Original Article

Protective Effect of *Physalis Angulata* Extract on Cisplatin-induced Hepatotoxicity in Rats

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Abstract

The *Physalis angulata* extract has various therapeutic potentials and antioxidant properties, making it a promising candidate in supportive therapies to reduce the side effects of cytotoxic drugs. This study aimed the protective effects of *P. angulata* against cisplatin (CSP)-induced hepatootoxicity. Forty adult rats were divided into five equal groups (n = 8) and randomly distributed: Group 1 (control group): Rats were given water and food *ad libitum* daily for 30 days. Group 2 (CSP group) was administered CSP (5 mg/kg, intraperitoneally) once on the 7th days from the experiment. Groups 3, 4, and 5 (CSP plus *P. angulata* groups): Rats were injected with the same previous dose of CSP (5 mg/kg) intraperitoneally on the 7th day of the experiment, followed by oral administration of the extract at a dose of (150 mg/kg), (250 mg/kg), or (350 mg/kg), respectively, daily for 30 days. Twenty-four hours after the last dose, samples of both blood and tissues were collected for various laboratory tests (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) and light microscopic examinations were performed. CSP administration significantly increased of liver weight, ALT level, and AST. Histology changes, CSP caused vasodilation, and congestion with infiltration of inflammatory cells. Treatment with *P. angulata* restored the levels of hepatic biochemical markers toward normality and histological architecture of hepatic tissues.

Keywords: Alanine aminotransferase, aspartate aminotransferase, cisplatin, *Physalis angulata*

Introduction

Physalis angulata is a member of the Solanaceae family, an annual herbaceous plant, widely distributed throughout the world is grown in both tropical and subtropical regions(1). It contains active compounds such as flavonoids, steroids, and withanolides, that have antioxidants, anti-inflammatory, as well as antimicrobial impacts(2,3). This plant has been traditionally used in folk medicine to treat infections, malaria, diabetes, and liver diseases(4,5). These antioxidant phytochemicals alleviate cellular stress by neutralizing ROS, inhibiting ROS-generating enzymes, blocking free radical chain reactions, and enhancing antioxidant defences(6). Recent studies have shown its ability the *P. angulata* to protect against CCl_4-induced liver fibrosis, making it a promising candidate in supportive therapies to reduce the side effects of hepatotoxic drugs(7).

Cisplatin (CSP) was the inaugural platinum-based pharmaceutical sanctioned by the Food and Drug Administration for cancer treatment in 1978(8). It is effective against many solid tumors, including breast, ovarian, bladder, and colon cancer(9). CSP's mechanism of action in cell death is via binding to biological molecules, namely DNA and RNA, cross-linking with DNA strands ultimately leads to programmed cell death (apoptosis)(10). However, it has numerous adverse effects on multiple organs, especially the liver, its use has been severely restricted due to its potentially serious side effects, including gastrotoxicity, ototoxicity, nephrotoxicity, and hepatotoxicity(11,12). Several studies have linked the hepatotoxicity of CSP to reactive oxygen species, which causes destruction of the liver cell membrane through lipid peroxidation and leakage of enzymes from the liver cells. This is evidenced by a significant increase in the concentrations of alanine aminotransferase (ALT), alkaline phosphatase, and aspartate aminotransferase (AST)(13,14).

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Cell death associated with oxidative stress also leads to an inflammatory response(15). CSP disrupts the structure of the hepatic lobule and increases the diameter of the sinusoids in the liver(16).

Commonly, hepatotoxicity is observed in patients treated with CSP; therefore, it is necessary to develop natural liver-protective products to improve clinical outcomes in oncology patients(17).

Materials and Methods

Plant collecting and extract preparation

P. angulate was collected from Al-Khalidiyah city in Anbar Governorate, afternoon to be saturated with sunlight. All parts of the plant (except roots) were spread out in a well-ventilated place away from light and direct sunlight, taking into account continuous turning(18). After it was completely confirmed that the plant was completely dry, it was ground using an electric pulverizer, and then the plant powder was placed in special boxes until use. The alcoholic extract was prepared by soaking 50 g of the plant powder after grinding it in 500 ml of ethyl alcohol at a concentration of (70% ethanol + 30% distilled water) placed in a beaker. The beaker was closed with silicone and placed in a shaking water bath for 24 h at a temperature of 40°C–60°C. After that, the mixture was filtered. Then, the solution free of impurities was taken and placed in an ultrasonic device at a power of 65 Hz for half an hour. Then, the result was placed on a magnetic stirrer until the alcohol and water evaporated until the product was concentrated in the form of a gelatinous substance. Then, the extract dried, after which a dry layer was formed that was scraped and collected until use(19).

