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RESEARCH ARTICLE

Combretol Mitigates Paclitaxel-Instigated Hepatotoxicity Via Counteracting Oxidative Stress, Apoptosis and Inflammation

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ABSTRACT

Paclitaxel (PTX) is one of the front-line chemotherapeutic drugs that exhibit anti-cancer effects against different types of tumors. On the other hand, it has the tendency to disrupt normal functioning of non-targeted organs including liver. Combretol (CBT) is a plant-based compound with potential medicinal properties. The present research investigated the ameliorative potential of CBT against PTX provoked hepatic injury in albino rats. Thirty-two rats were divided into four equal groups (n=8) including, control, PTX (7.5mg/kg) treated, PTX + CBT (7.5mg/kg + 20mg/kg) co-treated and CBT (20mg/kg). The trial was conducted for 28 days and upon completion of the trial, the results showed that PTX exhibited significant deleterious impacts on hepatic tissues. PTX administration increased the levels of inflammatory markers (NF-κB, TNF-α, IL-6, IL-1β and COX-2), pro-apoptotic markers (Bax, Caspase-3, and Caspase-9), hepatic function indices (AST, ALP and ALT) and oxidative stress markers (MDA and ROS). Moreover, PTX provision compromised the integrity of hepatic tissues via inducing histological anomalies and reducing the level of anti-apoptotic marker (Bcl-2). Moreover, the activities of antioxidant enzymes (SOD, GST, GPx, GSR, CAT) and GSH contents were reduced following PTX administration. However, CBT supplementation protected the hepatic tissues from PTX-provoked disruptions due to its antioxidant, anti-apoptotic, anti-inflammatory, and hepatoprotective properties.

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INTRODUCTION

Cancer is a multifactorial disease characterized by intricate interactions between genetic mutations, metabolic reprogramming, epigenetic modifications, immune evasion and environmental influences that collectively drive malignant transformation and progression. It is regarded as one of the most frequently occurring chronic diseases and it has led to the highest number of mortalities after cardiovascular diseases (Nisari *et al.,* 2019). Recent investigations have reported that cancer is a predominant cause of death in the economically advanced countries (Dagenais *et al.,* 2020; Yusuf *et al.,* 2020). Chemotherapy is one of the most common techniques for the treatment of cancer. Chemotherapeutic drugs are normally administered orally or intravenously. These drugs enter the circulatory system and spread throughout the body where they affect tumor cells that have produced malignancies in different body parts (American Cancer Society, 2025). Paclitaxel (PTX) is a natural anticancer drug which is isolated from the bark of *Taxus brevifolia*, commonly known as western yew or pacific yew (Xue *et al.,* 2013). It is an effective drug for cancer treatment that is used to treat various tumor types including lung, breast, colon, ovarian, head, neck, bladder and esophageal cancer (Stage *et al.,* 2018; Zang and Kagan, 2018). PTX exhibits anti-tumor mode of action via arresting mitosis, promoting apoptosis and stabilizing microtubules (Wei *et al.,* 2017; Zang *et al.,* 2018; Zhao *et al.,* 2022).

The drawback of PTX usages is that it carries the risk of damaging the normal cells and tissues of the body. In addition to its application in human oncology, PTX is also used in veterinary medicine, especially in feline and canine oncology (Kim *et al.,* 2015; Chae *et al.,* 2022). Despite

being isolated from natural plant source, the pharmacokinetics of PTX involves extensive hepatic metabolism, primarily by CYP2C8 and CYP3A enzymes, thereby leading to the production of reactive oxygen species (ROS) and systemic organ toxicity (Bajpai *et al.,* 2014; Wang *et al.,* 2024). PTX is reported to induce multi-organ toxicity including testicular (Ileriturk *et al.,* 2023), renal (Biswas *et al.,* 2025), cardiac (Aktas *et al.,* 2024a) and hepatic (Yakut *et al.,* 2024) toxicity. Liver is highly vulnerable to PTX instigated damages as it receives 80% of blood via gastrointestinal tract and it metabolizes and detoxifies the drugs (Xie *et al.,* 2015). It has been reported that, PTX damages the different organs of the body including liver, via increasing the generation of ROS and inducing apoptosis as well as inflammation (Gur and Bilgic, 2023; Ileriturk *et al.,* 2023). Moreover, PTX induces hepatic damage and increases the levels of hepatic function markers i.e., ALT, AST and ALP, in blood (Gur *et al.,* 2022). Furthermore, PTX is also reported to induce histopathological damages in hepatic tissues via causing micro-vesicular steatosis, mononuclear cell infiltration and sinusoidal dilatations (Gur and Bilgic, 2023).

