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Evaluation of *Terminalia arjuna* in Comparison to Taurine against Experimental Hepatotoxicity due to Cisplatin in Rats

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ABSTRACT

Toxic effects of cisplatin (CP) and protective role of *Terminalia arjuna* (TA) and taurine were assessed on hepatic biomarkers using a total of 36 male *Wistar* albino rats that were grouped randomly into six groups (n=6). Group 1 acted as normal control. Groups 2, 5 and 6 were treated with CP @ 5 mg/kg b.wt, intraperitoneally on day 1 for cisplatin exposure. Thereafter, groups 3 and 5 were treated with TA @ 400 mg/kg b.wt. and groups 4, 6 with taurine @ 1000 mg/kg b.wt. orally for 14 days. Later rats were euthanized for histopathology of liver. Serum ALT was significantly ($P < 0.05$) increased in group 2. The tissue enzyme assays revealed a significant ($P < 0.05$) increase in TBARS and protein carbonyls and significant ($P < 0.05$) decrease in GSH in group 2 as compared to other groups. The concentration of cytokines showed a significant ($P < 0.05$) increase in TNF-*alpha* and IL-10 in group 2 when compared with group 1. Sections of liver tissue showed marked changes *i.e.,* central vein dilation with oedema, congestion and degenerative changes with pyknotic and condensed nuclei in few hepatocytes. The groups 5 and 6 treatedwith respective dose of TA and taurine showed mild to moderate improvement in all the parameters in comparison to group 2. It is concluded that supplementation of *Terminalia arjuna* and taurine was found beneficial in countering the toxic effects of cisplatin on liver.

HIGHLIGHTS

- *Terminalia arjuna* offers protection, have hepato-protective activity due to free radical scavenging and antioxidant property.
- Taurine has been shown to prevent cisplatin-mediated hepatic injuries by decreasing oxidative stress.

Keywords: Cisplatin, Hepatotoxicity, taurine and *Terminalia arjuna*

Cisplatin (CP) is platinum based antineoplastic drug has the highest cure rates over 90% in testicular cancers (Jadon *et al.,* 2019) and is used for treatment of numerous types of cancers including testicular, head and neck, ovarian, cervical and many other types of cancers (Ramya *et al.,* 2013). The mechanism of the anticancer activity of CP is not completely understood, but it has long been established that the mechanism involves DNA intra-strand cross link formation, altering the molecular conformation of the double helix leading to apoptosis (De Luca *et al.,* 2019). Although CP has been a main stay for cancer therapy, its use is mainly limited by two factors: acquired resistance to CP and adverse effects in normal tissues (Florea and Busselberg, 2011). The molecular mechanism of CP resistance has been studied extensively, which may involve decreased uptake or increased efflux of CP, neutralization of CP by glutathione and other sulfur-containing molecules, increased DNA repair and defective apoptotic signalling in response to DNA damage (Zhu *et al.,* 2016). The other major limiting factor in the use of CP is the deleterious effects in normal tissues, which include hepatotoxicity, ototoxicity, neurotoxicity, cardiotoxicity, gastrointestinal toxicity, nephrotoxicity and hemotoxicity

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(Okon *et al.,* 2020). For years, different approaches have been attempted to curtail these adverse effects. One of the strategies is to synthesize and screen for novel CP analogues that show decreased toxicity level in normal tissues. In this direction, several CP analogues, such as carboplatin, have been identified with less severe side effects (Manohar and Leung, 2018). Another approach that has been used with some success is to hydrate the patients during CP treatment (Horinouchi *et al.,* 2013). Despite these efforts, the side effects of CP, particularly hepatotoxicity, remain major threats that limit its use in cancer therapy.

Medicinal plants play a very important role in primary health-care system, from the ancient times. According to WHO, 60% of the world's population depends on herbal medicine and in developing countries, 80% of the population relies almost totally on medicinal plants for their primary health care needs (Khan and Ahmad, 2019).

