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The Promising Role of the Potential Medical Benefits of Cannabidiol Derived from an Herbal Plant to Enhance the Hepatic Defense in Adult Male Rats

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Abstract

A critical natural chemical substance present in *Cannabis sativa* plants that may have therapeutic benefits is Cannabidiol or CBD. The inquiry was made to assess CBD's possible protection against liver injury. Fifty Sprague-Dawley male rats weighing (150±25g) were divided into five equal groups. Group I received distilled water orally, while Group II received an intraperitoneal injection of Doxorubicin (18 mg/kg bwt). Group III received CBD orally, while Group IV received 1 ml of CBD (26 mg/kg bwt) and Group V received Trimetazidine (10 mg/kg bwt), in addition to a single dose of Doxorubicin (18 mg/kg bwt) on the 11th day for both groups (IV, V). The results revealed that the administration of CBD (26 mg/kg bwt) demonstrated a significant improvement in lowering liver enzyme activity (ALT and AST), as well as an impact on decreasing tumor necrosis factor-alpha (TNF- α), interleukin 6 (IL-6), and MDA in liver tissue linked to liver histopathology results, resulting in an increase in serum levels of albumin, total protein, and oxidative stress parameters (SOD and GSH) in rats. In conclusion, Cannabidiol's potential protective properties may be due to its anti-inflammatory and antioxidant properties. Thus, CBD-derived compounds have long saved interest as a cure for a broad choice of hepatic disorders .

KEYWORDS
Cannabidiol, Liver injury, Doxorubicin, Trimetazidine, Tumor necrosis factor alpha (TNF-α).

INTRODUCTION

Liver disease is a prominent pathological ailment that can be slackened down in its preliminary stages without proper clinical control of fibrosis. Advanced liver injury may clue to cirrhosis and eventually to liver failure or major liver cancer, which are permanent conditions. To cure fibrotic injury to the liver, its premature phases should be the focus of consideration. Some increments and complementary and alternative medicine rate a specific mention, as a result of their already standard natural technique of healing and long-lasting beneficial effects (Rabia and Sahar, 2021).

Doxorubicin is one of the anthracycline groups of chemotherapy, unique of the greatest commonly used and effectual methods for handling hematological malignancies, compact tumors, and lymphoma (Van der Zanden *et al*., 2021; Johnson-Arbor and Dubey, 2022). The critical mechanism of doxorubicin comprises creating oxidation and impeding topoisomerase II in cancer cells, although, oppositely, it is lethal to numerous organs, comprising the heart (Li *et al*., 2021). The liver is unique to the organs artificial by doxorubicin injuriousness (Ikewuchi *et al*., 2021).

Herbal increments are used globally for causes such as treating various disorders, performance augmentations, or fitness maintenance (Hassen *et al*., 2022). *Cannabis sativa* L. (*Cannabis*) and its bioactive combinations, comprising cannabinoids and non-cannabinoids, have been broadly studied for their biological properties in the latest decades. Cannabidiol (CBD), a key non-intoxicating cannabinoid in *Cannabis*, has arisen as a promising mediator for cancer research. Cannabidiol (CBD) has been precluding growing interest in medicine due to its healing properties and a superficial lack of negative side effects (Singh and Neary, 2020; Heider *et al*., 2022).

Endocannabinoids are a class of lipid mediators that act primarily through stimulating G protein-dependent membrane receptors complicated by the guideline of reactive oxygen species and stages of pro/anti-inflammatory cytokines. Oxidative stress encourages the amplified action of enzymes involved in the procedure of tissue phospholipids, which marks the creation of additional lipid mediator sets (Biernacki *et al*., 2021).

The topical study target was to provide insights into CBD and its hepatic defense against liver injuries.

MATERIALS AND METHODS

The study was mainly in the Scientific and Medical Research Center (ZSMRC) in Faculty of Medicine at Zagazig University, Egypt. The protocol was revised and accepted by ZU-IACUC Committee, and the International Animals and Use Committee with appreciation number (ZU-IACUC/3/F/205/2021 dated: 29/12/2021).

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Material Preparation

Cannabidiol (CBD) was obtained from Zova.Co from a San Diego pharmacy in California, USA. Cannabidiol (CBD) (20g) and acacia gum (20g) were added to 100ml warm distilled water, after mixing to a volume of 1000 ml of water, each ml contained 10 mg, of this suspension it was used as a daily dose (26 mg/kg bwt.).