In recent years, antioxidant therapy using flavonoids has become popular in the treatment of drug-induced organ toxicities due to its ability to mitigate oxidative stress and inflammation (Ali *et al.,* 2023; Çomaklı *et al.,* 2023). Plant-based polyphenolic compounds, such as flavonoids, are a rich source of antioxidants that are reported to exhibit excellent therapeutic activities (Abeyrathne *et al.,* 2022; Ketnawa *et al.,* 2022). 5-Hydroxy-3,3′,4′,5′,7-pentamethoxyflavone or combretol (CBT) is a flavonoid which is obtained from *Rhodomyrtus tomentosa* (Fahmi *et al.,* 2004) and *Cassipourea madagascariensis* (Chaturvedula *et al.,* 2006). CBT exhibits antimicrobial and anti-parasitic activities (Kennedy *et al.,* 2011). In the current research, it was hypothesized that CBT may exhibit significant antioxidant and anti-inflammatory potentials. Multiple flavonoids, including quercetin and hesperidin, have been extensively studied for their hepatoprotective effects in chemical induced liver injury models. However, CBT has received comparatively less attention than other flavonoids despite possessing potential therapeutic properties. To the best of our knowledge, this is the first study that investigated the hepatoprotective effect of CBT against PTX induced toxicity. Therefore, the current research was formulated to understand the protective role of CBT against PTX-instigated hepatotoxicity.

MATERIALS AND METHODS

Chemicals: PTX (Paclitaxel AqVida, 300mg/50ml) was brought from AqVida GmbH (Hamburg, Germany) while CBT was procured from MedChemExpress (New Jersey, USA).

Animals and treatments: Thirty-two adult albino Wistar rats of 180-220g weight and aged between 6 to 8 weeks, were kept in rodent cages. They were provided with optimum laboratory conditions i.e., 12-hour light/dark cycle, 55 to 60% humidity, and 22 to 25°C temperature. A balanced diet for rodents along with tap water was provided throughout the research. Animals were handled as per ARRIVE guidelines regarding animal research (Percie du Sert *et al.,* 2020). A total of four groups, each containing an equal number of rats, were formed and each group underwent a separate regimen as provided below:

Group I served as experimental control and received intraperitoneal (*ip*) injections of 0.9% saline once a week. Moreover, 0.5% carboxymethylcellulose (CMC) was administered through oral gavage on daily basis.

Group II received *ip* injections of PTX (7.5mg/kg) mixed in 0.9% saline once a week. Moreover, 0.5% CMC was also administered to this group via oral gavage on daily basis.

Group III was subjected to co-treatment of PTX and CBT. It received *ip* injections of PTX (7.5mg/kg) mixed in 0.9% saline once a week. Furthermore, CBT (20mg/kg/day) was given orally with 0.5% CMC which served as a vehicle.

Group IV was given CBT (20mg/kg/day) mixed with 0.5% CMC through oral administration. Meanwhile, *ip* injections of 0.9% saline were also administered once a week.

After 28-days of experiment, the rats were anesthetized using *ip* injections of ketamine (60mg/kg) and xylazine (6mg/kg). Once full anesthesia was confirmed, the animals were euthanized via decapitation. Blood samples were taken using heparin syringes. Liver was excised from the body of animals and cut into 2 parts. One part of each liver was preserved for histopathological analysis while the other part was stored at -20°C for biochemical analysis.

Assessment of hepatic antioxidant and oxidative stress markers: MDA and ROS levels were determined via the methodologies of Ohkawa *et al.* (1979) and Hayashi *et al.* (2007), respectively. The activities of SOD and CAT were assessed via the methodologies of Kakkar *et al.* (1984) and Aebi (1984), respectively. Moreover, GSR activity and GSH contents were measured as per research of Carlberg and Mannervik (1975) and Moron *et al.* (1979), respectively. Additionally, the activities of GST and GPx were assessed via the techniques of Younis *et al.* (2016) and Lawrence and Burk (1976), respectively.

