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The Beneficial Effects of Garlic and Mountain Tea Hydroalcoholic Extract on Methotrexate-induced Liver Toxicity through Attenuation Oxidative Stress

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Abstract

Background: Methotrexate (MTX), a chemotherapeutic and immunosuppressant drug, is generally well-tolerated by most patients. However, its cytotoxic nature contributes to life-threatening side effects including hepatotoxicity and nephrotoxicity. Several studies have already confirmed that the oxidative stress plays a major role in the pathogenesis of MTX-induced damage in the various organs. This study was carried out to determine whether garlic extract has a protective effect against MTX-induced hepatotoxicity and nephrotoxicity.
Materials and methods: 56 rats were divided randomly into six groups: Group I (control): treated with normal salin. Group II (MTX): was received sin-dose MTX($20\frac{mg}{kg}$i.p, 7th). The third, fourth and fifth groups of the extract received 100, 250 and 500 mg/kg doses per day, respectively, and on day 7, methotrexate was given intraperitoneally at a dose of 20. Sixth, seventh and eighths of the group received the tea extract from 30, 50 and 70 mg/kg doses per day, respectively, and on day 7 received methotrexate intraperitoneally at a dose of 20 mg/kg. After 11 days, the liver tissue was removed for measure the MDA, TAC, GSH and CAT, SOD activity in tissue homogeneity and histopathologic studies.
Results: The results showed that CAT($P < 0.001$), TAC($P < 0.01$) and GSH ($P < 0.05$)levels decreased in methotrexate group compared to control group. These values increased in the third to the eighth groups compared to the methotrexate group. Also, the MDA content in methotrexate group increased compared with the control group($P < 0.001$), which decreased in the third to eighth groups compared to the methotrexate group. MTX had no significant effect on SOD levels.

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Introduction

Methotrexate (MTX) is widely used as a therapeutic agent in the treatment of high-dose malignancies and low-dose autoimmune diseases(Öktem et al., 2006). However, taking high dose methotrexate or prolonged use may cause liver damage, including progressive fibrosis and cirrhosis. The MTX-induced liver toxicity mechanism is still unclear(Demiryilmaz et al., 2012; Muhsin & Latif, 2012). However, oxidative stress is suggested to be an important mechanism involved in the pathogenesis of MTX-induced liver toxicity(Ali, Rashid, Nafees, Hasan, & Sultana, 2014; Dalaklioglu, Genc, Aksoy, Akcit, & Gumuslu, 2013). MTX weakens the antioxidant defense system and makes the cells

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sensitive to active oxygen species(Ali et al., 2014). For this reason, the use of antioxidants that naturally found in fruits and vegetables may reduce the oxidative stress And numerous studies also shown that antioxidants make a protective effect against MTX-induced liver injury(Çetin et al., 2008). The garlic with the scientific name Allium sativum L is a plant belonging to the Liliaceae family, which contains sulfur and non-sulfur compounds. Its therapeutic properties include hepatoprotective, antioxidant, anti-radical, anti-cancer, anti-hypertensive, anti-lipid blood fat and anti-hyperglycemic properties(Ezeala, Nweke, Unekwe, El-Safty, & Nwaegerue, 2009). Stachys lavandulifolia Vahl is commonly known as mountain tea, a perennial herb with dense long hair, covered with purple or yellow flowers. This plant grows native in many regions of Iran, Iraq and Anatolia. In traditional Iranian medicine, it is used as an anxiety and sedative. Pharmacological properties of the plant have been reported, such as anti-inflammatory, anti-anxiety, antibacterial, anticoagulant, anti-cancer and antioxidant activity(Aghaei, Hossein Mirjalili, Nazeri, & biodiversity, 2013; Modarresi, Hosseinzadeh, Nematy, Siavash-Haghighi, & Ghanbari, 2014). Therefore, the aim of this study was to investigate the protective effect of garlic extract and mountain tea on MTX-induced liver injury by investigating oxidative stress markers in liver tissue and histopathologic studies.

Materials and Methods

Materials

Tri-chloroacetic acid (TCA), 2- Thiobarbituric acid (TBA), Nitrobiotetrazolim chloride (NBT), Hydrogen peroxide (H2O2)

Animals

In this study, 56 male Wistar rats (in the range of 300-250 g) were tested for all ethical considerations. All groups were fed in terms of water and food and environmental conditions in a suitable laboratory with a temperature of 23 ± 2 ° C, relative humidity of 40 to 60% and fed with standard food.