Chemical Agents

Adricin, 50mg/25ml vial (Doxorubicin hydrochloride 2mg/ml)

Adricin was made by Hikma specialized pharmaceuticals, Badr city, Cairo, A.R.E on the market and was intraperitoneally injected as only one dose (18 mg/kg bwt) (Moustafa and Ali, 2021) in groups (II, IV, and V).

Tricardia (Trimetazidine dihydrochloride (TMZ), 20mg) per film-coated tablet.

TMZ was obtained from the Tenth of Ramadan for Pharmaceutical industries and Diagnostic Reagents (rameda). TMZ tablet was dissolved in distilled water after grinding in a mortar and adding 0.06g acacia gum for an oral daily dose (10 mg/kg bwt) to group V (Gabriel *et al*., 2021).

Experimental Animals

Fifty Sprague Dawley male rats were purchased from the Veterinary Laboratory Animal Farm, Zagazig University. Rats were reduced in metallic cages (5 rats/cage) and persistent in the laboratory condition model of temperature and exposure to air. The calculated animals were endorsed with free contact with an ordinary diet (a viable rodent food) and ad libitum water. All the animals were kept under observation and acclimation for 2 weeks just before the optimum setting already initial the experimental time.

Experimental Design

Rats with an initial body weight of 150±25g were randomly divided into five equal groups. Grouping I (the control group) was orally set distilled water. Group II served as a Doxorubicin collection (rats were given distilled water orally for fourteen days and only a dose (18 mg doxorubicin /kg bwt) intraperitoneally was introduced on the 11th day after 16 h. Group III served as a CBD group (animals were administered orally with 0.4 ml CBD for 2 weeks, and on day 11, a distinct intraperitoneal dose of 10 ml/kg bwt normal saline was given after a 16 h. Group IV served as a CBD + Doxorubicin group (received CBD orally for 14 days, and on the 11th day, a single intraperitoneal injection of doxorubicin (18 mg/kg bwt) after a 16 h. Group V served as Trimetazidine (TMZ)+ Doxorubicin (they received TMZ orally for 14 days (10 mg/kg bwt) that was administered before the administration of a single intraperitoneal injection of doxorubicin (18 mg/kg bwt on the 11th day after 16 h). Blood samples were drawn from fasted rats to prepare serum samples. The liver from all rats in all groups was wiped per typical cold saline, dry with filter paper, and sustained in 10% formalin-Saline for the histological studies.

Laboratory Examination

On the final day of dosage, blood samples were collected under light ether anesthesia in non-heparinized tubing. Serum was alienated by centrifugation for 20 min at 4000 rpm, and was preserved at -20°C to determine the activities of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), serum tumor necrosis factor alpha (TNF-α), serum interleukin 6 (IL-6) (Total and Direct) bilirubin, serum alkaline phosphatase, total protein, and albumin. In addition to oxidative stress biomarkers, malonedialdehyde (MDA), superoxide dismutase (SOD), and reduced glutathione (GSH) of the liver homogenates were also estimated. After the rats were sacrificed, the whole liver was taken from each rat in total groups, scrubbed with typical saline, dehydrated with screen paper, and stayed with 10% formalin-Saline at room temperature for the histological examinations. The serum activity of ALT and AST were determined by the kinetic method utilizing once-made packs in conformity with the procedure according to the International Federation of Clinical Chemistry (IFCC) using a fully automated analyzer SAT 450 system with catalog no.261002 and 265002 for ALT kit. Serum alkaline phosphatase was determined using a spectrum clinical system (kinetic-IFCC method) with catalog number 217001. Spectrum Kit was used for the diagnostic determination of albumin with catalog number R1110021. Serum total and direct bilirubin using AGAPPE clinical systems are intended for the quantitative in vitro diagnostic determination of bilirubin with catalog number 51003004. Tumor necrosis factor alpha (TNF-α) was stately by Elisa kit with Cat. No E0082Hu and interleukin 6 (IL 6) by Bioassay Technology Laboratory ELISA kit with the cat. No E0090Hu. SOD of liver homogenate was determined by rat SOD ELISA kit with catalog No. CSB-E08555r, GSH levels were determined using the Cusabio biotech company ELISA kit (GSH catalog # CSB-E12144r), and Rat MDA ELISA kit for liver homogenate.

Statistical Analysis

Using SPSS statistics 19, statistical data were indicated by way of mean±SD. The levels of indicators were considered by ANOVA.