Assessment of hepatic serum indices: The levels of ALT (Cat number: ELK2683) ALP (Cat Number: ELK5635) and AST (Cat number: ELK5657) were assessed via rat ELISA kits (ELK Biotechnology CO., Ltd., Texas, USA). The guidelines given by the manufacturer were strictly followed during the assessment. All the samples were run in triplicate and mean values were used for statistical analysis.

Assessment of hepatic inflammation markers: The levels of IL-1β (Cat number: ELK1272), COX-2 (Cat number: ELK7718), TNF-α (Cat number: ELK1396), IL-6 (Cat number: ELK1158), and NF-κB (Cat number: ELK1693) were determined via rat ELISA kits (ELK Biotechnology CO., Ltd., Texas, USA). The instructions given by the manufacturer were strictly followed during the assessment. All the samples were run in triplicate and mean values were used for statistical analysis.

Assessment of hepatic apoptotic markers: The levels of Bax (Cat number: ELK5698), caspase-9 (Cat number: ELK1531), Bcl-2 (Cat number: ELK9198) and Caspase-3 (Cat Number: ELK1528) were determined via rat ELISA

kits (ELK Biotechnology CO., Ltd., Texas, USA). The instructions given by the manufacturer were strictly followed during the assessment. All the samples were run in triplicate and mean values were used for statistical analysis.

Histopathological analysis: Liver samples were excised from the rats and put in 10% formalin for 24h. Then they were dehydrated in increasing grades of ethanol. Ultimately, tissues were put in paraffin wax and cut into 4-5µm thick sections using a rotatory microtome. The specimens were mounted on the slides and stained with H&E. Subsequently, the changes in histology were observed at 400X using a compound microscope (de Menezes *et al.,* 2019).

Statistical analysis: Data was analyzed using Minitab software and presented as Mean±SE. Normality of the data was determined using Shapiro-Wilk test, while the homogeneity of variances was calculated using Levene test. Obtained data was estimated using one-way ANOVA followed by Tukey's test for the comparisons among group. The difference in Mean±SE values with ($P<0.05$) was considered significant.

RESULTS

Effect of PTX and CBT on biochemical profile: PTX administration significantly ($P<0.05$) increased MDA and ROS concentrations while decreasing the activities of antioxidant enzyme, as compared to the control. However, PTX + CBT co-administration remarkably ($P<0.05$) increased the activities of antioxidant enzymes and suppressed MDA and ROS concentrations, as compared to PTX group. Nonetheless, only CBT supplemented group showed non-significant variations as compared to the control (Table 1).

Table 1: Impact of PTX and CBT on biochemical parameters

PARAMETERS	GROUPS			
	Control	PTX	PTX+CBT	CBT
CAT (Umg^{-1} protein)	24.04 ± 0.90^{a}	9.69 ± 0.844^{c}	19.50 ± 0.53^{b}	25.28 ± 0.62^{a}
SOD (Umg^{-1} protein)	18.43 ± 1.19^{a}	8.55 ± 0.89^{b}	15.82 ± 1.18^{a}	19.48 ± 1.30^{a}
GPx (Umg^{-1} protein)	31.67 ± 0.83^{a}	12.70 ± 0.86^{c}	26.17 ± 0.82^{b}	32.65 ± 0.96^{a}
GSR (nM NADPH oxidized/min/mg tissue)	13.81 ± 0.83^{a}	5.76 ± 0.37^{b}	11.44 ± 0.99^{a}	14.65 ± 1.13^{a}
GST (nM/min/mg protein)	38.68 ± 0.90^{a}	18.78 ± 0.99^{c}	33.53 ± 0.99^{b}	40.04 ± 0.87^{a}
GSH (µM/g tissue)	26.91 ± 0.48^{ab}	16.60 ± 0.71^{c}	24.45 ± 0.53^{b}	28.12 ± 0.96^{a}
ROS (Umg^{-1} tissue)	1.39 ± 0.21^{b}	7.65 ± 0.36^{a}	2.04 ± 0.27^{b}	1.27 ± 0.24^{b}
MDA (nmol/mg protein)	0.61 ± 0.27^{c}	4.92 ± 0.24^{a}	1.92 ± 0.19^{b}	0.52 ± 0.30^{c}

*Different superscripts show that the values are significantly ($P<0.05$) different.