Cisplatin

CSP, an antineoplastic agent, was acquired from the Turkish firm Kocakfarma and includes 50 mg of the active component.

Experiment design

This study utilized 40 male rats, with close ages and weights, aged 8–10 weeks and weighing 200–250 g. The rats were randomly allocated to plastic cages equipped with metal covers, with 8 animals per cage, located in the animal house of the Department of Life Sciences at the College of Education for Girls at the University of Anbar. The laboratory rats were allocated into five groups as detailed below: Group 1 (control group): Rats were given water and food *ad libitum* daily for 30 days. Group 2 (CSP group) was administered CSP (5 mg/kg, intraperitoneally)(20) once on the 7th days from the experiment. Groups 3, 4, and 5 (CSP plus *P. angulata* groups): Rats were injected with the same previous dose of CSP (5 mg/kg) intraperitoneally on the 7th day of the experiment, followed by oral administration of the extract at a dose of (150 mg/kg), (250 mg/kg), or (350 mg/kg), respectively, daily for 30 days.

The animals were placed under laboratory circumstances featuring an 11-h light cycle and a 13-h dark phase, with a temperature maintained at 22°C ± 2°C, along with the provision of food and drink. The cages were maintained in a clean and sterilized state weekly, allowing a 10-day period for acclimatization to the new settings and to confirm their disease-free status.

Collection of blood samples

Blood samples were extracted directly from the heart utilizing a sterile 5 ml nondropper syringe to secure a greater volume of blood. The samples were promptly transferred to sterile(21). Test tubes devoid of anticoagulants were centrifuged at 3000 rpm for a duration of 15 min. Serum was subsequently collected and stored at −20°C for the assessment of hepatic function markers(22).

Biochemical measurement

This study utilized the Standard Kits from the Italia company GIESSE to quantify ALT and AST levels via spectrophotometry(23).

Histopathological examination

After drawing blood samples, the animals were dissected directly by making an incision in the abdominal cavity from the bottom upwards toward the heart, then the liver was removed after removing the fatty tissue and the surrounding connective tissue, then washed with distilled water to remove the blood on them, then dried by placing them on filter paper and weighing them. These tissues are preserved in a 10% formalin solution. Following mounting, a 5 µm slice of each tissue was cut and subsequently immunostained with H and E. A pathologist blindly assessed and rated histopathological alteration(24).

Ethics approval

This study was approved by Anbar University under document number (219) dated December 23, 2024.

Statistical analysis

Findings were presented as Mean ± Standard Deviation for comparative analysis. The data were analyzed with SPSS (GIESSE Company, Rome, Italy) software employing one-way analysis of variance. Statistically significant was established as a P value inferior to 0.05. Subsequently, we analyzed the biochemical testing data to estimate the percentage changes resulting from exposure to CSP(25).

Results and Discussion

Effect of *Physalis angulata* extract on liver weights

The results of the investigation, as shown in Table 1, revealed substantial variations at the level of probability ($P < 0.05$) in average liver weights, with the CSP-injected group (5 mg/kg) demonstrating a marked increasing in weight of liver reaching values of (8.19) g relative to the control group. Significant differences were noted at the level of probability ($P < 0.05$) in the average liver weights across the two groups administered *P. angulata* extract at varying concentrations (150, 350 mg/kg) and injected with CSP (5 mg/kg), as the findings indicated a notable reduction in liver weights in these groups reaching values of (6.85, 6.49) g, respectively, relative to the positive

control group receiving CSP (5 mg/kg). Group 4 showed a non-significant decrease in liver weight (6.98 g) compared to Group 2.