Terminalia arjuna (TA) is an ayurvedic plant with important medicinal value. It is commonly known as Arjuna, which belongs to family Combretaceae. Medicinal properties of TA include antioxidant, hypotensive, anti-inflammatory, anti-carcinogenic and gastro-protective effects (Amalraj and Gopi, 2017). The aqueous extract of TA possesses protective action against hepatic dysfunction by antioxidant mechanism (Paarakh, 2010). The antioxidant, free radical scavenging and anti-inflammatory activity of TA will help in inhibition of oxidative stress produced by CP (Sherif, 2015).

Taurine is the major intracellular free ß-amino acid with diverse cytoprotective activity. It also acts as an antioxidant in a variety of *in vitro* and *in vivo* systems (Schaffer and Kim, 2018). Taurine appears to have multiple functions and plays an important role in many physiological processes, such as osmoregulation, immunomodulation and bile salt formation (Ginguay *et al*., 2016). Objectives of investigation are to study the hepatotoxicity due to cisplatin and to evaluate and compare hepatoprotective potential of *Terminalia arjuna* with taurine.

MATERIAL AND METHODS

Chemicals

All chemicals used in this work were of analytical grade and they are obtained from Qualigens Pvt. Ltd., Mumbai and SRL Pvt. Ltd., Mumbai, India.

Plant material and preparation of leaf extract

The fresh leaves of TA plant were collected from Hyderabad, India. The plant species was authenticated by Scientist, Agricultural College, Hyderabad, India. The fresh leaves of TA were washed 2 times with distilled water and shade dried at room temperature for 40 days. Leaves were powdered using a mechanical blender. Then, 1 gram of powder was mixed with 100 ml of boiled distilled water and stirred on hot plate for 10-15 min. After that process, extract was then filtered through Whatman No. 1 filter paper. The filtrate was kept at low temperature (4 °C) for further use (Raj *et al.,* 2020).

Animals and experimental design

Total thirty-six male *Wistar* rats aged about 10-12 weeks with an average body weight of 180 ± 10 grams were obtained from Vyas labs, Hyderabad. They were randomly divided into six equal groups (n=6) with different treatments (Table 1). The rats were housed in polypropylene cages, under controlled environmental conditions (20–22ºC) and 12 hour dark and light cycles with sterilized dried, clean and autoclaved rice husk as bedding material, which was changed on alternate days. The animals were maintained with standard balanced diet and drinking water *ad libitum* throughout the experimental period. All the experimental procedures and protocols used in this work were reviewed and approved by the Institutional Animal Ethical Committee (No.5/22/C.V.Sc., Hyd. IAEC- Rats/29.02.2020) and were in accordance with the guidelines of the CPCSEA.

Table 1: Experimental design of laboratory rats treated with cisplatin (5mg/kg), *Terminalia arjuna* (400mg/kg) and taurine (1000mg/kg)

Group	Treatment	No. of animals
1	Normal saline (0.25 ml) for 14 days.	6
2	Cisplatin @ 5 mg/kg body weight i.p, single dose on day 1.	6
3	Aqueous leaf extract *Terminalia arjuna* @ 400 mg/kg body weight peroral for 14 days.	6

4	Taurine @ 1000 mg/kg body weight orally for 14 days.	6
5	Cisplatin @ 5 mg/kg b.wt i.p on day 1 + Aqueous leaf extract of *Terminalia arjuna* @ 400 mg/kg b.wt peroral for 14 days.	6
6	Cisplatin @ 5 mg/kg b.wt i.p on day 1 + Taurine @ 1000 mg/kg b.wt orally for 14 days.	6

Blood collection

After completion of 14 days, blood samples were collected from retro-orbital plexus of experimental rats for assay of alanine transaminase (ALT). Later, the rats under study were euthanized by carbon dioxide exposure and liver tissues were collected immediately and kept in ice cold phosphate buffer. A small portion of the liver was homogenized with tissue homogenizer to make 10% homogenate to assay the reduced glutathione (GSH), thiobarbituric acid reacting substances (TBARS)/ malondialdehyde (MDA) and protein carbonyls. Pieces of liver tissues were immediately kept in 10% of formalin fixative to study histological alterations.