Effect of PTX and CBT on hepatic function enzymes: PTX administration substantially ($P<0.05$) increased the levels of hepatic function markers, as compared to the control. Nonetheless, the co-supplementation of CBT and PTX significantly ($P<0.05$) reduced the levels of hepatic markers, as compared to PTX-administered group. The downregulation in the levels of hepatic enzymes demonstrated the protective potential of CBT. However, these levels of hepatic markers were almost similar in the control and CBT group (Table 2).

Table 2: Impact of PTX and CBT on hepatic markers

PARAMETERS	GROUPS			
	Control	PTX	PTX+CBT	CBT
ALT (U/L)	56.61 ± 1.46^{c}	131.63 ± 1.19^{a}	65.91 ± 1.35^{b}	55.08 ± 0.97^{c}
AST (U/L)	79.21 ± 1.04^{c}	280.05 ± 3.39^{a}	143.14 ± 3.06^{b}	77.94 ± 1.26^{c}
ALP (U/L)	99.55 ± 2.45^{c}	331.73 ± 4.97^{a}	180.91 ± 1.46^{b}	96.83 ± 2.79^{c}

* Different superscripts show that the values are significantly ($P<0.05$) different.

Effect of PTX and CBT on inflammatory markers: PTX administration notably ($P<0.05$) increased the levels of inflammatory markers, as compared to the control. Nevertheless, CBT and PTX co-treatment markedly ($P<0.05$) lowered the levels of these biomarkers, as compared to PTX treated group. Nonetheless, CBT only treatment exhibited the levels of these markers approximately similar to the control animals (Table 3).

Table 3: Impact of PTX and CBT on inflammatory markers

PARAMETERS	GROUPS			
	Control	PTX	PTX+CBT	CBT
NF-κB (ngg^{-1} tissue)	19.55 ± 2.11^{bc}	86.92 ± 2.62^{a}	28.43 ± 1.67^{b}	17.81 ± 2.45^{c}
TNF-α (ngg^{-1} tissue)	16.99 ± 1.44^{c}	81.57 ± 1.50^{a}	31.67 ± 1.58^{b}	15.87 ± 1.28^{c}
IL-1β (ngg^{-1} tissue)	13.37 ± 1.32^{c}	53.27 ± 2.08^{a}	20. 87 ± 1.51^{b}	12.72 ± 1.09^{c}
IL-6 (ngg^{-1} tissue)	10.10 ± 1.17^{c}	68.46 ± 1.60^{a}	16.51 ± 0.58^{b}	9.79 ± 1.19^{c}
COX-2 (ngg^{-1} tissue)	27.31 ± 1.83^{c}	73.83 ± 1.30^{a}	37.01 ± 2.47^{b}	25.77 ± 2.09^{c}

* Different superscripts show that the values are significantly ($P<0.05$) different.

Effect of PTX and CBT on apoptotic markers: PTX treatment markedly increased ($P<0.05$) Bax, Caspase-9 and Caspase-3 levels and lowered the level of Bcl-2, as compared to the control. Nonetheless, Caspase-9, Caspase-3 and Bax levels were remarkably ($P<0.05$) reduced, and Bcl-2 levels were elevated in the rats co-administered with PTX and CBT, as compared to PTX group. However, no significant differences were found in the levels of apoptotic markers in CBT and the control group. (Table 4).

Table 4: Impact of PTX and CBT on apoptotic indices

PARAMETERS	GROUPS			
	Control	PTX	PTX+CBT	CBT
Bax (pg/mL)	6.51 ± 0.74^{c}	32.88 ± 0.69^{a}	16.53 ± 1.06^{b}	5.98 ± 0.72^{c}
Caspase-3 (pg/mL)	5.29 ± 0.60^{c}	25.59 ± 1.06^{a}	13.25 ± 0.86^{b}	5.01 ± 0.66^{c}
Caspase-9 (pg/mL)	3.73 ± 0.45^{b}	14.87 ± 0.83^{a}	5.61 ± 0.61^{b}	3.57 ± 0.37^{b}
Bcl-2 (ng/mL)	18.39 ± 0.86^{a}	6.85 ± 0.75^{c}	14.55 ± 0.77^{b}	19.31 ± 0.91^{a}

* Different superscripts show that the values are significantly ($P<0.05$) different.

