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Protective activity of hydroalcoholic extract of *zingiber officinale* rosc. on doxorubicin-induced hepatic toxicity in male rats

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Abstract

Background: Research has shown that the extract of some plants has an effective protective effect on liver cells against toxins and oxidants. In this research, the effect of hydroalcoholic extract of ginger against hepatotoxicity caused by doxorubicin (Dox) in adult male rats was investigated.

Methods: In this experimental study, 63 adult male rats were divided into 7 groups (n = 9 per group). The experimental treatments included the control and placebo groups without the use of medicines, experimental group I that received Dox at a dose of 20 mg/kg, experimental groups II and III with 300 and 600 mg/kg of ginger hydroalcoholic extract, and experimental groups IV and V that received 20 mg/kg Dox + 300 and 600 mg/kg of ginger hydroalcoholic extract, respectively. After the end of the test period, serum levels of total bilirubin and direct bilirubin were measured. In addition, the histological changes in the liver were examined after hematoxylin and eosin (H&E) staining.

Results: Serum levels of total bilirubin and direct bilirubin in the Dox group showed a significant increase compared to the control group. In contrast, serum levels of total bilirubin and direct bilirubin in Dox + ZIN 600 and Dox + ZIN 300 had a significant reduction compared to the Dox group ($P < 0.05$). Ginger extract prevented apoptosis and Dox-induced liver tissue damage in dose-dependent designs.

Conclusion: The hydroalcoholic extract of ginger improves the changes of serum bilirubin and liver tissue after receiving Dox due to its antioxidant compounds.

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Introduction

Doxorubicin (Dox) is an anti-cancer drug that prevents the growth and development of cancer cells in the body (1). This medicine is used in the treatment of various types of cancer that affect the breast (2), bladder (3), ovary (3), thyroid (4), stomach (5), lung (6), bone (7), nervous tissue (8), muscles (9), joints (10), and soft tissues, as well as in the treatment of Hodgkin lymphoma and acute leukemia (11, 12). This medicine performs by binding to DNA and inhibiting nucleic acid production by disrupting the molecular structure and creating steric hindrance. Cell structure studies have shown rapid cell penetration and binding to nuclear chromatin, rapid inhibition of mitotic activity, and nucleic acid synthesis, as well as induction of mutations and chromosomal abnormalities (13, 14).

Doxorubicin leads to myocardial toxicity by causing oxidative stress caused by an imbalance between reactive oxygen species (ROS) and endogenous antioxidants (15). Doxorubicin treatment impairs liver mitochondrial function in sedentary animals due to changes in mitochondrial oxidative capacity, as well as biogenesis, degradation, and acetylation of protein (16).

The ginger plant is used as medicine, spice, and delicious food worldwide (17). This rhizome is prepared from the *Zingiber officinale* plant. The cultivation of ginger plants was first in Asia, which then spread to West Africa and then the Caribbean (18). The special smell and taste of ginger are due to the mixture of volatile oils (gingerols, shogaols, and zingerone) that make up 3% of the weight of fresh ginger (19). In laboratory animals, gingerols increase the stimulation of the digestive tract and have analgesic, antipyretic, and antibacterial properties (20). Ginger oil has an anti-cancer effect on mice (21), and studies have shown the lethality of gingerols on ovarian cancer cells (22). To date, more than 160 compounds, including volatile oils, gingerol analogs, diarylheptanoids, phenylalkanoids, sulfonates, steroids, and monoterpenoid glycoside compounds, have been isolated and identified from ginger. This medicinal plant has a wide range of biological activities, especially the protective effects of the digestive system, anticancer, and prevention of obesity (22, 23).

Studies have shown that ginger can reduce the severity of hepatocellular toxicity caused by diethylnitrosamine (24, 25). The extract of this plant effectively protects the liver against the toxic effects of polychlorinated biphenyls and declines liver and kidney dysfunction as well as oxidative stress (26, 27). Some studies have shown that malathion leads to liver and kidney poisoning, and adding a ginger and zinc mixture has protective effects. The ginger extract can also prevent liver and kidney damage caused by iron sulfate (28, 29). Research has shown that *Z. officinale* has a protective effect against rat liver fibrosis through its ability to modulate the transforming growth factor β_1 (TGF-β_1)/Smad$_3$ (Mothers against decapentaplegic homolog 3) and nuclear factor-κB (NF-κB)/IκB (Nuclear factor kappa B) signaling pathways (30). The ginger was found to have protective effects against piroxicam hepatotoxicity by reducing serum marker enzymes, liver fibrosis, and apoptosis (31).

