Original Article

Tribulus terrestris L. Hydroalcoholic Extract Revokes the Hepatotoxicity Induced by Cytarabine in Male Wistar Rats

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ABSTRACT

Background: Liver is a critical organ that detoxifies poisonous compounds, metabolizes drugs, and excretes waste products. Liver is sensitive to damage and anticancer therapy. Cytarabine is the primary drug used to treat non-Hodgkin lymphoma and acute myeloid leukemia. However, due to its side effects, a new combination is needed to improve treatment outcomes. *Tribulus (T.) terrestris* is a long-known plant with anticancer activity and many chemical and biologically active substances with anti-inflammatory and antioxidant properties.

Objectives: This study investigated the effect of *T. terrestris* L. extract against the hepatotoxicity induced by cytarabine in rats.

Methods: A total of 24 adult male rats were divided into 4 groups (n=6): Control (saline 1 mL/kg), cytarabine (25 mg/kg), *T. terrestris* (250 mg/kg), and cytarabine + *T. terrestris* extract. Saline and cytarabine were administrated intraperitoneally, and *T. terrestris* extract was administered by oral gavage every day for 4 weeks. At the end of the treatments, blood serum samples were used for enzymes and antioxidant measurements, and liver samples were used for histological examination.

Results: In the cytarabine group, aspartate aminotransferase (AST), alanine transaminase (ALT), and malondialdehyde (MDA) significantly increased, and the levels of antioxidant enzymes significantly decreased compared to the control group. Also, the liver tissue had shown severe damage. In the cytarabine and *T. terrestris* extract group, the level of antioxidant enzymes increased, and MDA level, liver enzymes, and liver tissue damage decreased compared to the cytarabine group.

Conclusion: Our results indicate that *T. terrestris* with a dose of 250 mg/kg could significantly protect against cytarabine hepatotoxicity.

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Introduction

Liver is a critical organ due to its numerous essential biological activities [1]. Hepatic disorders are a primary global health concern. Drug toxicity, xenobiotic toxicity, and oxidative stress all have a significant impact on the liver [2]. Since liver is crucial for metabolizing many medications and poisons, including cytotoxic chemotherapy regimens, it is particularly vulnerable to harm [3]. Hepatotoxicity is a highly complex process. Some drugs affect the liver and lead to acute and chronic liver injuries. The potential for toxicity might arise from the initial chemical, a reactive metabolite, or an immunologically mediated reaction [4].

Chemotherapy is a successful treatment technique for many cancers, but it also has several drawbacks due to the employment of a combination of highly toxic substances. The high toxicity and limited specificity of this type of treatment could be a problem [5].

Cytarabine (Ara-C) treats non-Hodgkin lymphoma and acute myeloid leukemia [6]. It belongs to the antimetabolic drug class and causes damage to the DNA molecule in the S phase of the cell cycle [7]. In addition, DNA and RNA polymerases and nucleotide reductase are inhibited by Ara-C. It affects all cancerous cells or cells with high division that require DNA replication [8]. The toxic effects of Ara-C have been shown in both human and rat models, resulting in many adverse health outcomes such as leukopenia, thrombocytopenia, anemia, digestive system abnormalities, fever, conjunctivitis, pneumonitis, and liver dysfunction. In a subset of patients, Ara-C-based chemotherapy regimens can result in a suboptimal clinical outcome [9]. Drug-induced liver damage caused by chemotherapy medicines is a major source of morbidity and mortality. The principal processes behind chemotherapy-related hepatotoxicity are based on forming reactive metabolites produced by phase I oxidation events, immunological damage, or changes in mitochondrial activity. Various clinical approaches have been proposed to minimize significant toxicity, such as reducing the dose of cytarabine or using hepatoprotective compounds and extracts [10-12].

Tribulus (T.) terrestris is a member of the Zygophyllaceae family and is found worldwide [13]. *T. terrestris* as a medicinal plant has been well-established due to its historical usage in traditional medicine practices of significant cultures in various regions, such as China and India, and traditional medicine in south-eastern Europe [14]. Fruits of *T. terrestris* have been used to cure mammary duct obstruction, skin itching, headaches, vertigo, erectile dysfunction, diuretic effects, inflammatory diseases, and nephritis. Recent research showed that the main chemical compounds in this plant are steroidal saponins and flavonoids with anti-inflammatory and anti-aging properties [15]. Research has shown that this plant cures liver fibrosis [16], improves the level of liver enzymes, down-regulates proinflammatory markers in liver damage [17], has anti-proliferative and pro-apoptotic properties, and improves the signs of non-alcoholic fatty liver [18].

The current study was conducted to investigate the effect of *T. terrestris* L. hydroalcoholic extract against the hepatotoxicity induced by cytarabine in male Wistar rats by measuring liver enzymes' antioxidant capacity and investigating the histopathology of the liver.