Effect of PTX and CBT on hepatic histopathology: Histopathological analysis revealed that morphology of hepatic tissues of the rats remained normal in both the control and CBT-only treated group. However, PTX administration notably induced liver damages such as hepatocyte membrane disruptions, sinusoidal dilations, pyknotic nuclei and various impairments in central venules of hepatic tissues, as compared to the control. However, the co-treatment of PTX + CBT markedly recovered these damages, as compared to PTX group (Fig. 1).

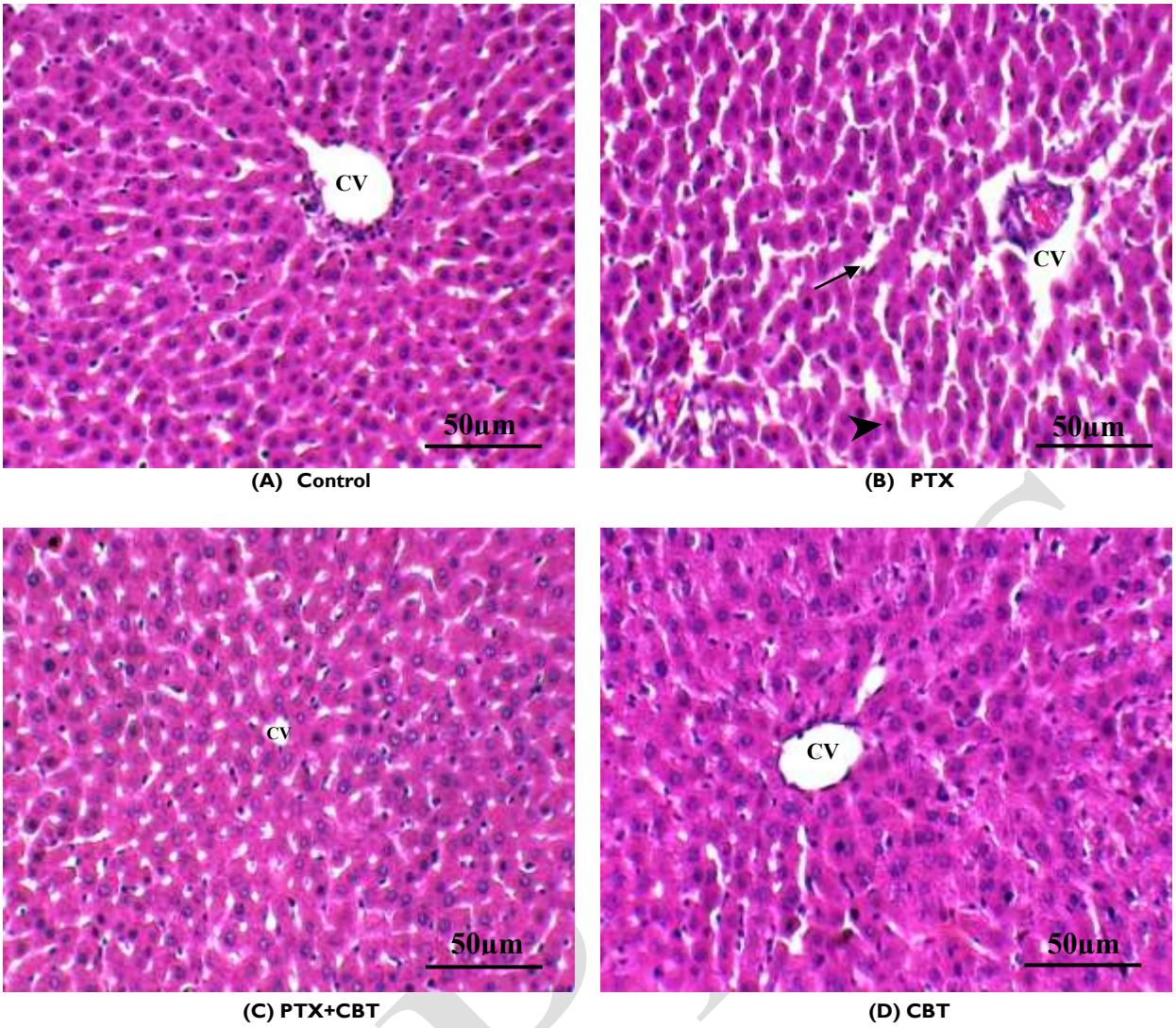

Fig. 1: Normal histological structure is observable in (A) Control and (D) CBT groups. (B) PTX group showing disrupted histology of hepatic tissues as evidenced by damaged central venule (CV), sinusoidal dilations (arrow), and pyknotic nuclei (arrowhead). (C) PTX + CBT co-treatment showing that CBT supplementation improved the histology of hepatic tissues.