Effect of *Physalis angulata* extract on liver function enzymes

The results in Figure 1 demonstrated a substantial elevation at a significant level ($P \leq 0.05$) in AST and ALT levels in the second group injected with CSP at a dose of 5 mg/kg (206.20, 84.40) U/L in comparison with the controlling group, while the groups that were dosed with the plant extract, as a preventive role were not affected, as they were close to the normal value. The results regarding the preventive effect of the extract indicated a significant decrease in AST and ALT levels in the treatment groups that received *P. angulata* at concentrations of 150, 250, and 350 mg/kg following CSP (5 mg/kg) administration. The AST levels were 141.60, 133.80, and 151.60 U/L, and ALT levels were 59.80, 54.60, and 68.20 U/L, respectively, compared with the second group treated with CSP alone

Histological study of the liver tissues

Histological images of the livers of rat from the different groups are shown in Figure 2. Light microscopic observations of liver tissue from the control group (G1) showed normal tissue architecture with a normal central vein and portal tract, cord-shaped hepatocytes, and interstitial blood sinusoids. Liver sections of rat treated with Cis showed histological damage (G2), vasodilation, and congestion were observed with inflammatory cell infiltration. In contrast, the groups receiving *P. angulata* and CSP (G3, G4) showed damage represented by hydropic and fatty degeneration of hepatocytes, vascular dilation and congestion with slight inflammatory cell infiltration, hepatocyte hyperplasia, and disappearance of liver sinusoids. Meanwhile, the group receiving *P. angulate* (350) and CSP (G5) demonstrated the protective role of the plant, with liver tissue appearing more like normal tissue.

The current study established the protective benefits of *P. angulata* extract against CSP-induced hepatotoxicity in rats. CSP, although advantageous in oncological therapy, has side effects, including liver toxicity, which limit its dosage(26).

From Table 1, treating rats with CSP resulted in a significant increase in relative liver weight. This increase in relative liver weight may be due to organ enlargement, indicating inflammation(27). Increased hepatic weight is obviously associated with liver injury; our results are in agreement with those of Gad El-Hak *et al*.(28). However, co-treatment with the *P. angulata* extracts resulted in a decrease in these parameters.

This study's results showed a correlation between structural changes in the liver resulting from exposure to CSP and changes in liver function. It was also evident that the average

Table 1: Comparison among various groups in the liver

Group	Liver weight (g), mean±SD
G1	6.81±0.32^{b}
G2	8.19±0.56^{a}
G3	6.85±0.39^{b}
G4	6.98±0.16^{a,b}
G5	6.49±0.60^{b}
LSD value	1.301*

*($P \leq 0.05$), ^{a,b}significant differences between groups at $P \leq 0.05$. LSD: Least significant difference, SD: Standard deviation

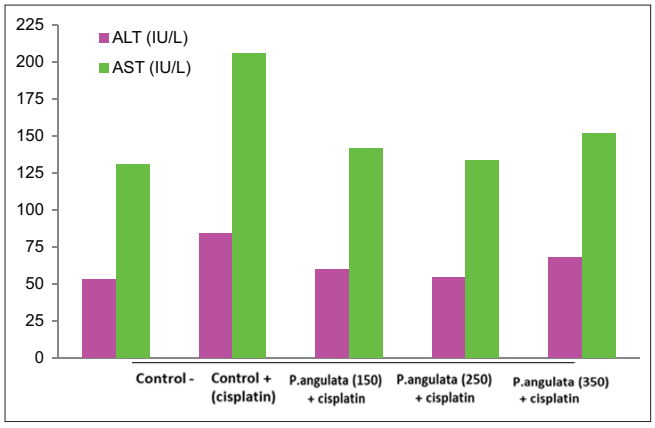

Figure 1: Comparison between different groups in alanine aminotransferase and aspartate aminotransferase. ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