Materials and Methods

Plant extract

To prepare the hydroalcoholic extract of *T. terrestris*, the plant was prepared from the Arak Agricultural Jihad Center. Then, 100 g of the whole plant was dried. After grinding, this powder was dissolved in 150 mL of 70% alcohol and kept in the laboratory for 3 days. After three days, the solution was first passed through a paper filter, and the filtrate was purified using a vacuum rotatory evaporator to obtain extract [19].

Study animals

Male Wistar rats (200-220 g, about 8 weeks old) were prepared from Pasteur Institute (Tehran, Iran) and kept in plexiglas cages with appropriate laboratory conditions (25-28 ˚C, 40%-60% humidity, ventilation, and the light system was 12 hours per day. Each cage consists of not more than four rats. Rats were fed on the standard chow and drinking water ad libitum throughout the experiment. To acclimatize, they were kept fifteen days before the experimental assay.

Experiment design

A total of 24 male rats were divided into 4 groups (n=6): Control group (saline 1 mL/kg, IP), cytarabine group (Ara-C 25 mg/kg, IP) [20], *T. terrestris* extract group (250 mg/kg. orally), [21] and cytarabine (Ara-C 25 mg/kg, IP) + *T. terrestris* extract group (250 mg/kg. orally). Based on previous studies, the LD_{50} and 95% confidence limits of *T. terrestris* were 813 and 894-739 mg/kg, respectively [22].

Treatments were done every day for 4 weeks. At the end of the treatments, rats were anesthetized with 3.5% chloral hydrate (35 mg/100 g IP), and blood sample collection was performed with a heart puncher. Blood samples were centrifuged using a refrigerated centrifuge (universal device, made in Germany) at 4 ˚C (13300 rpm for 10 min), and the supernatant was frozen at −20 ˚C in aliquots until using biochemical assays. Liver samples were also collected, washed in 0.9% saline, and preserved in 10% neutral buffered formalin for further investigation.

Enzymes measurements

The levels of angiotensin-converting enzyme (ACE) (BioSystems kits, Spain), aspartate aminotransferase (AST) (BioSystems kits, Spain), gamma-glutamyl transferase (GGT) (BIOLABO kit, France) and alanine transaminase (ALT) (Spectrum kit, Egypt) in blood serum samples were evaluated to determine the enzymatic activities of the livers in all groups. The activity of serum enzymes was measured using commercially available kits according to the manufacturer's instructions.

Antioxidant assessments

Blood serum was used to measure antioxidant power in different experimental groups. The amount of malondialdehyde (MDA) was measured using the thiobarbituric acid (TBA) method. In this method, aldehydes entered a reaction with thiobarbiturate and formed pink complexes. This complex can be measured by spectrophotometry in 535 nm wavelength and expressed as µmol/L [23] The level of superoxide dismutase (SOD) enzyme activity was measured using pyrogallol. Pyrogallol oxidizes spontaneously in aqueous and alkaline environments. The enzyme SOD prevents the spontaneous oxidation of pyrogallol. Enzyme activity is measured at a wavelength of 420 nm and expressed as U/mL [24]. The catalase (CAT) activity measurement involved incubating enzymes in a substrate solution of hydrogen peroxide in sodium-potassium phosphate buffer at 37 ˚C for 3 minutes. The experiment was concluded by using ammonium molybdate. Enzyme activity is measured at a wavelength of 374 nm and expressed as kU/L [25].

Histopathological studies

Liver sections, 5-µm thick, obtained from the largest liver lobes of rats were processed routinely, hematoxylin and eosin-stained. The fixed tissues of rats were dehydrated with ethanol. Then, the tissues were passed through a xylene solution to remove the ethanol and facilitate molten paraffin wax infiltration. After that, they were embedded in a wax block. Paraffin sections were cut with the rotary microtome (Leitz, 1512) and stained by the hematoxylin-eosin method [26]. The stained slides were examined using a light microscope (BX40, Olympus, New York, USA) connected to a camera (Olympus, DP12) and quantitatively analyzed by Image J software.

Statistical analysis

The SPSS software, version 24 was used for statistical analysis. The results in which one-way (ANOVA) calculated the significant difference between groups were defined as $P<0.05$. The least significant difference (LSD) test was performed to investigate the considerable levels among averages of treatments.

Results

Comparing serum ACE and GGT between experimental groups

The current study shows that the amount of ACE and GGT in the cytarabine group did not significantly differ from the control group ($P>0.05$). However, there is a significant decrease in serum ACE and GGT in the group treated with cytarabine + *T. terrestris* extract ($P<0.05$) compared to the cytarabine group. There is no significant difference in levels of serum ACE and GGT between the control group and the *T. terrestris* group ($P>0.05$) (Figure 1A and 1B).

Comparing serum AST and ALT between experimental groups

The current study shows a significant increase in serum AST and ALT in the cytarabine group compared to the control group. The amounts of AST and ALT in the group treated with cytarabine + *T. terrestris* extract significantly decreased compared to the cytarabine group and reached the control group. There is no significant difference in levels of serum AST and ALT between the control group and the *T. terrestris* group ($P>0.05$) (Figure 1C and 1D).

