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Investigating the Efficacy of Cannabidiol Against Arsenic-Induced Liver Cell Damage

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ABSTRACT

Arsenic (As) exposure is known to have harmful effects, prompting the search for effective countermeasures. This study investigated the protective effects of cannabidiol (CBD) against arsenic toxicity in liver cell cultures (THLE-2). The IC_{50} values for As were determined, finding 10 µM in 2D and 15 µM in 3D cell lines. To assess CBD's protective efficacy, 5 µM of CBD was administered alongside arsenic at its IC_{50} concentration. The levels of oxidative stress markers, including Glutathione (GSH), malondialdehyde (MDA), myeloperoxidase (MPO), and catalase (CAT), as well as inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), were measured using ELISA kits. Inductively Coupled Plasma Mass Spectrometry (ICP-MS) analysis was conducted to evaluate As uptake in the cells. The results showed that CBD significantly enhanced cell proliferation and reversed the oxidative stress and inflammatory responses induced by arsenic exposure. Furthermore, CBD effectively reduced arsenic uptake into the cells. These findings provide compelling evidence for CBD's protective role against arsenic-induced toxicity, highlighting its potential as a therapeutic agent in mitigating the harmful effects of arsenic.

Keywords: Arsenic, Cannabidiol, Toxicity, THLE-2, ICP-MS.

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Introduction

The increasing environmental pollution associated with industrialization and urbanization has led to soil contamination reaching levels that can pose a threat to living organisms. Both the escalating environmental and soil pollution, along with the industrialization, contribute to an increasing likelihood of human exposure to toxic metals. Among these toxic metals, arsenic (As) exposure holds a significant place. As is used in industrial chemicals (primarily wood preservatives), agricultural chemicals (herbicides and desiccants), as well as in the production of glass, batteries, and semiconductor devices in the industry [1]. After exposure to As, the resultant oxidative stress and inflammation can lead to cellular damage and various problems [2, 3]. Health problems caused by As include hyperpigmentation [4], basal cell carcinoma on non-melanin skin [5], hepatomegaly [6], cirrhosis [7], increased incidence of hypertension [8], myocardial damage, cardiomyopathy [9], cardiac arrhythmias [10], confusion and memory loss [11], nephritis, prostate, kidney, ureter cancer [12], and an increased risk of diabetes mellitus [13].

The most commonly used method for heavy metal poisoning is chelation therapy, which aims to increase the elimination of metals [14]. A variety of chelating agents containing sulfhydryl groups such as meso-2,3-dimercaptosuccinic acid, 2,3-dimercapto-propan-1-sulfonate, and British Anti-Lewisite (2,3-dimercaprol) are used in the treatment of As toxicity. The use of these substances aims to increase the elimination of metal from the body [15, 16]. However, these chelators have a range of side effects and are not suitable for high-dose and long-term treatment. Therefore, the search for reliable new substances for prevention or treatment of As poisoning is of great importance.

Cannabidiol (CBD) is one of the compounds derived from the hemp plant [17]. CBD is the primary non-psychotropic cannabinoid derived from hemp plant, commonly referred to as marijuana. It was first isolated in 1940, with its structure and stereochemistry elucidated in 1963 CBD does not produce nearly any psychoactive effects. Additionally, CBD has antiemetic, analgesic, anti-inflammatory, and antioxidant effects [17, 18]. The protective role of CBD is attributed to multiple molecular mechanisms, including its ability to mitigate oxidative stress and inflammation, as well as its potential to interfere with the cellular uptake and accumulation of heavy metals [19].

In our study, the aim was to determine the protective effect of CBD on oxidative stress and inflammation occurring in liver cell cultures after As exposure.

Methods

Acquiring CBD

CBD was obtained in its purest form from the company CB21 Pharma S.R.O. in the Czech Republic.