DISCUSSION

PTX is used as an efficient drug in the treatment of metastatic lung, breast, and pancreatic cancer (Klein and Lehmann, 2021). However, PTX increases oxidative stress (OS), apoptosis and disrupts antioxidant defense system of the body, which are the major reasons of PTX induced damages (Aktas *et al.,* 2024b). Liver is a vital organ that performs multiple important functions in the body including immune system support, metabolism, homeostasis, xenobiotics breakdown and endocrine control (Trefts *et al.,* 2017). PTX is reported to compromise the integrity of hepatic tissues via disturbing histological structure and levels of hepatic enzymes (Gür and Bilgic, 2023). Plant-based compounds have been extensively used now-a-days due to their promising medicinal potential against chemical, drug or pollutant induced organ damage and toxicity. Zhang *et al.* (2019) reported that the concurrent supplementation of plant-based antioxidants protects the cells and tissues from the adverse effects of chemotherapy. Flavonoids are reported to possess excellent medicinal and health promoting properties (Zheng *et al.,* 2025). CBT belongs to flavonoid family; therefore, it was hypothesized in this investigation that CBT may mitigate PTX provoked hepatic damage.

It was revealed in our study that MDA and ROS levels were increased while the activities of antioxidant enzyme were reduced following PTX exposure. The increased concentration of ROS leads to the destruction of cellular biomolecules that ultimately result in oxidative stress (Liakopoulos *et al.,* 2017). Antioxidants (i.e., GPx, CAT, GSH, SOD, and GSR) are the potential agents that combat ROS (Liu *et al.,* 2021). Therefore, the supplementation of antioxidants from external sources enhances the internal defense system of the body (Chaudhary *et al.,* 2023). SOD accelerates the disproportion of superoxide ion (O^{2-}) into H_2O_2 and O_2. CAT breakdowns hydrogen peroxide into O_2 and H_2O (Mora-Esteves and Shin, 2013). Furthermore, GSH contents are regulated by GSR (Ali *et al.,* 2020). GSH is essential for the activity of GPx as it acts as a primary substrate and a crucial regulator. Moreover, GPx scavenges the ROS and safeguards the body from lipid peroxidation as well as regulates cellular homeostasis (Gupta *et al.,* 2007). Moreover, MDA is an indicator of lipid peroxidation and oxidative stress, as it is the terminal product of lipid peroxidation, specifically of

polyunsaturated fatty acids (Aksu *et al.,* 2017). The investigation of Ileriturk *et al.* (2023) affirmed our results and documented that PTX treatment may increase oxidative stress and lower the levels of antioxidant enzymes. However, CBT administration mitigated the deleterious impacts of PTX and improved the levels of antioxidants while reducing MDA and ROS levels. Moreover, similar antioxidative effects and ROS scavenging properties have been reported for other flavonoids i.e., silymarin (Gur and Bilgic, 2023) and chrysin (Çomaklı *et al.,* 2023) against PTX-induced oxidative stress. Our findings are aligned with these reports and further suggest that CBT shares a similar mechanistic profile.

The outcomes of the current trial showed that PTX administration markedly elevated the levels of hepatic function markers. ALT, AST and ALP are commonly assessed parameters from blood to determine the normal function of liver (Ulasoglu *et al.,* 2019). It is documented that severe oxidative stress damages the membranes of hepatic cells that lead to the increased levels of hepatic markers in blood (Al Saihati *et al.,* 2024). The results of our research are consistent with the study of Gur and Bilgic (2023), who documented that PTX administration could increase the levels of hepatic function markers in rat models probably due to the leakage of these markers from damaged cell membrane into the blood. Nonetheless, the co-supplementation of CBT protected the hepatic tissues from PTX provoked toxicity via reducing the levels of these hepatic markers. The decline in the levels of hepatic enzymes after CBT administration suggests that CBT prevents these enzymes from leaking in the blood by protecting cell membrane integrity due to its antioxidative effects. These outcomes are consistent with previous studies suggesting that the administration of antioxidants significantly lowers the levels of hepatic function markers and reduces PTX provoked damages (Gür and Bilgic, 2023; Yakut *et al.,* 2024).