Comparing serum antioxidant levels between experimental groups

In the group treated with cytarabine, there was a significant decrease in the level of SOD and CAT ($P<0.05$) enzymes and a significant increase in the level of MDA ($P<0.01$) compared with the control group. In the combination group, treatment with *T. terrestris* extract could

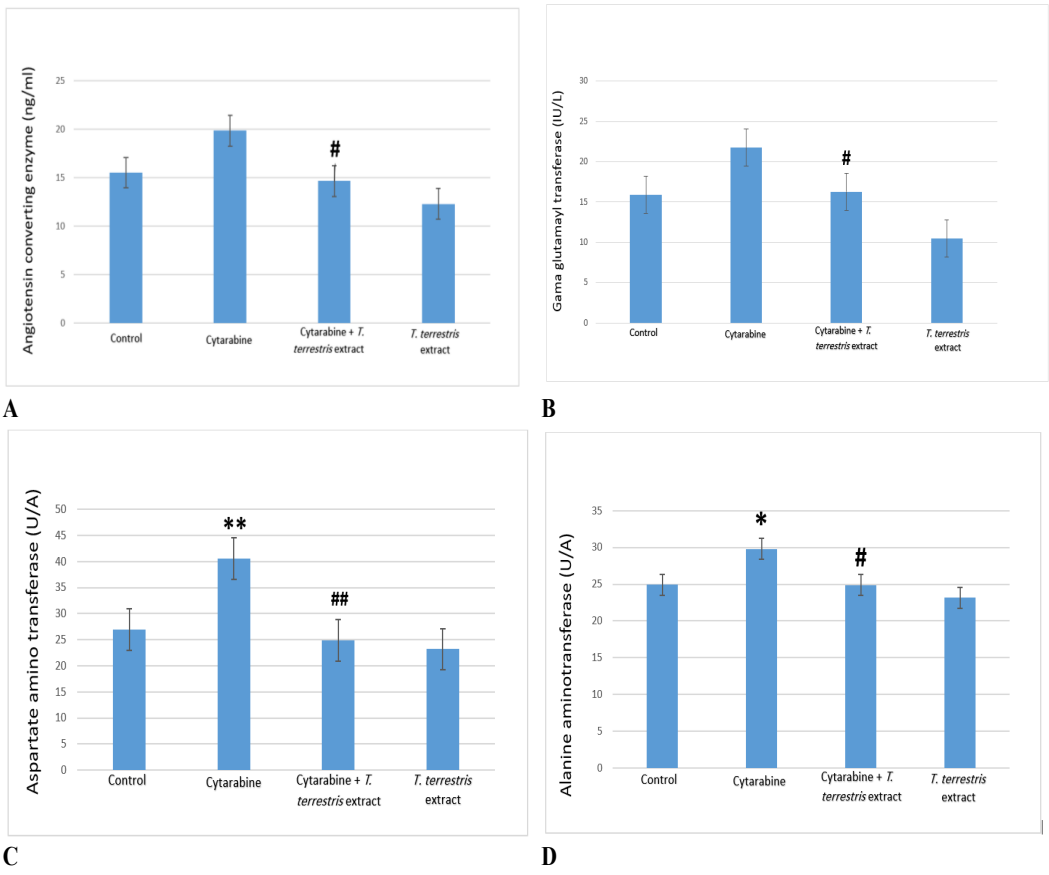

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Figure 1. Comparing serum angiotensin-converting enzyme (A), Gamma-glutamyl transferase (B), Aspartate aminotransferase (C), and alanine transaminase (D) in the experimental groups

Note: Groups treated with normal saline (1 mL/kg), cytarabine (25 mg/kg, IP), cytarabine (25 mg/kg, IP) + *T. terrestris* extract (250 mg/kg, orally) and *T. terrestris* extract (250 mg/kg, orally). The results are represented as Mean±SEM.

*P<0.05 and **P<0.01 compared with the control group. #P<0.05 and ##P<0.01 compared with the cytarabine group.

not change the amounts of MDA and CAT compared to the cytarabine group. However, in comparison with the cytarabine group, the amount of SOD significantly increased (P<0.05). There is no significant difference in levels of SOD, CAT, and MDA between the control group and the *T. terrestris* group (P>0.05) (Table 1).

Histological study

The liver specimens from the control group exhibited typical histological features with a normal central vein (white arrow) surrounded by hepatocyte cords (black arrow) and significant blood sinusoids (yellow arrow). Hepatocytes have large prominent nuclei and remarkable granular cytoplasm (Figure 2A).

In the cytarabine group, liver tissue revealed significant histological alterations of the hepatic lobule with severe congestion in the central vein and hepatocyte cords (black arrow), marked infiltration of inflammatory cells around blood vessels (white arrow), and significant hyperplasia in bile ductile (yellow arrow) (Figure 2B).