Antioxidant markers

GSH was estimated on the reaction of reduced glutathione (GSH) with 5-5' dithiobis-2-nitrobenzoic acid (DTNB) to give a compound that absorbs light at 412 nm. Malondialdehyde has been identified as the product of lipid peroxidation that reacts with thiobarbituric acid to give a red compound absorbing light maximally at 535 nm. Protein carbonyls were estimated based on the reaction of amino carbonyls with 2, 4-dinitrophenyl hydrazine to form hydrazones, which can be assessed using spectrophotometer at 372 nm.

Functional marker enzymes

ALT was analyzed by International Federation of Clinical Chemistry method at 340 nm and kits are from ERBA diagnostics Ltd., Surat, India.

Cytokine profile

The assay employs a quantitative sandwich enzyme immunoassay technique to measure TNF – *alpha* and IL-10. The ELISA kit was procured from Krishgen Bio systems, Mumbai.

Histology

For light microscopy examination, the formalin fixed liver tissues were dehydrated through ascending grades of alcohol, cleared in three changes of xylene and were embedded in paraffin. Liver sections each of four-micron thickness were cut and stained with H & E stain.

Statistical analysis

Data were subjected to statistical analysis by applying one-way analysis of variance using the statistical package for social sciences (SPSS; version 21). Differences between means were tested using Duncan's multiple comparison tests and significance was set at $P < 0.05$.

RESULTS AND DISCUSSION

The serum ALT activity (IU/L) was significantly ($P < 0.05$) increased in group 2 (68.13 ± 0.15) as compared to group 1 (36.27 ± 0.11). The treated groups 5 and 6 showed a significant ($P < 0.05$) decrease as compared to group 2 at the end of experiment. Groups 3 and 4 were comparable to group 1 (Table 2). Liver plays vital role in the detoxification process so it faces the threat of maximum exposure to xenobiotics and their metabolic by-products. The susceptibility of liver tissues to this stress due to exposure to CP is a function of the overall balance between the degree of oxidative stress and the antioxidant capability (Khan *et al.,* 2012). ALT is located in the cytoplasm and enters the circulation as a result of cellular damage. It is useful for evaluating the function and integrity of hepatocytes, and indicator of the serum about hepatic injury and cellular impairment following necrosis (Karale and Kamath, 2017). Co-administration of CP with TA and taurine (groups 5 and 6, respectively) has significantly reversed the changes recorded in serum ALT when compared to the cisplatin treated group 2.

The concentration of GSH (n moles/mg protein) in liver homogenate revealed a significant ($P < 0.05$) decrease in group 2 (20.09 ± 0.14) as compared to group 1 (40.98 ± 0.42). The treatment groups 5 and 6 showed a significant ($P < 0.05$) increase in GSH as compared to group 2 at the end of the study. The concentration of TBARS (n moles of MDA released/mg protein) in liver homogenate revealed a significant ($P < 0.05$) rise in group 2 (19.45 ± 0.11) as compared to group 1 (9.10 ± 0.07). The treated groups

Table 2: ALT (IU/L), GSH (nm/mg protein), TBARS (nm MDA released/mg protein), Protein carbonyls (nm/mg protein), TNF-*alpha* (pg/mg tissue) and IL-10 (pg/mg tissue) in different groups of rats