In the current research, PTX substantially increased the levels of inflammatory markers in hepatic tissues. Chemotherapeutic drugs have been found to induce inflammation via activating NF-κB, which further triggers other inflammatory parameters (IL-6, TNF-α and IL-1β) (Famurewa *et al.,* 2020). In addition to these parameters, NF-κB also stimulates COX-2 enzyme that is linked with ROS generation and inflammatory response (Elshawi and Nabeel, 2019). Therefore, PTX provoked inflammatory response may result in hepatic dysfunction. Our outcomes are consistent with the study of Ileriturk *et al.* (2023), who documented that PTX treatment resulted in increased levels of inflammatory cytokines in testicular tissues. Nevertheless, CBT supplementation protected the hepatic tissues from PTX instigated inflammatory response due to its anti-inflammatory properties. Therefore, it may be deduced that CBT exhibits hepatoprotective effects similar to other reported flavonoids like vitexin (Ijaz *et al.,* 2021) and silymarin (Gur and Bilgic, 2023) and effectively lowers the level of inflammatory markers.

Our investigation revealed that PTX treatment elevated the levels of Capsase-3, Caspase-9 and Bax while reducing the Bcl-2 levels. Although, apoptosis removes the harmful, damaged and unnecessary cells of the body and regulates homeostasis (Guicciardi *et al.,* 2013), but it also damages the normal cells and induces cellular stress (Akcilar *et al.,* 2015). Bax and Bcl-2 are important proteins that regulate apoptosis. Bcl-2 inhibits apoptosis via blocking cytochrome (cyt)-C efflux from the pores of mitochondrial membrane while Bax facilitates apoptosis by increasing the outflux of cyt-C from the pores of mitochondrial membrane (Ghobrial *et al.,* 2005). Inside the cytosol, cyt-C activates Caspase-9 proenzymes which further cleaves as well as triggers Caspase-3. The induction of Caspase-3 results in the apoptotic response in the body (Ghobrial *et al.,* 2005; McIlwain *et al.,* 2013). These findings are supported by Çomaklı *et al.* (2023), who stated that PTX provision could provoke apoptotic response in the hepatic tissues. Nonetheless, the supplementation of CBT reduced the levels of pro-apoptotic markers and increased levels of anti-apoptotic marker. Thus, CBT protects the hepatocytes from apoptotic damage, an effect also observed with other reported flavonoids, including chrysin (Çomaklı *et al.,* 2023) and astragalin (Hamza *et al.,* 2023).

The histological assessment of hepatic tissues showed that PTX administration provoked significant damages in the tissues as evident by central venule impairments and sinusoid dilation. These results are parallel with the outcomes of antioxidant, apoptotic and inflammatory parameters, where significant disruptions were found after PTX administration. Previous investigations have shown that PTX treatment could reduce the numbers of hepatocytes (Sakin *et al.,* 2020). Research conducted by Gur and Bilgic (2023) also reported that PTX disturbed hepatic histology and caused mononuclear cell infiltration and sinusoidal dilatations. However, CBT co-supplementation along with PTX improved the hepatic histology of rats. This palliative property of CBT may be attributed to its anti-oxidant effects.

Conclusions: Our results evidenced that PTX exposure could lead to hepatotoxicity via increasing the levels of inflammatory, hepatic function, pro-apoptotic, and oxidative stress markers. Moreover, it also induced histopathological anomalies in hepatic tissues and reduced the levels of anti-apoptotic markers as well as the activities of antioxidant enzymes. Nonetheless, CBT supplementation protected the hepatic tissues from PTX-triggered disruptions due to its anti-oxidant, anti-apoptotic and anti-inflammatory properties.

Authors contribution: MUI, HA and MZS designed the experiment. MB, HN and MZS conducted the experiment. MB and HH performed statistical analyses. All authors participated in manuscript writing and approved the final draft.

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