In the group treated with cytarabine + *T. terrestris* extract, the liver tissue showed reversible histological changes manifested by mild congestion in the central vein and sinusoids (black arrow), mild hepatocyte degeneration, and the presence of hepatocytes vacuolation (white arrow) and mild hepatocyte degeneration with a proliferation of newly formed bile ductulus (yellow arrow) (Figure 2C).

The histopathological analysis of the liver tissue from the group treated with *T. terrestris* revealed no significant histological alterations. The liver tissue seemed to be similar to normal liver histology, with slight congestion in the central vein (black arrow) and minimal hepatocyte degeneration (white arrow) (Figure 2D).

Table 1. Comparing serum SOD, CAT, and MDA levels in the experimental groups

Groups / Parameter	Control	Cytarabine	Cytarabine + *T. terrestris*	*T. terrestris*	P
SOD (U/mL)	149.45±23.69	80.58±20.72*	171.21±39.89#	210.03±25.2	0.030
CAT (kU/L)	0.980±0.02	0.784±0.06*	0.880±0.06	0.987±0.05	0.049
MDA (µmol/L)	1.917±0.27	3.325±0.15**	2.679±0.43	1.948±0.23	0.008

Abbreviation: SOD: Superoxide dismutase; CAT: Catalase; MDA: Malondialdehyde.

Note: The results are represented as Mean±SEM. *P<0.05 and **P<0.01 compared with control group. #P<0.05 compared with the cytarabine group.

Discussion

This study shows a significant increase in liver enzymes, especially AST and ALT, in the cytarabine group compared with the control group. The cytarabine + *T. terrestris* extract group treated with *T. terrestris* extract significantly decreased liver enzymes (GGT, AST, and ALT) and ACE and reached the control group.

ACE is an essential enzyme in regulating blood pressure and fluid balance. The liver controls the renin-angiotensin-aldosterone system, and any damage to the liver will lead to an increase in ACE [27]. GGT has been recognized as a clinical indicator in proinflammatory processes. It has been identified as a significant prognostic indicator in cases such as all-cause mortality, cancer, diabetes, and cardiovascular disease [28]. ALT and AST are enzymes commonly found within liver cells and involved in various metabolic processes. When liver cells are damaged or destroyed, these enzymes leak into the bloodstream, causing an increase in their levels [29].

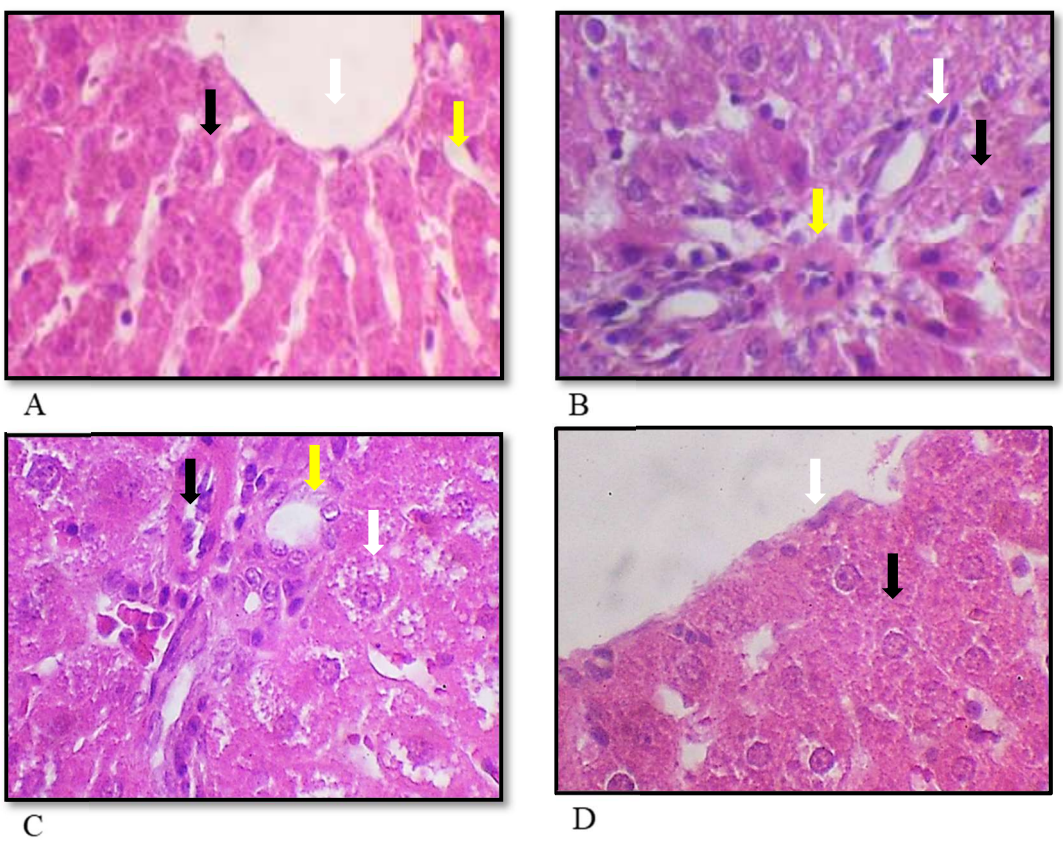

Figure 2. Photomicrograph of the hepatic section in the control group (A), cytarabine group (B), in the group treated with Cytarabine + *T. terrestris* extract (C) and *T. terrestris* extract group (D), (H&E staining, ×400 magnification).