Providing Test Material

As ionic standard was obtained from Sigma-Aldrich. Glutathione (GSH) (BT LAB, China, Cat.No:EA0142Hu), malondialdehyde (MDA) (Elabscience, USA, Cat.No:E-EL-0060), myeloperoxidase (MPO) (BT LAB, China, Cat.No:E0880Hu), and catalase (CAT) (BT LAB, China, Cat.No:E30053Hu), as well as tumor necrosis factor-α (TNF-α) (BT LAB, China, Cat.No:E0082Hu), interleukin-1β (IL-1β) (BT LAB, China, Cat.No:E0143Hu), and interleukin-6 (IL-6) (BT LAB, China, Cat.No:E0090Hu) ELISA kits, were sourced from commercial companies. The THLE-2 non-cancerous liver cell line (ATCC) was obtained from the Ege University Central Research Test and Analysis Laboratory Application and Research Center.

Development of Cell Lines in 2 Dimensions (2D) and Three-Dimensional (3D)

In the project, a liver cell line called THLE-2 was used to determine the toxic effects of As. THLE-2 cells were produced in two dimensions (2D) in 75 cm^2 and 25 cm^2 flasks at 37°C with 5% carbon dioxide in an incubator using Dulbecco's Modified Eagle's Medium (D-MEM) (High Glucose) supplemented with 10% Fetal Bovine Serum, 1% Gentamycin, and 1% Penicillin. As the surface of the flask was covered by 80% of the cells, the cells were passaged using trypsin.

THLE-2 cell lines were also developed in 3D format. Cells were grown in a spheroid shape using the hanging drop method. The cell lines were expanded globally using the three-dimensional hanging drop method. Subsequently, the cells were cultured at 37°C with 5% CO_2 in an incubator.

As Toxicity Analysis

In our study, As trioxide (As_2O_3) compound was used. To determine the toxic effect levels of As, XTT assay kit (Biological Industries) was used for 2D cell lines, and ATP assay kit (Elabscience) was employed for 3D cell lines. The analyses were conducted following the manufacturer's instructions

Cytotoxicity Experimental Groups

Group I (Control(CONT)): The cell line was only passaged, similar to the other groups, without the application of any additional test substance.

Group II (As): As was added to the cell line's medium at concentrations of 1µM, 5µM, 10µM, 25µM, 50 µM, and 100 µM, and then the cells were passaged in this manner [20]. The determined IC_{50} concentrations for As, which were 10 µM for 2D cell lines and 15 µM for 3D cell lines, were used in the experiments.

Group III (CBD): CBD was added to the cell line's medium at concentrations of 1 µM, 5 µM, 10 µM, 25 µM, 50 µM, and 100 µM, and then the cells were passaged in this manner [21]. The determined IC_{50} concentrations for CBD, which were 1 µM for 2D cell lines and 5 µM for 3D cell lines, were used in the experiments.

Group IV (As+CBD): As at concentrations of 10 µM for 2D cell lines and 15 µM for 3D cell lines, along with CBD at concentrations of 1 µM for 2D cell lines and 5 µM for 3D cell lines, was added to the cell line's medium. Subsequently, the cells were passaged in this manner [20, 21].

Cytotoxicity Analysis of CBD in 2D and 3D Cell Models

To determine the cytotoxic effect of As and CBD on cells, an XTT assay was conducted. Cells were seeded onto 96-well plates in a manner that resulted in 5000 cells per well. As solution and CBD were separately and jointly applied to the cell models. The prepared solutions were dispensed into wells in serial dilutions. After 72 hours, the formazan dye from the XTT kit was added to each well, and the plate was incubated for 2 to 5 hours. Subsequently, optical densities were determined using an ELISA reader. The calculated results from the reading determined the LD_{50} on cells treated with both the toxic metal and CBD [19].

In the case of cells developed in a 3D environment, the morphologies of the cells were first examined under a microscope to determine the IC_{50} dose. Subsequently, the determined concentration ranges were added to the cells. Then, the viability of the cells was examined using the ATP detection assay (Colorimetric) method. Each sample was conducted in at least three replicates. The viability rates, calculated in comparison to negative and positive controls, were used to plot dose-response curves. Application to cells was performed based on the obtained IC_{50} value [19].