Group	ALT	GSH	TBARS	PC	TNF-alpha	IL-10
1. Normal Control	36.27 ± **0** .11 ^{d}	40.98 ± **0**.42 ^{a}	9.10 ± **0**.07 ^{c}	5.19 ± **0**.04 ^{c}	8.70 ± **0**.12 ^{d}	10.14 ± **0**.13 ^{c}
2.CP Control (5 mg/kg b.wt)	68.13 ± **0** .15 ^{a}	20.09 ± **0**.14 ^{d}	19.45 ± **0**.11 ^{a}	12.45 ± **0**.06 ^{a}	22.93 ± **0**.08 ^{a}	16.45 ± **0**.16 ^{a}
3. TA (400 mg/kg b.wt)	38.03 ± **0** .27 ^{c}	37.93 ± **0**.25 ^{b}	9.63 ± **0**.16 ^{c}	5.07 ± **0**.76 ^{c}	10.14 ± **0**.10 ^{c}	10.45 ± **0**.06 ^{c}
4. Taurine (1000 mg/kg b.wt)	37.74 ± **0** .22 ^{c}	38.17 ± **0**.19 ^{b}	9.76 ± **0**.25 ^{c}	5.74 ± **0**.08 ^{c}	10.01 ± **0**.11 ^{c}	10.29 ± **0**.27 ^{c}
5.CP (5 mg/kg b.wt) + TA (400 mg/kg b.wt)	41.22 ± **0**.25 ^{b}	32.09 ± **0**.18 ^{c}	12.76 ± **0**.19 ^{b}	7.99 ± **0**.12 ^{b}	12.78 ± **0**.14 ^{b}	12.71 ± **0**.10 ^{b}
6.CP (5 mg/kg b.wt)+ Taurine (1000 mg/kg b.wt)	41.09 ± **0**.13 ^{b}	32.32 ± **0**.13 ^{c}	12.46 ± **0**.45 ^{b}	7.84 ± **0**.13 ^{b}	12.84 ± **0**.09 ^{b}	12.52 ± **0**.21 ^{b}

Values are mean±SE (n=6); one way ANOVA. Means with different alphabets differ significantly (P <0.05).

5 and 6 showed a significant (P < 0.05) decrease in the concentration of TBARS as compared to group 2 at the end of the experiment. The concentration of protein carbonyls (n moles of carbonyl/mg protein) in liver homogenate revealed a significant (P< 0.05) rise in group 2 (12.45 ± 0.06) as compared to group 1 (5.19 ± 0.04). The treated groups 5 and 6 showed a significant (P < 0.05) decrease in the concentration of protein as compared to group 2 at the end of the experiment. Values of groups 3 and 4 were comparable to group 1 (Table 2). CP generates highly reactive free radicals such as superoxide and hydroxyl radicals, which can directly interact and modify many subcellular components including DNA, proteins, lipids and other macromolecules, and eventually causes cell death (Sahu *et al.,* 2014). Increase in the lipid peroxidation and protein carbonyls contributes to the elevation of free radicals. Glutathione, a strong antioxidant, moderates cellular damage that is related to increased production of reactive oxygen species (ROS) and modulates apoptosis (Karimi *et al.,* 2018). CP induced ROS and MDA (the final product of lipid peroxidation) are the best indices of oxidative stress (Sahu *et al.,* 2014).Formation of ROS by CP includes two main mechanisms in which the first is the hydrolysis of CP. The second mechanism implicated is mitochondrial dysfunction and increase in the ROS production via the disrupted respiratory chain (Dasari and Tchounwou, 2014). Un *et al.* (2020) reported that CP treatment significantly decreased liver CYP2E1 expression and induced hepatotoxicity in rats.CP treatment caused a significant increase in MDA levels in Karimi *et al*. (2018) study compared to the control group. Increased ROS production following CP treatment causes DNA and protein damage as well as lipid membrane oxidation (Waseem *et al.,*2014). MDA is a metabolite of lipid peroxidation, which is an oxidative stress marker. MDA is released because of the toxic effects of active oxygen radicals that would lead to break down of unsaturated fatty acids in the cell membrane (Bentli *et al.,* 2013). TA scavenges free radicals, stabilizes membrane permeability and prevents the release of enzymes into the serum (Pinar *et al.,* 2020).

In the present study, The TNF-*alpha* levels (pg/mg tissue) in liver homogenate revealed a significant (P < 0.05) increase in group 2 (22.93 ± 0.08) as compared to group 1 (8.70 ± 0.12). The treatment groups 5 and 6 showed a significant (P < 0.05) decrease in TNF-*alpha* levels as compared to group 2 at the end of the experiment. The IL-10 levels (pg/mg tissue) in liver homogenate showed a significant (P < 0.05) increase in group 2 (16.45 ± 0.16) as compared to group 1 (10.14 ± 0.13). The treatment groups 5 and 6 showed a significant (P < 0.05) decrease in IL-10 levels as compared to group 2 at the end of the experiment. Cytokines levels of groups 3 and 4 were comparable to group 1 without any significant difference (Table 2). A significant elevation in the concentration of TNF-α in CP administered rats was observed by Sahu *et al.* (2014). Oxidative stress, present in both ischemic and CP induced injury, is an activator of the NFκB transcription factor, which, in turn, promotes the production of pro-inflammatory cytokines, including TNF-α (Sahu *et al.,* 2014). Jamdade *et al.* (2016) reported that CP increased the expression of TNF-α, which is a pro-inflammatory cytokine involved in a variety of inflammatory responses, including