Cytarabine is a chemotherapy medication that prevents DNA replication in cancer cells and leads to cell death. However, it can also affect normal cells, including liver cells, and may cause toxicity [30]. Cytarabine can generate reactive oxygen species (ROS) in liver cells and affect the function of mitochondria. Mitochondrial dysfunction can damage liver cells and increase liver enzyme levels. Also, cytarabine activates programmed cell death pathways, damaging liver cells and increasing liver enzyme levels [31].

T. terrestris may protect the liver by reducing inflammation. Inflammation is a typical response to liver damage, and chronic inflammation can lead to further liver damage and the development of liver disease. Studies have shown that *T. terrestris* contains compounds such as saponins and terpenoids that have anti-inflammatory properties and may help reduce inflammation in the liver [32]. *T. terrestris* may also help protect the liver by raising the production of certain enzymes, including detoxifying deleterious materials in the liver [33].

This research shows a significant decrease in the level of SOD and CAT and a significant increase in the level of MDA in the cytarabine group compared with the control group. In cytarabine + *T. terrestris* extract group did not show any significant changes in the levels of CAT and MDA compared with the cytarabine group but the level of SOD significant increase and reached the control group.

SOD and CAT are enzymes that play an essential role in protecting cells from oxidative stress [34]. Several studies have reported that cytarabine can decrease the levels of SOD and CAT and increase MDA in various tissues, leading to an increase in oxidative stress and liver damage [35, 36]. Additionally, cytarabine may generate ROS directly, which can overwhelm the cells' antioxidant defenses and diminish SOD and CAT levels. Also, cytarabine treatment decreased the gene expression of the SOD [37] and CAT [38] and suggested that this decrease may contribute to oxidative stress in liver cells.

Some studies have investigated the effects of *T. terrestris* on antioxidant enzymes, and It seems that this plant contains bioactive compounds with antioxidant properties that stimulate the expression or activity of SOD and CAT enzymes [39]. Additionally, *T. terrestris* may increase the availability of essential micronutrients and bioactive compounds such as zinc, selenium, saponins, protodioscin [40], and flavonoids, which are essential cofactors for SOD and CAT activity. These compounds have been shown to scavenge free radicals and diminish oxidative stress in vitro and animal models [41].

In the cytarabine group, liver tissue revealed histological alterations such as severe congestion in the central vein, marked infiltration of inflammatory cells around blood vessels, and hyperplasia in bile ductility. Cytarabine is a chemotherapy drug that treats various cancers but can also have some side effects on healthy cells [42]. Cytarabine can cause liver toxicity, which may result in liver histological alterations such as steatosis, necrosis, and fibrosis [43].

The combination group treated with *T. terrestris* extract caused reversible histological changes in liver tissue. This group showed mild congestion in the central vein and sinusoids, mild hepatocyte degeneration, and proliferation to form a new bile ductulus.

This result may occur due to *T. terrestris* containing a beneficial chemical to the liver. One of the main active components of *T. terrestris* is saponins, a plant compound shown to have anti-inflammatory and antioxidant properties. These properties may help to protect the liver from injury caused by oxidative stress and inflammation [44]. *T. terrestris* may help reduce the production of ROS in the liver tissue, which could benefit liver health. Some animal studies have suggested that *T. terrestris*-may have hepatoprotective effects, which could help protect the liver from damage caused by toxins or other harmful substances [45].

Conclusion

Hepatotoxicity caused by cytarabine increases the level of liver enzymes and causes oxidative stress, which leads to destructive changes in liver tissue. This research suggests that *T. terrestris* may have potential therapeutic benefits in mitigating liver damage caused by cytarabine treatment in animal models. *T. terrestris* can effectively prevent tissue damage caused by cytarabine by reducing liver enzymes and increasing the SOD enzyme. In summary, *T. terrestris* shows promise as a protective agent for liver health, but additional research is needed to validate its efficacy in humans undergoing chemotherapy.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of the School of Biology, Arak University (Code: IR.ARAKMU.REC.1402.067) and carried out by laboratory animal care's ethical standards and principles (NIH publication).

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Authors' contributions

Writing: Niloufar Darbandi; Investigation and formal analysis: Ruba Fadhel Jabbar; Review and editing: All authors.