Determination of Oxidative Stress Parameters

Following the application of As and CBD, the levels of GSH, MDA, MPO, and CAT in cells were measured to assess oxidative stress. The levels of these parameters in cells were determined using ELISA microplate readers, following the instructions provided by the commercial test kits. This analysis aimed to evaluate the oxidative stress response induced by As exposure and the potential protective effects of CBD.

Determination of Proinflammatory Cytokines

Following the application of As and CBD, the levels of TNF-α, IL-1β, and IL-6 were measured to assess the inflammatory response. The levels of these cytokines in cells were determined using ELISA microplate readers, following the instructions provided by the commercial test kits. This analysis aimed to evaluate the inflammatory effects induced by As exposure and the potential modulatory effects of CBD.

Toxicological Analysis

Cells obtained from the experimental groups were treated with nitric acid (HNO_3), hydrogen peroxide (H2O2), and ultrapure water. These treatments were applied to evaluate how cellular As uptake is influenced by CBD administration. The concentrations of As in the cells were determined using Inductively Coupled Plasma-Mass Spectrometry (ICP-MS).

Statistical Analysis

The results were presented as mean ± standard deviation. The data analysis was performed using the IBM SPSS Statistics 23.0 software package. The distribution characteristics of the data were determined using the

Kolmogorov-Smirnov test. For data showing a normal distribution, one-way analysis of variance (ANOVA) was conducted, followed by Tukey's post hoc test. For data that did not exhibit a normal distribution, Kruskal-Wallis test was applied, followed by Dunnett's T3 post hoc test. The p-value of less than 0.05 was considered statistically significant.

Results

Cell Line Analysis Results

The protective effect of CBD on the toxic effects of As in a liver cell line was investigated in the project. The cytotoxic effect levels (IC_{50}) of As on liver cell lines were determined in both 2D and 3D cell models at different dose ranges (Table 1 and Table 2). According to the obtained results, the IC_{50} value was determined as 10 µM for 2D cell lines and 15 µM for 3D cell lines. In 3D cell models, the toxic dose was found to be higher compared to 2D cell lines. 3D cell models, due to their production in a manner similar to in vivo systems, contain thousands of cells in their structure. Therefore, the dose given to 2D cell lines may not be effective on 3D cells.

Table 1. Cell proliferation rate (%) in 2D THLE-2 cell lines

Groups	Dosage range	24 h	48 h	72 h
As	1 µM	66	60	43
	5 µM	59	55	35
	10 µM	56	48	30
	25 µM	36	30	21
	50 µM	10	5	3
CBD	1 µM	82	74	68
	5 µM	75	64	60
	10 µM	70	65	60
	25 µM	68	65	55
	50 µM	61	56	49
As + CBD	10 µM + 1 µM	68	61	51
CONT	-	100	100	100

Abbreviations: CONT, control group; CBD, group treated with only CBD; As + CBD, group treated with both As and CBD; As, group treated with only As.

Table 2. Cell proliferation rate (%) in 3D THLE-2 cell lines

Groups	Dosage range	24 h	48 h	72 h
As	1 µM	73	64	50
	5 µM	69	56	48
	10 µM	60	53	41
	25 µM	50	40	38
	50 µM	45	32	25
	100 µM	30	21	10
CBD	1 µM	90	83	75
	5 µM	88	76	70
	10 µM	75	70	63
	25 µM	62	58	50
	50 µM	49	40	35
	100 µM	41	32	28
As + CBD	15 µM + 5 µM	76	68	50
CONT	-	100	100	100

Abbreviations: CONT, control group; CBD, group treated with only CBD; As + CBD, group treated with both As and CBD; As, group treated with only As.

As seen in Table 1 for 2D cell lines, exposure to As alone causes more damage to the cells. However, it was observed that when CBD was applied in addition to As, there was less damage developed in the cells. As seen in Table 2 for 3D cell lines, As alone caused more damage to the cells. However, it was observed that when CBD was applied in combination with As, there was less damage developed in the cells.