RESULTS

Cannabidiol (CBD) (26 mg/kg bwt) Effect on Numerous Liver Enzymes in Rats in Normal and Combination Groups

The statistics presented in Fig. 1 showed that oral pretreatment of Cannabidiol (26 mg/kg bwt) instigated a major reduction in liver enzymes (ALT and AST) with group IV $P<0.0001$ when compared with DOX group and combination group pretreatment with TMZ. Subsequently, CBD showed a respectable control according to the standard control.

The impact of CBD on liver parameters in rats with normal and induced injuries

The data in Table 1 demonstrated that oral administration and pretreatment of CBD resulted in a significant improvement to liver parameters, with a decrease in (total and direct) bilirubin and alkaline phosphatase in the combination group of (CBD + DOX), $P<0.0001$ when compared to the group receiving a single intraperitoneally injected dose of doxorubicin. Additionally, pretreatment with CBD led to a significant increase in albumin and total protein levels, which fell with the DOX group. According to TMZ, CBD performed well as a reference drug and was in line with normal control.

CBD's anti-inflammatory properties

The results (Fig. 2) revealed a significant rise in TNF-α levels in the Doxorubicin (G2) group (P<0.0001), (80.82±1.55) ng/L and an increase in IL6 (P<0.0001) with a value of 393.94±16.51 related to the control group. Pretreatment using CBD was considerably reduced (P<0.0001), (43.18±3.51) and (282.44±18.78), the time required for the control group to return to normal values when compared to pretreatment with the drug TMZ and rats exposed to the toxin in the doxorubicin group, respectively.

MDA levels, GSH, and SOD activities in liver tissue homogenat.

According to the findings (Table 2), there was a significantly

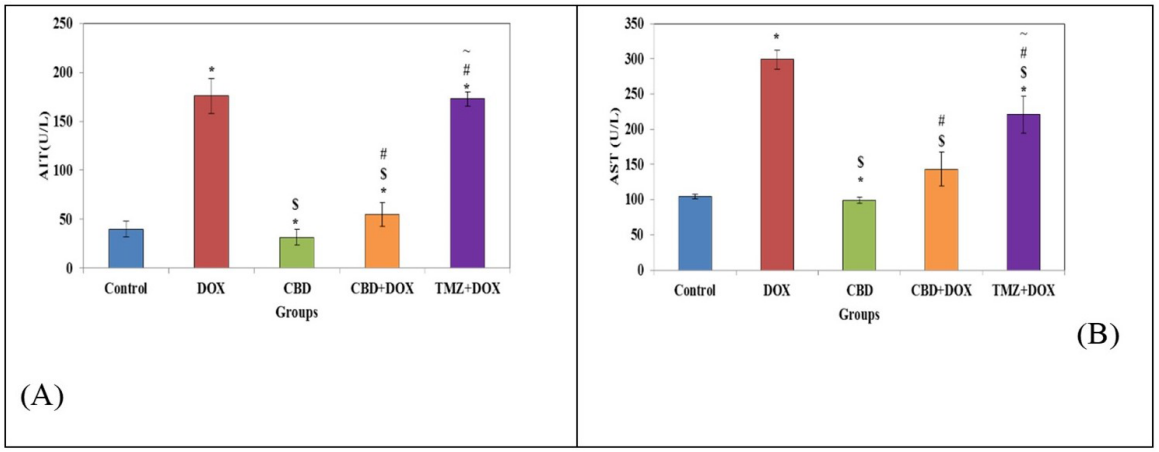

Fig. 1. Effect of CBD and drug TMZ on ALT and AST in combination pretreatment. (A) ALT, (B) AST where Control, *=Significant VS control, $=Significant VS DOX, #=Significant VS (CBD), and ~ =Significant VS (CBD+DOX).