The long-term use of Dox can cause serious side effects on non-tumor tissues, and as a result, its clinical use is limited. Doxorubicin has several side effects, including hepatotoxicity and renal and cardiac toxicity. Its toxic effects on the reproductive system and the nervous system are irreversible. Hepatotoxicity caused by Dox may occur through the formation of free radicals and the production of ROS, which can cause oxidative damage to organs. So far, no study has been conducted on the effect of hydroalcoholic extract of ginger on modulating liver damage in rats. Accordingly, this study aimed to investigate the effect of hydroalcoholic extract of ginger on total and direct bilirubin levels, as well as the structural changes in liver tissue in rats induced with Dox.

Methods

Animal care

In this experimental study, 63 adult male Wistar rats were used with an approximate weight of 200 to 220 g and 2.5 to 3 months old. Rats were placed in special cages with a standard space and under the ambient temperature of 23-25 °C, a humidity of 50%-55%, and a 12-hour light/dark cycle. All rats had free access to food and water *ad libitum*. This research has an ethical approval code of IR.IAU.IAUG.REG.1399.021, and all ethical principles were observed regarding working with laboratory animals.

Experimental treatments

Laboratory animals were divided into 7 groups (n = 9 per group), and the experimental treatments were as follows:
Control group: The control group did not receive any medication or solvent.
Placebo group: The animals received the solvent extract or solution used for medicine.

Experimental group I: Animals received Dox at a cumulative dose of 20 mg/kg intraperitoneal injection.
Experimental group II: The animals received 300 mg/kg of ginger hydroalcoholic extract for 2 months orally.
Experimental group III: The animals received 600 mg/kg of ginger hydroalcoholic extract for 2 months.
Experimental group IV: Animals received a cumulative dose of 20 mg/kg of Dox and 300 mg/kg of ginger hydroalcoholic extract for 2 months.
Experimental group V: These animals received a cumulative dose of 20 mg/kg of Dox and 600 mg/kg of ginger hydroalcoholic extract for 2 months.

Preparation of hydroalcoholic extract of ginger

The collected ginger samples were taken to the botanical laboratory of the Kazeroon Branch, Islamic Azad University, for species identification. In this experimental study, the ginger rhizome was grated after peeling. Five grams of grated ginger was mixed with 10 mL of 96% ethyl alcohol solution and sonicated for 30 minutes, and then filtered. To separate the solvent from the extract, the obtained solution was kept in an oven for 1 day and then at room temperature for 3 days, and the ginger extract was kept in a refrigerator until the test (32).

Blood sampling and biochemical analysis

At the end of the experimental period, all groups were starved 12 hours before blood sampling with free access to water. The animals were anesthetized with ether, and approximately 10 mL of blood was taken from their hearts. The blood samples were kept for 1 hour in the laboratory environment for coagulation, centrifuged at 5000 rpm for 15 minutes, and measured after the operation by Pars Azmoun Company (using a BS-300 Autoanalyzer manufactured by Mindray Company). Total bilirubin and direct bilirubin were analyzed according to the method described by Doumas et al (1987) using an Autoanalyzer (Technicon RA-1000, USA) and a standard kit (Pars Azmoon, Iran) (33).

Histological examinations of the liver

For histological examinations of the liver, the liver tissue was removed from the animal's body, washed with physiological serum, and placed in containers containing 10% formalin. After fixing the samples and cutting them, they were stained using the hematoxylin and eosin (H&E) staining method. Then, 7 slides were prepared from each tissue sample, and histological studies were performed on them under the supervision of a pathologist (34).

Statistical analysis

After confirming the normality of the data based on the Kolmogorov-Smirnov test, 1-way analysis of variance (ANOVA) and Tukey tests were used to analyze and compare the data using SPSS version 19 (SPSS Inc, Chicago, IL, USA), respectively. P values less than 0.05 were considered statistically significant.