Inverted microscope images of 3D cell lines are provided. As observed, the cell density in the group treated with As alone was lower, while the cell density in the group treated with CBD + As was similar to the CONT (Figure 1).

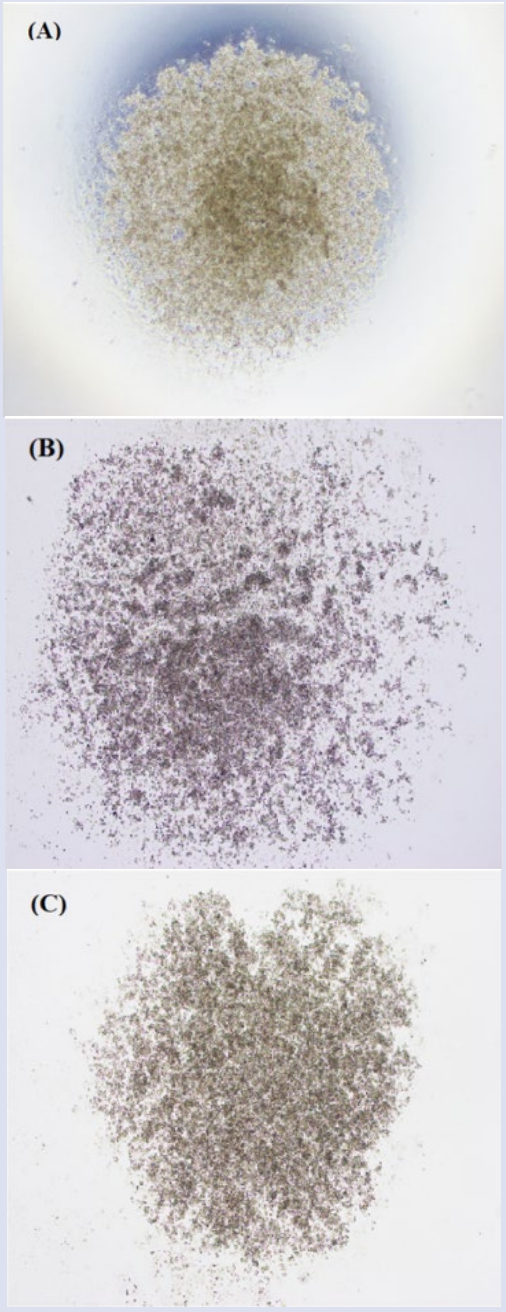

Figure 1. Effects of As and CBD application on 3D cell line. (A) THLE-2 CONT (48 h), (B) THLE-2 cell model treated with As (48 h), (C) THLE-2 cell model treated with As and CBD (48 h)

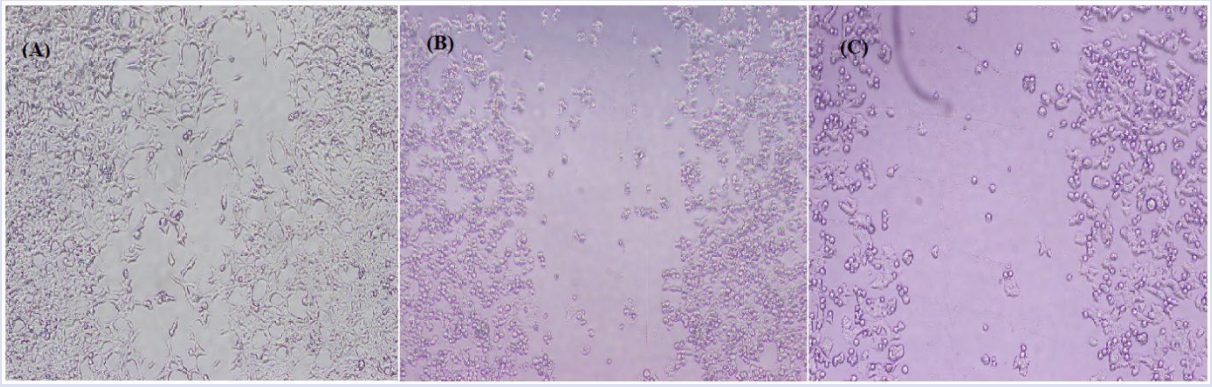

Figure 2. Effects of As and CBD application on 2D cell line. (A) THLE-2 Control (48 h), (B) THLE-2 cell model treated with As (48 h), (C) THLE-2 cell model treated with As and CBD (48 h).