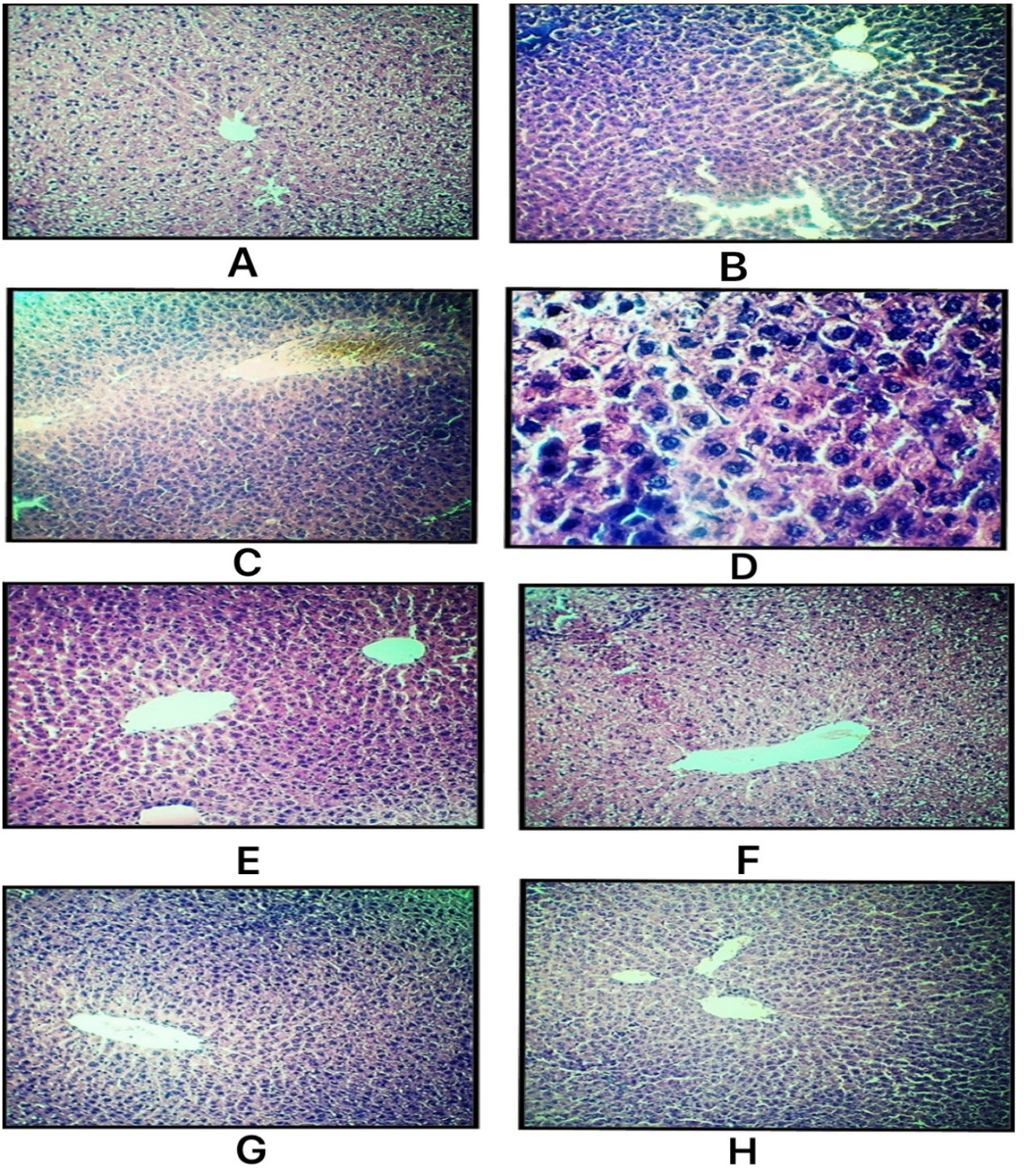

Fig. 1. The photomicrograph of A (H&E × 100) correspond to normal liver tissues in normal animal group. Photomicrograph of B (H&E × 100) showing dissolution of hepatic cords, C (H&E × 100) showing marked central vein dilation with moderate oedema, congestion and D (H&E × 400) showing pyknotic and condensed nuclei belongs to CP treated rats. The photomicrograph of E (H&E × 100) showing mild oedema, congestion and F (H&E × 100) showing mild elongation of central vein corresponds to TA treated animal group and G (H&E × 100) showing mild central vein congestion and H (H&E × 100) showing mild inflammation belongs to taurine treated animal group

differentiation, maturation and activation of inflammatory cells such as neutrophils, macrophages, T cells and natural killer cells. TNF-α is also able to stimulate the expression of other cytokines and chemokines. Concurrent with the induction of a stress-activated inflammatory response, many agents with anti-inflammatory properties (IL-10) are produced that may prevent tissue injury or help in tissue repair/remodelling in different organs and tissues. IL-10 is a multifunctional anti-inflammatory cytokine that has been reported to attenuate different tissue pathologies (Cure *et al.,* 2016). It was reported that the pro-inflammatory cytokines like TNF-α play an important role in the pathogenesis of a large number of liver diseases. TNF-α is released from the activated Kupffer cells. Following its release, it aggravates both the inflammatory response and oxidative stress in the hepatic cells (Yousef and Hussien, 2015).

HISTOLOGY

Light microscopic examination of the liver tissue in control rats of group 1 showed the normal histological structure (A) H&E × 100. Histological findings of liver tissue in rats of different experimental groups are depicted in fig. A to H. Rats treated with CP (group 2) showed severe histopathological alterations. The microscopic examination of liver tissue from group 2 showed dissolution of hepatic cords (arrow) and moderate degenerated hepatic cord arrangement (B) H&E × 