Results

The results of 1-way ANOVA and Tukey post hoc test showed that the level of total bilirubin showed a significant increase after consuming Dox (0.15 ± 0.027 mg/dL) compared to the control (0.048 ± 0.011 mg/dL) and placebo groups (0.05 ± 0.009 mg/dL). It was also shown that in the Dox + ZIN 300 (0.008 ± 0.062 mg/dL) and Dox + ZIN 600 (0.006 ± 0.067 mg/dL) groups, ginger extract significantly reduced the level of total bilirubin compared to the Dox group ($P < 0.05$; Figure 1). The results of this experiment showed that the consumption of ginger extract could reduce more than 40% of the total bilirubin compared to the Dox group.

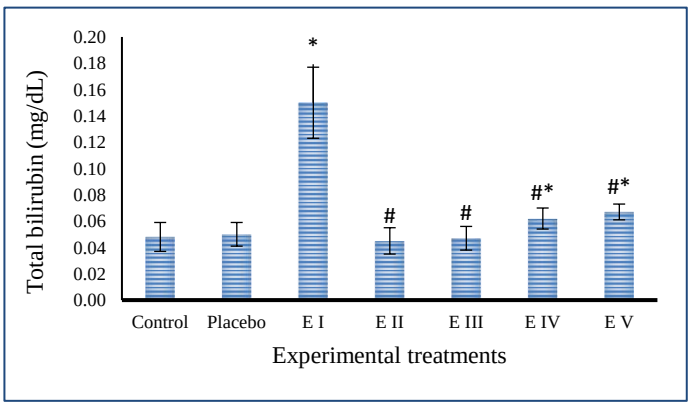

Figure 1. The effect of different experimental treatments on the total bilirubin serum concentration. E I: Dox, E II: ZIN 300, E III: ZIN 600, E IV: Dox + ZIN 300, E V: Dox + ZIN 600, *: significant difference with the control and placebo groups, and #: significant difference with the Dox group at the level of $P < 0.05$.

The level of direct bilirubin (0.061 ± 0.005) in the blood serum of rats increased by 160% with Dox. Dox + ZIN 300 and Dox + ZIN 600 treatments exhibited that with the consumption of hydroalcoholic extract of ginger, the level of direct bilirubin was reduced significantly by 0.043 ± 0.004 and 0.41 ± 0.006 mg/dL, respectively (Figure 2). The use of hydroalcoholic extract of ginger was able to reduce the level of direct bilirubin when taking Dox by more than 60%.

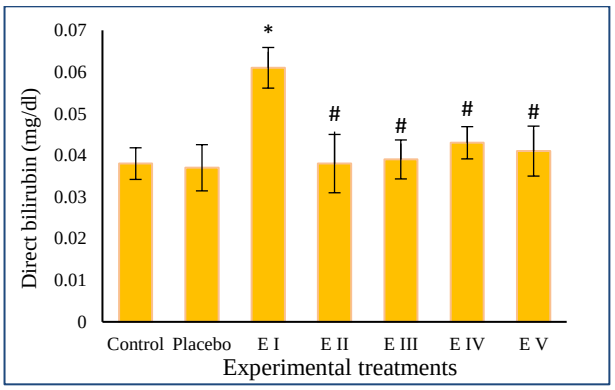

Figure 2. The effect of different experimental treatments on the direct bilirubin serum concentration. E I: Dox, E II: ZIN 300, E III: ZIN 600, E IV: Dox + ZIN 300, E V: Dox + ZIN 600, *: significant difference with the control and placebo groups and #: significant difference with the Dox group at the level of $P < 0.05$.

Table 1 shows that the Pearson correlation coefficient of total bilirubin and direct bilirubin was calculated as 0.99, indicating a very strong and positive relationship between these variables.

The linear regression between total bilirubin and direct bilirubin was estimated as y = 0.2227x + 0.0275. R2 (0.9792) revealed that the calculated equation had validity, and it is able to estimate the changes in the direct bilirubin level based on total bilirubin (Figure 3).