Inverted microscope images of 2D cell lines are provided. As observed, the cell density in the group treated with As alone was lower, while the cell density in the group treated with CBD + As was similar to the CONT (Figure 2).

Evaluation of ELISA and ICP-MS Results

The effect of CBD on As exposure was examined. Levels of GSH, MDA, MPO, CAT, TNF-α, IL-1β, and IL-6 were determined. The decrease observed in GSH and CAT levels in the As group was not observed in the As + CBD group ($p < 0.05$). The increase observed in MPO, MDA, TNF-α, IL-1β, and IL-6 levels in the As group was not observed in the As + CBD group ($p < 0.05$). The level of As detected in the cells of the As group was higher than that in the cells of the As + CBD group ($p < 0.05$) (Figure 3).

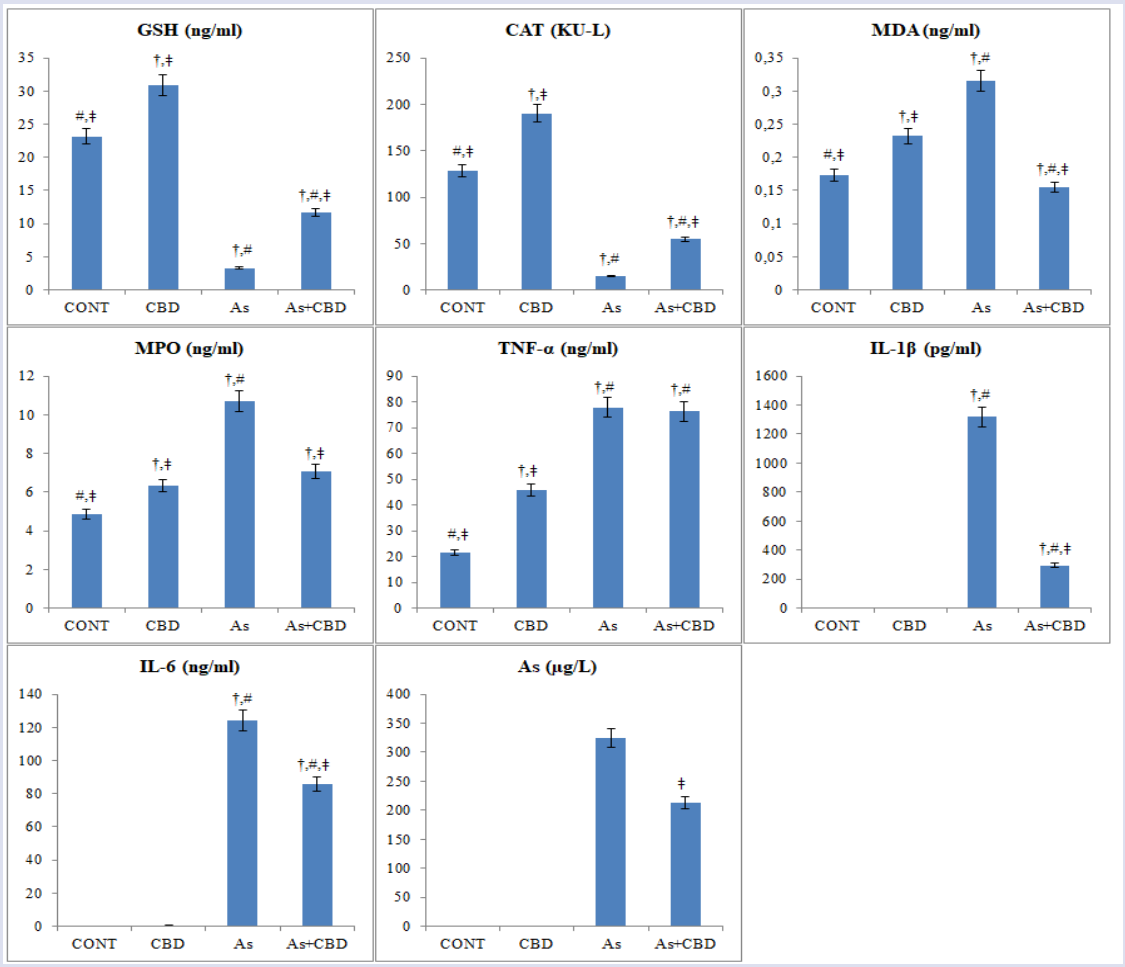

Figure 3. Results of ELISA and ICP-MS in As groups. Abbreviations: CONT, control group; CBD, group treated with only CBD; As+CBD, group treated with both As and CBD; As, group treated with only As. † indicates the group different from the CONT group ($p < 0.05$), # indicates the group different from the CBD group ($p < 0.05$), ‡ indicates the group different from the As group ($p < 0.05$).

Discussion

CBD, an active ingredient of the hemp plant, has attracted significant attention due to its potential therapeutic properties [22, 23]. In recent years, various positive attributes of CBD have been proposed, including its potential protective effects against numerous health conditions [24]. Booz (2011) suggested that CBD activates the immune system and exhibits therapeutic effects in diseases such as rheumatoid arthritis, type 1 and type 2 diabetes, atherosclerosis, Alzheimer's disease, hypertension, metabolic syndrome, ischemia-reperfusion injury, depression, and neuropathic pain induced by oxidative stress [18]. In line with these findings, our study observed a protective effect of CBD in As toxicity in the THLE-2 liver cell culture. Specifically, we found that CBD mitigated oxidative stress markers and proinflammatory cytokine levels elevated due to As exposure, indicating its potential role in counteracting As-induced toxicity. The findings from our study provide experimental evidence that supports the proposed protective effects of CBD, particularly its capacity to modulate oxidative stress and inflammatory responses in human liver cells exposed to As. While previous studies have suggested CBD's therapeutic efficacy in various conditions, including obesity, anorexia, and vomiting [25, 26], our findings contribute to understanding how CBD could potentially protect liver cells from As