Conflict of interest

The authors declared no conflict of interest.

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References

[1] Xu E, Zhang L, Yang H, Shen L, Feng Y, Ren M, Xiao Y. Transcriptome profiling of the liver among the prenatal and postnatal stages in chickens. Poult Sci. 2019; 98(12):7030-40. [DOI:10.3382/ps/pez434] [PMID] [PMCID]

[2] Jaeschke H, Gores GJ, Cederbaum AI, Hinson JA, Pessayre D, Lemasters JJ. Mechanisms of hepatotoxicity. Toxicol Sci. 2002; 65(2):166-76. [DOI:10.1093/toxsci/65.2.166] [PMID]

[3] Bischoff K, Mukai M, Ramaiah SK. Liver toxicity. In: Gupta RC, editor. Veterinary toxicology. 3th ed. London: Academic Press; 2018. [DOI:10.1016/B978-0-12-811410-0.00015-5]

[4] Hassan A. Antimicrobial evaluation, in silico ADMET prediction, molecular docking, and molecular electrostatic potential of pyrazole-isatin and pyrazole-indole hybrid molecules. J Iran Chem Soc. 2022; 19:3577–89. [DOI:10.1007/s13738-022-02551-6]

[5] Galbiatti AL, Padovani-Junior JA, Maníglia JV, Rodrigues CD, Pavarino ÉC, Goloni-Bertollo EM. Head and neck cancer: Causes, prevention and treatment. Braz J Otorhinolaryngol. 2013; 79(2):239-47. [DOI:10.5935/1808-8694.20130041] [PMID] [PMCID]

[6] Wu Y, Wang F, Zheng Q, Lu L, Yao H, Zhou C, et al. Hepatoprotective effect of total flavonoids from Laggera alata against carbon tetrachloride-induced injury in primary cultured neonatal rat hepatocytes and in rats with hepatic damage. J Biomed Sci. 2006; 13(4):569-78. [DOI:10.1007/s11373-006-9081-y] [PMID]

[7] Guerrero-Bustamante CA, Dedrick RM, Garlena RA, Russell DA, Hatfull GF. Toward a phage cocktail for tuberculosis: susceptibility and tuberculocidal action of mycobacteriophages against diverse Mycobacterium tuberculosis strains. mBio. 2021; 12(3):e00973-21. [DOI:10.1128/mBio.00973-21] [PMID] [PMCID]

[8] Xiao Z, Zhuang B, Zhang G, Li M, Jin Y. Pulmonary delivery of cationic liposomal hydroxycamptothecin and 5-aminolevulinic acid for chemo-sonodynamic therapy of metastatic lung cancer. Int J Pharm. 2021; 601:120572. [DOI:10.1016/j.ijpharm.2021.120572] [PMID]

[9] Raj S, Khurana S, Choudhari R, Kesari KK, Kamal MA, Garg N, et al. Specific targeting cancer cells with nanoparticles and drug delivery in cancer therapy. Semin Cancer Biol. 2021; 69:166-77. [DOI:10.1016/j.semcancer.2019.11.002] [PMID]

[10] Sultan ON, Taqa GA. Physiological and histological effects of apigenin and luteolin on Cytarabine injected rats. Baghdad Sci J. 2023; 21(1):1-9. [DOI:10.21123/bsj.2023.7000]

[11] Majed MS, Hassan MS, Mousa RF, Hassan MS, Alzaidi OH, Al-Sabbagh JK, et al. Histological study of L-carnitine effect against acute hepatotoxicity after cytarabine chemotherapy in male rats. Int J Health Sci. 2022; 6(S6):8063-71. [DOI:10.53730/ijhs.v6nS6.12202]

[12] Calgarotto AK, Longhini AL, Pericole de Souza FV, Duarte ASS, Ferro KP, Santos I, et al. Immunomodulatory effect of green tea treatment in combination with low-dose chemotherapy in elderly acute myeloid leukemia patients with myelodysplasia-related changes. Integr Cancer Ther. 2021; 20:15347354211002647. [DOI:10.1177/15347354211002647] [PMID] [PMCID]

[13] Ahmed A, Waseem Ali S, Afzaal M, Saeed MF, Saleem MA, Bilal M, et al. Tribulus terrestris L.: Gokshur/Gokharu. In: Sharma A, Nayik GA, editors. Immunity boosting medicinal plants of the western Himalayas. 1th ed. Singapore: Springer Nature Singapore; 2023. [DOI:10.1007/978-981-19-9501-9_23]

[14] Sharma D, Kumar A. Traditional medicinal plants of high value: Tribulus terrestris: A review. World J Pharm Res. 2020; 9(12):729-35. [Link]

[15] Zhu W, Du Y, Meng H, Dong Y, Li L. A review of traditional pharmacological uses, phytochemistry, and pharmacological activities of Tribulus terrestris. Chem Cent J. 2017; 11(1):60. [DOI:10.1186/s13065-017-0289-x] [PMID] [PMCID]

