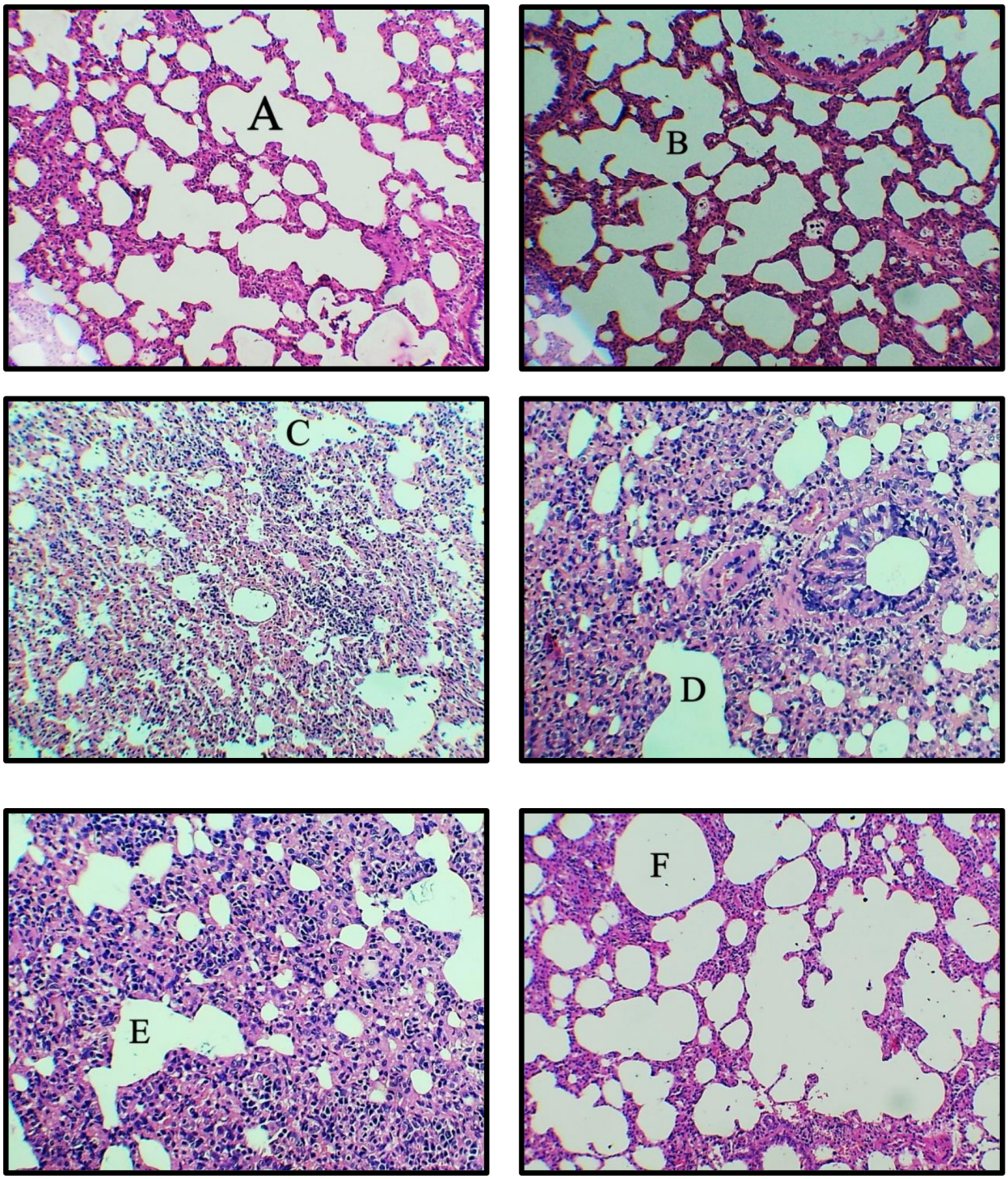


Figure 11. Histopathology of lung sections (H&E staining 100X). **(A)** Photomicrograph of the lung showing normal alveolar architecture and normal interalveolar septa, **(B)** MH receiving group showing normal alveolar architecture with normal interalveolar septa, **(C)** CYP receiving group showing marked inflammation of alveoli, thickened interalveolar septa with alveolar damage, **(D)** mild to moderate fibrous tissue proliferation with diffuse MNC infiltration and **(E)** moderate hyperplasia of type II pneumocytes with thickened alveolar septa, **(F)** treatment group receiving CYP+MH displayed a reconstructive appearance of alveolar epithelium and normal alveolar septa.