Preparation

After the harvest of garlic and mountain tea during its growing season and identification and confirmation of the scientific name, garlic bulbs and aerial parts of the mountain tea were dried and then minced. Then, it was placed in a hydroalcoholic solvent (30 water: 70 ethanol) for 3 days, then the extract was passed through the filter paper, and the solution was concentrated by rotary device and after placing at a temperature of 30-40 ° C dry extract was obtained.

Expriment design

After a week of adaptation, the rats were randomly divided into 8 groups of the same cages, each of which contained 7 rats in each group and divided as follows: Group 1: The control group received daily 0.5 ml mal salin orally for 10 days.

The second group received MTX at 20 mg (Yüncü, Eralp, & Celõk, 2006)per kg body weight on the 7th day intraperitoneally.

Group 3 received MTX at 20 mg per kg body weight on 7th by intraperitoneal injection + garlic extract at a dose of 100 mg per kg body weight per day, orally (gavage) For 10 days.

Group 4 received MTX at 20 mg per kg body weight on 7th by intraperitoneal injection + garlic extract at 250 mg per kg body weight per day orally (gavage) For 10 days

Group 5 received MTX at 20 mg per kg body weight on 7th by intraperitoneal injection + garlic extract at a dose of 500 mg per kg body weight per day, orally (gavage) For 10 days.

Group 6 received MTX at 20 mg per kg body weight on 7th by intraperitoneal injection + mountain tea extract at 30 mg / kg body weight daily for orally (gavage) For 10 days.

Group 7: Receiving MTX at 20 mg per kg body weight on 7th by intraperitoneal injection + mountain tea extract at a dose of 50 mg / kg body weight per day (oral gavage) for 10 Day.

Group 8: Receiving MT at 20 mg per kg body weight on 7th by intraperitoneal injection + mountain tea extract at a dose of 70 mg per kg body weight per day orally (gavage) to For 10 days.

Collection of tissue samples

On the eleventh day (4 days after MTX injection), rats were kept for 12 hours fasting. They were then anesthetized by diethyl ether and autopsied and sampled from their liver. The weight of the liver was then measured and part of it was placed in 10% formalin solution and used for histological and pathological tests. Another part of the liver tissue of each animal was taken to measure tissue factors (SOD), GSH, CAT and MDA and was stored at -70 ° C for experiment.

Measuring enzymes and tissue factors

- Protein levels were measured using the Bradford method (1976).
- Malondialdehyde (MDA) in samples was measured by Placer et al. (1966) with a few changes(Placer, Cushman, & Johnson, 1966).
- Superoxide dismutase activity (SOD) was measured using the Randox company kit.

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- The activity of the catalase enzyme (CAT) was performed by Koroliuk et al. (1988)(Koroliuk, Ivanova, Maĭorova, & Tokarev, 1988).
- Total antioxidant capacity was measured by the spectrophotometry method provided by Benzie and Strain (1999)(Benzie & Strain, 1996).
- Glutathione (GSH) was measured by Ellman et al. (1959) in microplate (Ellman & biophysics, 1959).

Results

Effect of garlic extract and mountain tea extract on oxidative stress markers in liver tissue

The results show that GSH levels in the MTX group were significantly reduced compared to the control group ($p < 0.05$, Table 1). In the dose of 100 mg / kg garlic extract and 30 mg / kg of mountain tea, there was no significant difference compared to MTX group, but the GSH level of these groups was significantly different with the control group ($p < 0.05$). In the groups receiving 250 mg / kg extract of garlic extract and 50 mg / kg of mountain tea extract , there was no significant difference compared to MTX group and control group. In groups receiving 500 mg / kg garlic extract and 70 mg / kg mountain tea, GSH levels were significantly increased in comparison with the MTX group($p < 0.05$), but the GSH levels of these groups did not show significant differences with the control group. The results show that CAT levels in the MTX group were significantly reduced compared to the control group ($p < 0.001$, Table 1). In the dose of 100 garlic extract and 30 mg / kg of mountain tea, there was no significant difference compared to MTX group, but the CAT level of these groups was significantly different with the control group (garlic extract ($p < 0.001$) and mountain tea ($p < 0.01$)). In the receiver group, 250 mg / kg of garlic extract showed no significant difference compared to the MTX group, but the CAT level of this group also showed a significant difference with the control group ($p < 0.001$). In the group receiving 50 mg / kg dose of mountain tea extract, CAT values were significantly increased in comparison with the MTX group ($p < 0.05$), but CAT values of these groups did not show significant differences with the control group. In the groups receiving 500 mg / kg dose of garlic extract and 70 mg / kg of mountain tea, CAT values were significantly increased in comparison with the MTX group ($p < 0.001$), but the CAT level of these groups did not show significant differences with the control group.