[16] Altay D, Dogan Y, Orhan C, Tuzcu M, Şahin N, Ozercan I, et al. Hepatoprotective effects of Tribulus terrestris, Ashwagandha and N-acetylcysteine on liver fibrosis in carbon tetrachloride-induced rats. Acta Pol Pharm Drug Res. 2019; 76(5):805-13. [DOI:10.32383/appdr/109201]

[17] Ali SI, Gaafar AA, Abdallah AA, El-Daly SM, Elbana M, Hussein J. Mitigation of alpha-cypermethrin-induced hepatotoxicity in rats by Tribulus terrestris rich in antioxidant compounds. Jordan J Biol Sci. 2018; 11(5):517-25. [Link]

[18] Almasi F, Khazaei M, Chehrei S, Ghanbari A. Hepatoprotective effects of Tribulus terrestris Hydro-Alcholic Extract on Non-Alcoholic Fatty Liver- Induced Rats. Int J Morphol. 2017; 35(1):345-50. [DOI:10.4067/S0717-95022017000100054]

[19] Garmus TT, Kopf SF, Paula JT, Aguiar AC, Duarte GH, Eberlin MN, et al. Ethanolic and hydroalcoholic extraction of Pitanga leaves (Eugenia uniflora L.) and their fractions by supercritical technology. Braz J Chem Eng. 2019; 36(2):1041-51. [DOI:10.1590/0104-6632.20190362s20180159]

[20] Namoju R, Chilaka NK. Alpha-lipoic acid ameliorates cytarabine-induced developmental anomalies in rat fetus. Hum Exp Toxicol. 2021; 40(5):851-68. [DOI:10.1177/0960327120975114] [PMID]

[21] Ojha SK, Nandave M, Arora S, Narang R, Dinda AK, Arya DS. Chronic administration of Tribulus terrestris Linn. extract improves cardiac function and attenuates myocardial infarction in rats. Int J Pharmacol. 2008; 4(1):1-10. [DOI:10.3923/ijp.2008.1.10]

[22] Arcasoy HB, Erenmemisoglu A, Tekol Y, Kurucu S, Kartal M. Effect of Tribulus terrestris L. saponin mixture on some smooth muscle preparations: A preliminary study. Boll Chim Farm. 1998; 137(11):473-5. [PMID]

[23] Buege JA, Aust SD. Microsomal lipid peroxidation. Methods Enzymol. 1978; 52:302-10. [DOI:10.1016/S0076-6879(78)52032-6] [PMID]

[24] Marklund S, Marklund G. Involvement of the superoxide anion radical in the autoxidation of pyrogallol and a convenient assay for superoxide dismutase. Eur J Biochem. 1974; 47(3):469-74. [DOI:10.1111/j.1432-1033.1974.tb03714.x] [PMID]

[25] Hadwan MH, Abed HN. Data supporting the spectrophotometric method for the estimation of catalase activity. Data Brief. 2015; 6:194-9. [DOI:10.1016/j.dib.2015.12.012] [PMID] [PMCID]

[26] Colak E, Ustuner MC, Tekin N, Colak E, Burukoglu D, Degirmenci I, et al. The hepatocurative effects of Cynara scolymus L. leaf extract on carbon tetrachloride-induced oxidative stress and hepatic injury in rats. Springerplus. 2016; 5:216. [DOI:10.1186/s40064-016-1894-1] [PMID] [PMCID]

[27] Ghanem M, Megahed HMA. Renin-Angiotensin-Aldosterone system role in Organ Fibrosis. In: Bhullar SK, Tappia PS, Dhalla NS, editors. The Renin Angiotensin System in Cancer, Lung, Liver and Infectious Diseases. 1th ed. Cham: Springer International Publishing; 2023. [DOI:10.1007/978-3-031-23621-1_12]

[28] Lee SY, Sung E, Chang Y. Elevated serum gamma-glutamyltransferase is a strong marker of insulin resistance in obese children. Int J Endocrinol. 2013; 2013:578693. [DOI:10.1155/2013/578693] [PMID] [PMCID]

[29] Reutemann B, Gordon FD. Evaluation of the patient with markedly abnormal liver enzymes. Clin Liver Dis. 2023; 27(1):1-16. [DOI:10.1016/j.cld.2022.08.007] [PMID]

[30] Abbas G, Cui M, Wang D, Li M, Zhang XE. Construction of genetically encoded biosensors to monitor subcellular compartment-specific glutathione response to chemotherapeutic drugs in acute myeloid leukemia cells. Anal Chem. 2023; 95(5):2838-47. [DOI:10.1021/acs.analchem.2c04255] [PMID] [PMCID]

[31] Chiou JT, Hsu CC, Hong YC, Lee YC, Chang LS. Cytarabine-induced destabilization of MCL1 mRNA and protein triggers apoptosis in leukemia cells. Biochem Pharmacol. 2023; 211:115494. [DOI:10.1016/j.bcp.2023.115494] [PMID]