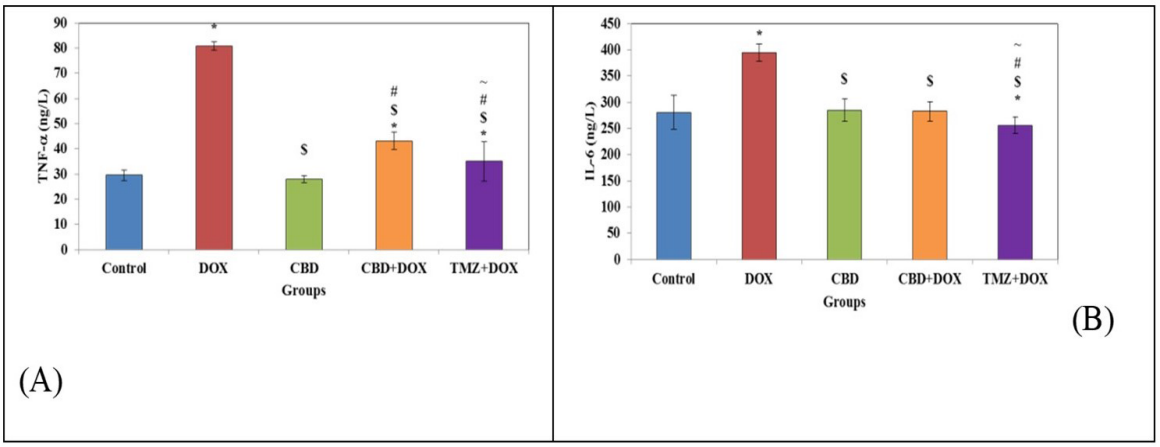

Fig. 2. Cannabidiol (CBD) improves inflammatory markers and vital role as an anti-inflammatory effect. (A) TNF-α, (B) IL 6, *=Significant VS control, $=Significant VS DOX, #=Significant VS (CBD), and ~ =Significant VS (CBD+DOX).

Table 1. Impact of Cannabidiol (CBD) at 26 mg/kg on the levels of different liver parameters and the drug TMZ in normal and injured rats.

Treatment	Total bilirubin (mg/dl)	Direct bilirubin (mg/dl)	Alkaline phosphatase (U/L)	Albumin (g/dl)	Total protein (g/dl)
Control	0.19±0.7	0.09±0.03	258.0±36.89	4.05±0.14	7.46±0.48
DOX	0.76±0.17$^{*\#\$\sim}$	0.33±0.45$^{*\#\$\sim}$	521.5±75.77$^{*\#\$\sim}$	2.37±0.16$^{*\#\$\sim}$	6.01±0.18$^{*\#\$\sim}$
CBD	0.34±0.38$^{*\#}$	0.17±0.42$^{*\#\sim}$	247.0±78.65$^{\#\sim}$	3.74±0.16$^{*\#\$\sim}$	7.05±0.22$^{*\#}$
CBD+DOX	0.24±0.32$^{\#\sim}$	0.13±0.37$^{*\#\$\sim}$	261.5±54.54$^{\#}$	3.41±0.16$^{*\#\$\sim}$	6.71±0.25$^{*\#}$
TMZ+DOX	0.38±0.07$^{*\#\sim}$	0.23±0.37$^{*\#\$\sim}$	305.5±28.66$^{\#\$}$	2.65±0.8$^{*\#\$\sim}$	6.82±0.10$^{*\#}$

$^{*\$\#\sim}$Mean± SD at the same column and bearing different superscripts are significantly different at P-value, P<0.0001, P<0.01, P<0.05.

Table 2. Liver homogenate's oxidative stress in the control and treatment groups.

Treatment	SOD (U/mg liver tissue)	GSH (ng/mg liver tissue)	MDA (nmol/mg liver tissue)
Control	126.14±16.71	96.06±3.78	3.79±1.51
DOX	24.82±2.43$^{*\#\$\sim}$	13.23±2.36$^{*\#\$\sim}$	31.36±1.91$^{*\#\$\sim}$
CBD	129.34±15.12$^{\#\$\sim}$	93.20±3.99$^{\#\sim}$	2.58±1.19$^{\#\$\sim}$
CBD+DOX	106.32±4.36$^{*\#\$}$	89.63±7.67$^{*\#}$	7.83±3.59$^{*\#\$}$
TMZ+DOX	100.42±1.96$^{*\#\$}$	84.50±4.60$^{*\#\$\sim}$	9.45±2.56$^{*\#\$}$

$^{*\$\#\sim}$Mean± SD at the same column and bearing different superscripts are significantly different at P-value, P<0.0001, P<0.01, P<0.05.