Table 1. The Pearson correlation of total and direct bilirubin

	Total bilirubin (mg/dL)	Direct bilirubin (mg/dL)
Total bilirubin (mg/dL)	1	
Direct bilirubin (mg/dL)	0.98954367**	1

** Statistically significant level, $P < 0.01$.

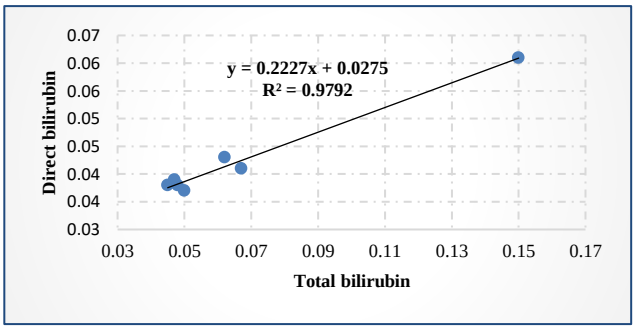

Figure 3. The linear regression of total and direct bilirubin

Histopathology of the liver

The histopathological results of rat liver tissue samples were examined in the groups stained with H&E. In the pathological evaluation of liver tissue in the control and placebo groups, the space around the portal canal, pagination and fibers of liver tissue, and the arrangement of liver sinuses were completely normal. No signs of necrosis, apoptosis, steatosis, congestion and lymphocytic infiltration, decreased port space, and local inflammation were seen in the control group. Also, no signs of necrosis, apoptosis, steatosis, or inflammation were seen in the placebo group, and the tissue had a normal appearance.
The histopathological evaluation of liver tissue in the Dox group exhibited necrosis and steatosis in different areas of liver tissue, hepatocyte destruction, and bleeding. There was also a loss of sinusoidal order and a decrease in the number of liver cells. The absence of necrosis and steatosis, which are signs of liver damage with bleeding, was not seen in any of the liver tissue samples obtained from the ZIN 300 and ZIN 600 groups. In the Dox + ZIN 300 and Dox + ZIN 600 groups, there were signs of decreased sinusoidal order,

lymphocytic infiltration, and bleeding. However, the appearance of lymphocytes was normal, and steatosis or necrosis was not seen (Figure 4).
The absence of necrosis and steatosis was not seen in any of the liver tissue samples obtained from the ZIN 300 and ZIN 600 groups. In the Dox + ZIN 300 and Dox + ZIN 600 groups, there were signs of decreased sinusoidal order, lymphocytic infiltration, and bleeding. However, the appearance of lymphocytes was normal, and steatosis or necrosis was not seen.

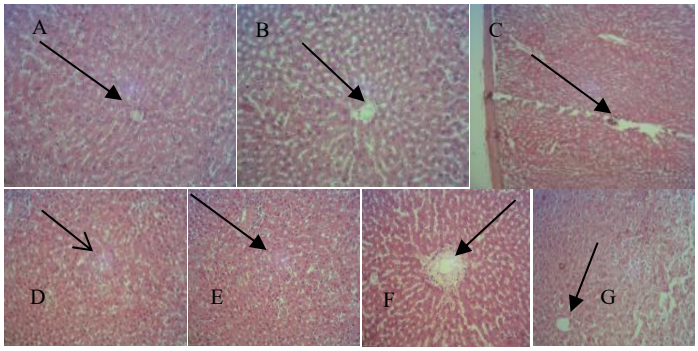

Figure 4. Photomicrograph of rat liver tissue in different experimental groups
The staining of 7 fixed samples with hematoxylin and eosin (H&E, x250). (A) Control group: Normal liver cells are protected by cytoplasm. (B) Placebo group: Normal liver cells. (C) Dox group: Necrosis of the nucleus and disintegration in the portal space. (D) ZIN 300 group: Normal liver cells with protected cytoplasm. (E) ZIN 600 group: Normal liver cells with no specific pathological. (F) Dox + ZIN 300: The formation of relatively small spaces between cells. (G) Dox + ZIN 600 group: Normal liver tissue around the central vein (×10 magnification).

Discussion

Doxorubicin is an anti-cancer drug that interferes with the growth and spread of cancer cells. This drug can weaken the immune system; thus, the blood status should be monitored regularly. It may increase the risk of bone marrow disorders or other types of leukemia (2, 10). As an important organ, the liver also plays a role in neutralizing toxins in addition to metabolic and secretory functions. Detoxification in the liver is done by cytochrome P_{450} in the endoplasmic reticulum. For this reason, liver cells are more vulnerable to these toxins (1, 12). In general, to estimate liver damage, serum transaminases, aspartate aminotransferase, alanine aminotransferase, bilirubin, alkaline phosphatase, sodium, and potassium are measured (16, 18).