[32] Jegadheeshwari S, Pandian R, Senthilkumar U. Bioactives and Pharmacology of Tribulus terrestris L. In: Pullaiah T, editor. Bioactives and pharmacology of medicinal plants. 1th ed. New York: Apple Academic Press; 2022. [DOI:10.1201/9781003281658-11]

[33] Yuan Z, Du W, He X, Zhang D, He W. Tribulus terrestris Ameliorates Oxidative Stress-Induced ARPE-19 Cell Injury through the PI3K/Akt-Nrf2 Signaling Pathway. Oxid Med Cell Longev. 2020; 2020:7962393. [DOI:10.1155/2020/7962393] [PMID] [PMCID]

[34] Salimi A, Shabani M, Nikjou A, Choupani M, Biniyaz M. Exploring the possible mitoprotective and neuroprotective potency of thymoquinone, betanin, and vitamin D against cytarabine-induced mitochondrial impairment and neurotoxicity in rats' brain. J Biochem Mol Toxicol. 2023; 37(2):e23256. [DOI:10.1002/jbt.23256] [PMID]

[35] Han S, Xiu M, Li S, Shi Y, Wang X, Lin X, et al. Exposure to cytarabine causes side effects on adult development and physiology and induces intestinal damage via apoptosis in Drosophila. Biomed Pharmacother. 2023; 159:114265. [DOI:10.1016/j.biopha.2023.114265] [PMID]

[36] Alexander TB, Lacayo NJ, Choi JK, Ribeiro RC, Pui CH, Rubnitz JE. Phase I study of selinexor, a selective inhibitor of nuclear export, in combination with fludarabine and cytarabine, in pediatric relapsed or refractory acute leukemia. J Clin Oncol. 2016; 34(34):4094-101. [DOI:10.1200/JCO.2016.67.5066] [PMID] [PMCID]

[37] Ma J, Liu B, Yu D, Zuo Y, Cai R, Yang J, et al. SIRT3 deacetylase activity confers chemoresistance in AML via regulation of mitochondrial oxidative phosphorylation. Br J Haematol. 2019; 187(1):49-64. [DOI:10.1111/bjh.16044] [PMID] [PMCID]

[38] Al-Harrasi A, Bhatia S, Aldawsari M, Behl T. Plant Profile, Phytochemistry, and Ethnopharmacological Uses of Terminalia bellirica, Terminalia chebula, and Terminalia arjuna. In: Al-Harrasi A, Bhatia S, Behl T, Aldawsari MF, Kaushik D, Chigurupati S, editors. Recent advances in natural products science. 1th ed. Boca Raton: CRC Press: 2022. [DOI:10.1201/9781003274124-4]

[39] Ivanova A, Lazarova I, Mechkarova P, Tchorbanov B. HPLC method for screening of Steroidal Saponins and Rutin as biologically active compounds in Tribulus Terrestris L. Biotechnol Biotechnol Equip. 2014; 24(Sup 1):129-33. [DOI:10.1080/13102818.2010.10817826]

[40] Sergeev M, Zaitsev G, Yermolin D. Determination of protodioscin in tribulus terrestris by reversed-phase high-performance liquid chromatography. E3S Web Conf. 2021; 284:03002. [DOI:10.1051/e3sconf/202128403002]

[41] Mohamed SS, Zeima NM, El-Melmoslemany AM. The Effect of Tribulus terrestris fruits and Urtica dioica leaves extracts on renal calculus induced by sodium oxalate in experimental rats. Bull National Nutr Inst Arab Repub Egypt. 2023; 61(1):100-37. [DOI:10.21608/bnni.2023.291548]

[42] Al-Jammas S, Al-Saraj A. The histological changes induced by cytarabine on rabbits kidneys (with and without vitamin E administration). Iraqi J Vet Sci. 2019; 33(2):311-6. [DOI:10.33899/ijvs.2019.162910]

[43] Sharma U, Pal D, Prasad R. Alkaline phosphatase: An overview. Indian J Clin Biochem. 2014; 29(3):269-78. [DOI:10.1007/s12291-013-0408-y] [PMID] [PMCID]

[44] Dinchev D, Janda B, Evstatieva L, Oleszek W, Aslani MR, Kostova I. Distribution of steroidal saponins in Tribulus terrestris from different geographical regions. Phytochemistry. 2008; 69(1):176-86. [DOI:10.1016/j.phytochem.2007.07.003] [PMID]

[45] Jiang YH, Yang CH, Li W, Wu S, Meng XQ, Li DN. Aqueous extracts of Tribulus terrestris protects against oxidized low-density lipoprotein-induced endothelial dysfunction. Chin J Integr Med. 2016; 22(3):193-200. [DOI:10.1007/s11655-015-2321-0] [PMID]

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