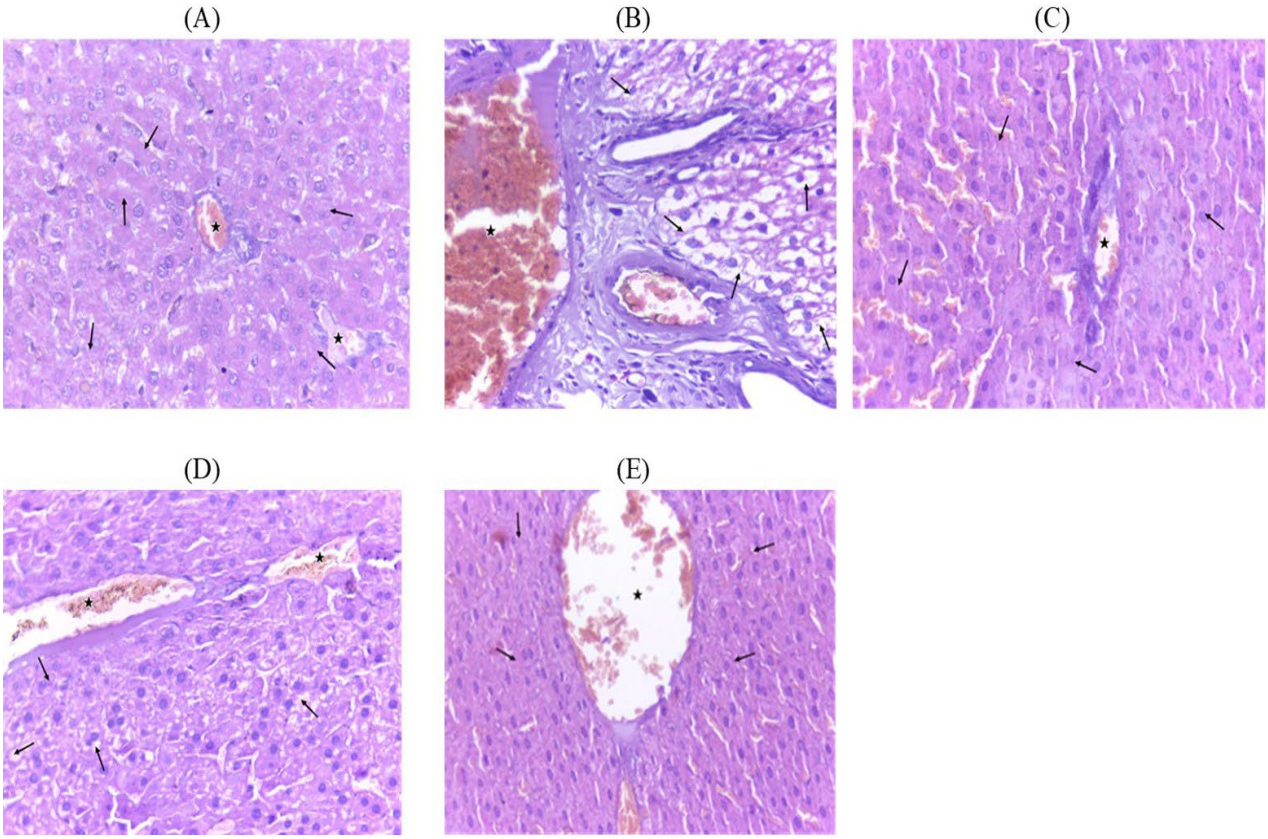

Fig. 3. photomicrographs of liver rats of all studied groups (H & Eosin X 400), fig. 3A (the control group) shows a small-sized central vein surrounded by trabecular of normal liver cells with central nuclei and eosinophilic, Fig. 3B shows a markedly dilated congested central vein surrounded by trabeculae of hepatocytes showing the marked fatty change with clear cytoplasm, Fig. 3C showing small sized central vein surrounded by trabecular of normal liver cells with central nuclei and eosinophilic, Fig. 3D moderately congested central vein and mild fatty change of hepatocytes and Fig. 3E shows a congested central vein and normal hepatocytes.

lower level of GSH and SOD activity plus an increase in levels of MDA when linked to the control group, with respective standards of 13.23±2.36, 4.82±2.43, treatment with CBD before doxorubicin monotherapy as 89.63±7.67, 106.32±4.36 and 7.83±3.59.

Photomicrographs of Liver Tissues of Normal and Treated Groups

In the current study (Figure 3) (the CBD+DOX) group (G4) was treated with CBD and then exposed to an intraperitoneally single dose of Doxorubicin (18mg/kg bwt) showing moderately congested central vein and mild fatty change of hepatocytes (Fig. 3d) in difference with Fig. 3B (G2) positive control of doxorubicin group, screening markedly dilated congested central vein surrounded in trabeculae of hepatocytes showing the marked fatty change with clear cytoplasm.