toxicity through these mechanisms. In support of the therapeutic potential of CBD, various studies have suggested its effectiveness in a range of diseases. For instance, CBD has been investigated for its potential in treating diabetes [27, 28]. In line with these findings, Chen et al. (2016) demonstrated that CBD has a protective effect against oxidative stress, apoptosis, and inflammation induced by hydrogen peroxide in nucleus pulposus cells, which are similar to the stress induced by As in our study [29]. Moreover, CBD has shown promise in alleviating inflammation and oxidative stress in various animal models. For example, Rajesh et al. (2010) reported that CBD administration alleviated myocardial dysfunction, cardiac fibrosis, and oxidative stress in diabetic cardiomyopathy in mice, which supports its broad-spectrum protective effects [30]. While our study did not directly evaluate the effects of CBD on cardiovascular tissues, the observed reduction in oxidative stress markers such as GSH, MDA, MPO, and CAT in the THLE-2 cells after CBD treatment parallels the findings in these animal studies, suggesting similar protective mechanisms. These findings imply that CBD's antioxidant and anti-inflammatory effects extend beyond its effects on the liver and may be relevant in other organ systems exposed to toxic stress.

Various studies have explored CBD's potential therapeutic effects in neurological diseases and other conditions in both animal models and humans. For instance, Campbell and Gowran (2007) evaluated the impact of CBD on Alzheimer's disease, while Sagredo (2012) and Devinsky et al. (2017) investigated CBD's role in Huntington's disease, epilepsy, and other neurological disorders, suggesting positive effects in these conditions [31–33]. Similarly, Hall et al. (2005) highlighted the potential of CBD in reducing pain associated with cancer, emphasizing its therapeutic promise [34]. In our study, although we did not investigate neurological diseases directly, the observed reduction in inflammatory cytokines (TNF-α, IL-1β, IL-6) following CBD treatment aligns with findings from these studies. The modulation of inflammatory responses is a critical aspect of CBD's therapeutic profile, and the suppression of pro-inflammatory cytokines observed in our study suggests that CBD may play a protective role in conditions where inflammation is exacerbated by toxic agents like As. This finding not only supports the anti-inflammatory potential of CBD but also highlights its broad applicability in treating diseases linked to chronic inflammation, including neurodegenerative conditions and cancer.