Currently, chemical drugs are used to protect liver cells, which themselves affect liver function. However, the use of antioxidants and plants that contain phenolic compounds can be useful and have a protective effect without side effects (16, 17, 32). The ginger family plays a significant role in the diets of people worldwide. Oleoresin, which is prepared from the root of the ginger plant, contains gingerol, which is a pharmacologically active substance. Many plants and spices have pharmacological and biochemical properties, including anti-inflammatory antioxidant properties, which seem to be involved in anti-carcinogenic and anti-mutagenic activities.
In this experiment, Dox significantly increased total and direct bilirubin levels, indicating liver damage. The hydroalcoholic extract of ginger at the levels of 300 and 600 mg/kg significantly reduced total and direct bilirubin levels compared to the Dox group. However, total and direct bilirubin levels in the groups receiving 300 and 600 mg/kg hydroalcoholic extract of ginger demonstrated no significant difference compared to the control group. Studies have shown that ginger can protect the liver from the harmful effects of hepatotoxicity, and the histological findings emphasize the beneficial effects of ginger extract (16, 20). With its antioxidant properties, ginger counteracts the harmful effects of ROS and protects the liver from toxicity (20). Essawy et al (2018) revealed that rosemary and ginger extracts are effective in improving the function and structure of liver cells through their strong antioxidant effects (35). The combination of rosemary and ginger extracts can be used as an auxiliary remedy for liver diseases. Essawy et al also reported that ginger extract relieved phosphamidon-induced hepatotoxicity. Ginger extract has a protective effect against bromobenzene-induced hepatotoxicity in rats by reducing the production of nitric oxide products and activating cyclooxygenase 2 and caspase 3 (35). Some studies have demonstrated that ginger extract has protective effects against diazinon-induced liver damage due to its antioxidant and anti-apoptotic activities. In a study, the protective effects of phenol-rich ginger extract were shown against oxidative stress and hepatotoxicity caused by aflatoxin B_1 (29, 31, 36). Also, in 2014, Poorrostami et al reported that the hydroalcoholic extract of ginger improved liver function in lamotrigine-induced hepatotoxicity (37).
Ginger and its active ingredient (6-gingerol) have significant antioxidant properties, and such activities have been reported to play a significant role in activating antioxidant protective cascades (16, 20). According to a study, the high antioxidant capacity of 6-gingerol may contribute to its therapeutic potential because its ability to inhibit free radicals may provide protection against oxidative damage caused by free ROS (25). Indeed, ginger hydroalcoholic extract has hepatoprotective effects against Dox toxicity and may be a vital tool in developing countermeasures to protect against the toxic effects of Dox.
Performing a direct bilirubin test or a total bilirubin test can easily determine the elevation of bilirubin. Generally, bilirubin is formed in the body when the hemoglobin protein in old red blood cells breaks down. The breakdown of old blood cells is a natural and healthy process, and if the liver is healthy, it clears most of the bilirubin from the blood. However, if the liver is damaged, bilirubin is released from the liver and leaks into the blood. The positive and high correlation between total bilirubin and direct bilirubin means that to check liver function, it is enough to measure one of them, and through the calculated regression equation, it is possible to measure one of them compared to estimating another item.

Conclusion

Polyphenolic extracts prevent the conversion of thioacetamide into the toxic metabolite of thioacetamide D-oxide by using the mechanisms of neutralizing free radicals, inhibiting cytochrome P_{450}, stimulating the repair of liver cells and inhibiting glucuronidase. In the production conditions of ROS, it can prevent destructive activity as a mediator with its antioxidant property. Therefore, oral administration of hydroalcoholic extract of ginger seems to have protective effects on the liver by neutralizing free radicals, and stimulating the activity of antioxidant enzymes. However, more research is needed to identify and isolate active compounds in ginger extract.

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Ethical statement

The study was approved by the Ethics Committee of the Islamic Azad University, Gachsaran Branch, Iran (code: IR.IAUG.REC.1399.021).

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Author contributions

This research was carried out under the guidance of Dr. Habibollah Johari and Dr. Mehrdad Shariati. The research topic, library research, and data collection were finalized by Marzieh Niakan. The obtained data was analyzed and interpreted through Dr. Ebrahim Talebi and the draft of the manuscript was prepared in collaboration with Dr. Davood Moghadamnia.

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