DISCUSSION

Liver ailments are major mutual health complications equally; they are acute to exogenous substances such as natural poisons and/or drugs that ultimately lead to countless hepatic syndromes, which are primarily brought on by interference with oxygen metabolism (Mohammed *et al*., 2021). In any case, taking medications in excess can result in organ damage. Doxorubicin is an anthracycline antineoplastic that causes hepatotoxicity by causing inflammatory liver tissue and free radicals (Moustafa and Ali, 2021)

The goal of the current inquiry was to examine the protective properties of Cannabidiol (CBD) and its antioxidant function in hepatic issues related to injury from a single overdose of DOX in addition to oxidative stress. Even though the hepatotoxic properties of doxorubicin are dose-dependent, minor prescriptions have been displayed to originate liver necrosis and ALF. Doxorubicin is a corporate antineoplastic drug interrelated to hepatotoxicity and fire with a major source of Drug-Induced Liver Injury (DILI). Doxorubicin's appliance of the act involves disorderly major enzymes in the antioxidant method (Hegazy *et al*., 2021).

The obtained findings are consistent with those of numerous researchers who found that doxorubicin treatment decreased levels of albumin and total proteins while increasing activities of liver enzymes (ALT and AST), alkaline phosphatase, and bilirubin level (Ikewuchi *et al*., 2021; Moustafa and Ali, 2021; Saleh *et al*., 2022). Acute liver damage can be attributed to inflammation. In an organized manner, oxidative stress, which is well-defined as disequilibrium among pro-oxidants and antioxidants, can cause a wide range of histopathological lesions, from asymptomatic hepatitis to hepatocellular carcinoma (Zhang *et al*., 2018). According to Song *et al*. (2019), DOX can lead to an imbalance of redox homeostasis, characterized by an increase in ROS and a decrease in antioxidant defenses. This imbalance can lead to the oxidation of lipids, DNA, and other macromolecules, which can harm the liver.

Pretreatment with CBD significantly prohibited biochemical modifications resulting from the doxorubicin dose. The rare accomplished clinical trials on phytocannabinoids, which are thought to grasp the most therapeutic promise (Cannabidiol or tetrahydrocannabivarin), remain inadequate, indicating that the promising therapeutic benefits have not yet been fully validated. The improvement of novel and creative therapeutics aimed at the treatment of CLDs, such as NAFLD, ALD, or equal hepatitis C-induced liver disorders, may therefore benefit from mounting research on less considered phytocannabinoids and their byproducts, with a focus on their method of action on liver metabolic rate (Mboumba *et al*., 2022).

The main *Cannabis* plant compound that is not psychoactive, CBD, is the subsequent most plentiful (Ligresti *et al*., 2016). *Cannabis* plants are the source of botanical cannabidiol (CBD), which has no psychoactive effects (Jiang *et al*., 2021).

Cannabidiol (CBD), a non-psychoactive substance derived from *Cannabis sativa*, has a wide choice of pharmacological ef-

fects, comprising the ability to protect the heart and nervous system, reduce inflammation and pain, and have anti-epileptic effects (Huang *et al*.,2019; Wang *et al*., 2021).

According to Neumann *et al*. (2019), CBD may facilitate doxorubicin entry through TRPV2 channels and prevent it from leaving the cells by impeding the P-glycoprotein ATPase transporter, both of which may promote doxorubicin-mediated cell death.

These findings collectively lay the groundwork for using enormous pore cation-non-selectional channels as "natural" preparation delivery structures to focus on particular cell types; CBD may have antioxidant properties, which may have helped CBD prevent liver damage. It has been established that liver inflammation plays a significant role in the development of liver syndrome. Furthermore, CBD had a notable anti-inflammatory impact on a variety of diseases. Additionally, according to our findings and those of other studies, CBD reduced liver damage caused by NAFLD by inhibiting NF-B and NLRP3 inflammation (Huang *et al*., 2019).

CONCLUSION

According to the current study, CBD may secure the liver from DOX-convinced liver inflammatory reactions in impeding TNF and IL-6. The antioxidant action of CBD is set up by antioxidants, and biological and histopathological inquiries that advance the ability of CBD's advantageous effects.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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