100. Moderate to marked central vein dilation with moderate oedema (arrow), marked congestion (arrow head) and mild to moderate focal round cell infiltration (thin arrow) observed in group 2 (C) H&E × 100 and moderate to marked nuclear changes in hepatocytes includes pyknotic nuclei (thin arrow), condensed nuclei (arrow) were observed with the degenerated hepatocytes (arrow head) (D) H&E × 400. Focal degenerative and changes along with mononuclear cell infiltration were also evident. Similar findings were observed by Abdellatief *et al.* (2011) who noticed the administration of single dose of CP @ 5mg/kg b.wt in 10 days experimental period resulted in damage of liver tissue structure with disarrangement of hepatic strands. Whereas the treated groups showed mild oedema (thin arrow), mild mononuclear cell infiltration (arrow) (E) H&E × 100 and mild elongation of central vein (arrow) and mild focal infiltration of inflammatory cells (thin arrow) (F) H&E × 100 in group 5, normal radiating appearance of hepatic cords with mild central vein congestion (arrow) (G) H&E × 100 and mild inflammation (H) H&E × 100 in group 6. These restorative changes of hepatocytes might be due to TA and taurine treatment given during the experimental period.

CONCLUSION

Results of this study confirmed that CP at a dose of 5 mg/kg resulted in significant hepatotoxicity as evidenced by significantly increased levels of ALT, TBARS, protein carbonyls and cytokines and decreased levels of GSH. In addition, CP induced severe hepatic damages as shown in histo-pathological examination. In CP treated rats, there was a significant increase in the oxidative stress markers suggesting the liver damage. The present study concludes that aqueous extract of leaves of TA has hepatoprotective activity may be due to the presence of phytochemicals like flavonoids and glycosides, which act as antioxidants. This study demonstrated that treatment with aqueous extract of TA leaves and taurine significantly attenuated the physiological and histopathological alterations induced by CP.

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