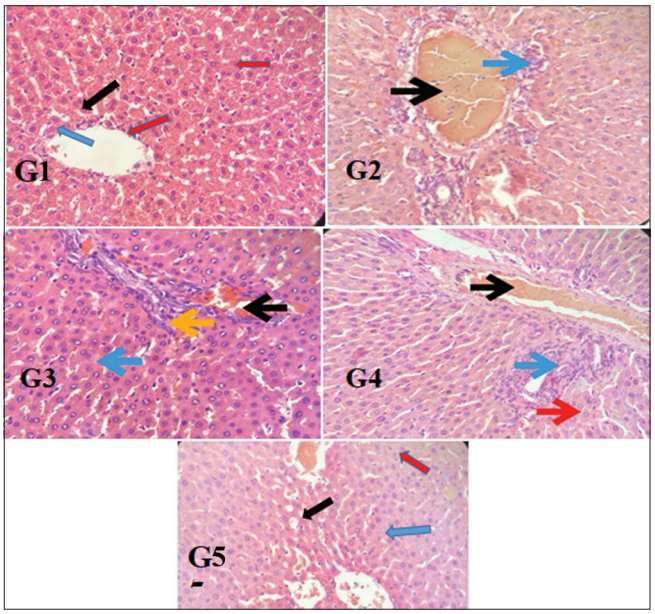

Figure 2: The liver tissue: (G1) the control group showed normal tissue architecture with a normal central vein and portal tract, cord-shaped hepatocytes, and interstitial blood sinusoids. This observation is based on H and E staining at a magnification of ×400. (G2) In the liver tissue, Vasodilation and congestion (black arrow) with infiltration of inflammatory cells (blue arrow) are shown by H and E stain (×400). (G3) The liver tissue, hepatic steatosis and fatty degeneration (blue arrow), vasodilation and congestion (black arrow) with infiltration of inflammatory cells (yellow arrow) is shown by H and E staining (×400). (G4) The liver tissue, dilatation and congestion of the central blood vessels (black arrow) with slight infiltration of inflammatory cells (blue arrow) and hepatocyte hyperplasia with disappearance of liver sinusoids (red arrow) is shown by H and E staining, (×400). (G5) The liver tissue shows a texture closer to the appearance of natural fabric is shown by H and E staining (×400)

levels of liver enzymes (ALT and AST) in the blood of the group exposed to CSP increased compared to the control group. CSP is believed to have the potential to increase serum ALT and AST activity, either as a result of CSP-induced liver injury and subsequent leakage of these enzymes into hepatocytes, or it may explain the development of liver degeneration and fibrosis(29). In agreement with the experimental results of Wang *et al*., the significant increase in ALT and AST occurs due to liver damage caused by CSP, which results from the attack of free radicals released by CSP on liver cells, thus leading to increased levels of liver enzymes released from damaged liver cells(30). The accumulation of CSP in hepatocytes causes histopathological changes characterized by microvesicular steatosis, necrosis, and infiltration of inflammatory cells(31,32). Tissue injury is often followed by an elevation in serum concentrations of aminotransferases, such as ALT and AST(33). Oral administration of *Physalis* extract to rats resulted in a decrease in liver enzymes. These results are consistent with a study(34), in which he researchers found that *Physalis* extract is rich in flavonoids and has hepatoprotective or antihepatoma activity.

The treatment of rats with CSP at a dose of 5 mg/kg resulted in histopathological changes in the liver in the form of vasodilation and congestion with infiltration of inflammatory cells. This was similar to the results of previous studies showing that the liver of rats receiving CSP at different doses (5, 7.5 mg/kg) showed dilation of the liver sinusoids, vascular congestion, infiltration of inflammatory cells in the liver stroma and portal triad, and focal sites of necrosis(35,36).

Phytochemical studies of *P. angulata* have shown that this plant contains phenolic compounds (flavonoids, tannins, and phenylpropane), secosteroids (physalis, tannins, etc.), and saponins(3). These phenolic compounds act as antioxidants by inhibiting the production of reactive oxygen species, repairing damage, and promoting cell growth(37). Sequenoids and saponins have anti-inflammatory and anti-proliferative effects, preventing the fibrosis process(3). *P. angulata* possesses three antifibrotic mechanisms. The first relies on phenolic compounds (such as flavonoids and tannins), whereas the second and third are associated with seco-steroids and saponins(3). Studies have demonstrated that the compound Physalin B exhibits antifibrotic activity and contributes to reducing liver fibrosis by lowering the levels of aspartate AST and ALT, indicating its potential in liver fibrosis repair(2,38). In a study conducted to evaluate the plant's efficacy in patients with scleroderma – a fibrotic disease affecting the skin – as an adjuvant treatment at a dose of 250 mg/kg three times daily for 12 weeks, the results showed a reduction in skin sclerosis scores. This effect is attributed to the plant's anti-inflammatory, antioxidant, and antiproliferative properties(39).

Conclusion

The *P. angulata* extract contains a bioactive component with potent antioxidant and anti-inflammatory activities. The extract's ability to reduce biomarkers such as ALT and AST in CSP-induced liver injury suggests its hepatoprotective activity. These observations were confirmed by histopathological observations.

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Conflicts of interest

There are no conflicts of interest.

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