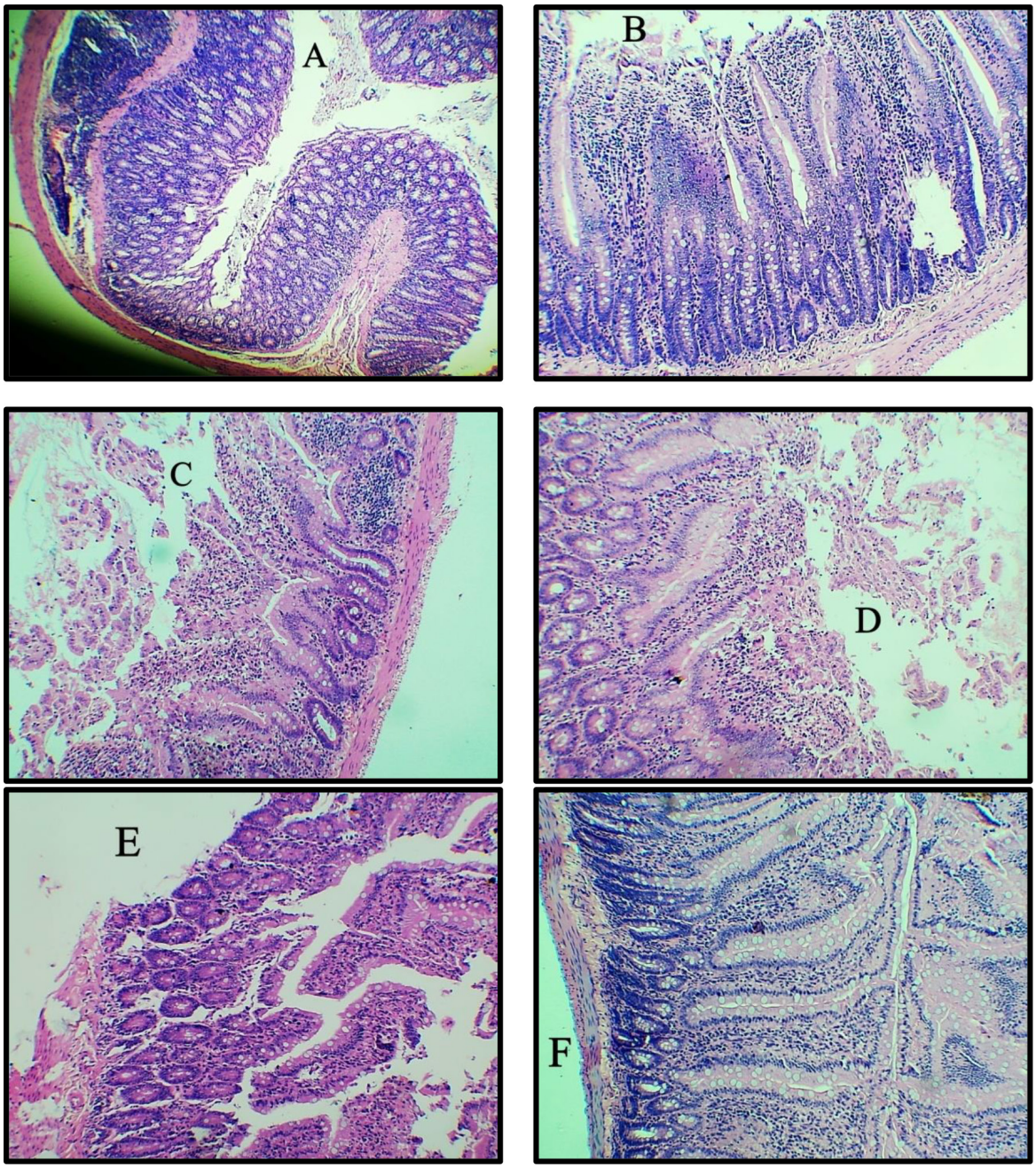


Figure 12. Histopathology of Intestine sections (H&E staining 100X). **(A)** Photomicrograph of intestine showing normal intestinal villi and epithelium, **(B)** MH receiving group showing normal morphology of intestine, **(C)** CYP receiving rat group showing marked ulceration in mucosa, blunt crypts with MNC infiltration, **(D)** marked epithelial degeneration at villi and mononuclear cell infiltration with vacuolar degeneration **(E)** marked thinning of the intestinal wall, loss of intestinal lining and MNC infiltration, **(F)** treatment group receiving CYP+MH showing mild vacuolar degeneration and mild MNC infiltration.

4. Conclusion

Considering the aforementioned observations, it can be inferred that repeated exposure to CYP results in organ damage through lipid peroxidation and excessive oxidative stress, leading to the production of Reactive Oxygen Species (ROS). These findings were further corroborated by modifications in the histopathology of the tissues. However, pretreatment with morin hydrate counteracted CYP-induced organ damage in rats, which may be

attributed to its antioxidant, anti-inflammatory and free radical scavenging properties. These findings suggest morin hydrate may have potential as a complementary therapy to reduce chemotherapy-related side effects.

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6. Authors Contribution

Conceptualization, P.S.K, M.U.R. and B.R.; methodology, A.R.K., H.P. and A.A.R.; software, A.R.K; validation, P.S.K. and M.K.; formal analysis, A.R.K. and A.A.R.; investigation, A.R.K. and H.P.; resources, P.S.K., M.U.R., B.R. and A.R.K; data curation, A.R.K and A.A.K.; writing-original draft preparation, A.R.K and P.S.K; writing-review and editing P.S.K; visualization, A.R.K and H.P.; supervision, P.S.K, M.U.R. and B.R. All authors have read and agreed to the published version of the manuscript.

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