In studies assessing oxidative stress in response to As exposure, similar protective effects of CBD have been observed. Zhao et al. (2022) investigated the effectiveness of grape skin extract in mitigating As toxicity in mice, reporting that it reversed the elevated levels of MDA and MPO and the reduced levels of GSH following As exposure [2]. In another study by Al Aboud et al. (2021), the protective efficacy of ebselen against As-induced hepatotoxicity in rats was evaluated, showing that ebselen reversed oxidative damage by restoring GSH and CAT levels, while reducing MDA levels [35]. In our study, the As-induced decrease in GSH and CAT levels, along with the increase in MDA levels, was similarly reversed by CBD. These results align with the aforementioned studies, supporting the hypothesis that CBD acts as an antioxidant and can mitigate oxidative stress caused by toxic agents like As. The restoration of these oxidative stress markers in the presence of CBD further confirms its protective role and suggests its potential as a therapeutic agent in preventing or alleviating As-induced liver damage.

In our study, the inflammatory response induced by As exposure, reflected by the elevated levels of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), was mitigated following CBD treatment. This result is consistent with the findings of Zhao et al. (2022), who reported that grape skin extract reversed the increased mRNA expressions of pro-inflammatory cytokines (TNF-α, IL-1β, IFN-γ) following As exposure in mice [2]. Additionally, CBD has been shown to have a protective effect in various cell types through the suppression of pro-inflammatory and anti-apoptotic pathways [29]. In our study, CBD treatment effectively reduced the cytokine levels that were elevated due to As exposure, suggesting that CBD may exert its protective effects through anti-inflammatory mechanisms. This observation highlights the potential of CBD in modulating the immune response and preventing chronic inflammation, which is often exacerbated by toxic stressors like As. By reducing these inflammatory markers, CBD demonstrates its potential to alleviate inflammation-related damage and may serve as a promising therapeutic option for conditions involving oxidative and inflammatory stress.

Dopp et al. (2004), in their in-vitro studies evaluating the relationship between the uptake, cytotoxic, and genotoxic effects of inorganic and organic arsenic (As) derivatives, indicated that after cellular uptake of inorganic As, it undergoes biotransformation into mono- and dimethylated metabolites. They stated that methylation reactions represent a toxification process rather than a detoxification process and emphasized the importance of cellular uptake mechanisms in the formation of As toxicity [36]. In our study, the lower amount of As observed in the group co-treated with CBD and As, compared to the As-only group, suggests that CBD may reduce cellular As uptake. This may have mediated the protective effect of CBD against As exposure by limiting the conversion of As into toxic metabolites through methylation. The combined reduction in oxidative stress, inflammatory response, and cellular As uptake offers a comprehensive understanding of how CBD may exert its protective effects against As-induced toxicity.

Conclusion

Our study demonstrates that CBD exerts a protective effect against arsenic (As)-induced toxicity in THLE-2 liver cells. By reducing oxidative stress, inflammatory responses, and cellular As uptake, CBD appears to mitigate the harmful effects of As exposure. These findings align with existing literature, which supports the potential of CBD in counteracting various forms of toxicity, including those induced by heavy metals. The observed reduction in As-induced oxidative stress, inflammation, and cellular damage underscores CBD's therapeutic potential in preventing or alleviating As toxicity. Further studies are warranted to explore the mechanisms underlying these effects in greater detail and to evaluate the clinical applicability of CBD in managing environmental toxicities.

Conflicts of interest

There are no conflicts of interest in this work.

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