Table 1. The protective effect of garlic extract and mountain tea extract on liver tissue oxidative stress markers in MTX-treated rats.

Grops	SOD (mU/mg)	GSH (nmol/mg)	MDA (nanomol/mg)	TAC (nanomol/mg)	CAT (mu/mg)
Control	132/94±12/86	70/18±4/59	41/81±2/33	49/63±2/62	74/49±4/88
MTX	95/63±9/25	41/46±2/72#	55/76±3/11###	30/74±1/63##	54/08±3/55###
MTX+100 GE (mg/kg)	101/66±9/84	45/72±3#	53/88±3###	32/95±1/74##	56/71±3/72###
MTX+250 GE (mg/kg)	120/56±11/66	62/03±4/06	46/88±2/62***	38/61±2/04*	62/2±4/08**
MTX+500 GE (mg/kg)	128/91±12/47	67/17±4/4*	43/43±2/42***	44/83±2/37**	69±4/52***
MTX + MT 30 mg/kg	115/12±11/14	43/13±2/83#	52/33±2/92###	29/45±1/56##	58/59±3/84##
MTX + MT 50 mg/kg	124/96±12/09	56/85±3/72	44/97±2/51**	38/02±2/01**	64/75±4/24*
MTX + MT 70 mg/kg	129/12±12/49	65/2±4/27*	41/93±2/34***	46/58±2/46***	68/44±4/48***

* Significant difference with the MTX group and the # is significant difference with the control group. * Significant differences ($p < 0.05$), ** significant differences ($p < 0.01$), *** Significant difference ($p < 0.001$), # Significant difference ($p < 0.05$), ## significant difference ($p < 0.01$) and ### significance difference ($p < 0.001$). GE= garlic extract .MT = mountain tea.

The results indicated that the MDA level in the MTX group was significantly increased compared to the control group ($p < 0.001$, Table 1). In the groups receiving 100 mg / kg of garlic extract and 30 mg / kg of mountain tea, there was no significant difference compared to MTX group, but the amount of MDA also showed a significant difference with the control group ($p < 0.001$). In the groups receiving 250 mg / kg extract of garlic extract ($p < 0.001$) and 50 mg / kg of mountain tea extract ($p < 0.01$), MDA levels decreased significantly compared with MTX group, but the MDA levels of these groups did not show significant differences with the control group. In the group receiving 500 mg / kg dose of garlic extract and 70 mg / kg of mountain tea extract, MDA levels decreased significantly compared to MTX group($p < 0.001$), but the MDA levels of these groups did not show significant differences with the control group. The results show that TAC in MTX group was significantly decreased compared to control group ($p < 0.01$, Table 1). In the dose of 100 mg / kg garlic extract and 30 mg / kg of mountain tea, there was no significant difference compared to MTX group, but the TAC level of these groups was significantly different with the control group ($p < 0.01$). In the group receiving 250 mg / kg dose of garlic extract, TAC was significantly increased in comparison with the MTX group ($p < 0.05$). In the group receiving the 50 mg / kg dose of mountain tea extract ($p < 0.01$), the TAC level was significantly decreased in

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comparison to the MTX group, but the TAC level in this group did not show significant differences with the control group. In the group receiving 500 mg / kg dose of garlic extract ($p < 0.01$) and 70 mg / kg of mountain tea extract ($p < 0.001$), the TAC level was significantly increased compared to MTX group, but the TAC level in this group With the control group did not show any significant difference.

MTX had no significant effect on SOD levels.

Effect of garlic extract and mountain tea on histopathological changes of the studied groups

The results of histopathologic studies showed that Crossed cuts in normal rats showed normal hepatocytes with healthy cytoplasm and a specific nucleus. In the MTX receptor rat, irregularities in the structure of the liver lobule, central venous hyperemia and also blood synosoids were observed.

In the group receiving the dose of 100 mg / kg of garlic extract and 30 mg / kg of mountain tea, the level of hyperemia and inflammation was higher than the other two groups of the extract and the rate of recovery was lower than the other two groups. In the recipient group 250 mg / kg of garlic extract and 50 mg / kg of mountain tea, the level of hyperemia and inflammation has been moderately reduced. In rats receiving a dose of 500 mg / kg of garlic extract and 70 mg / kg of mountain tea, no pathological lesions were observed and all of them had a nearly normal structure.

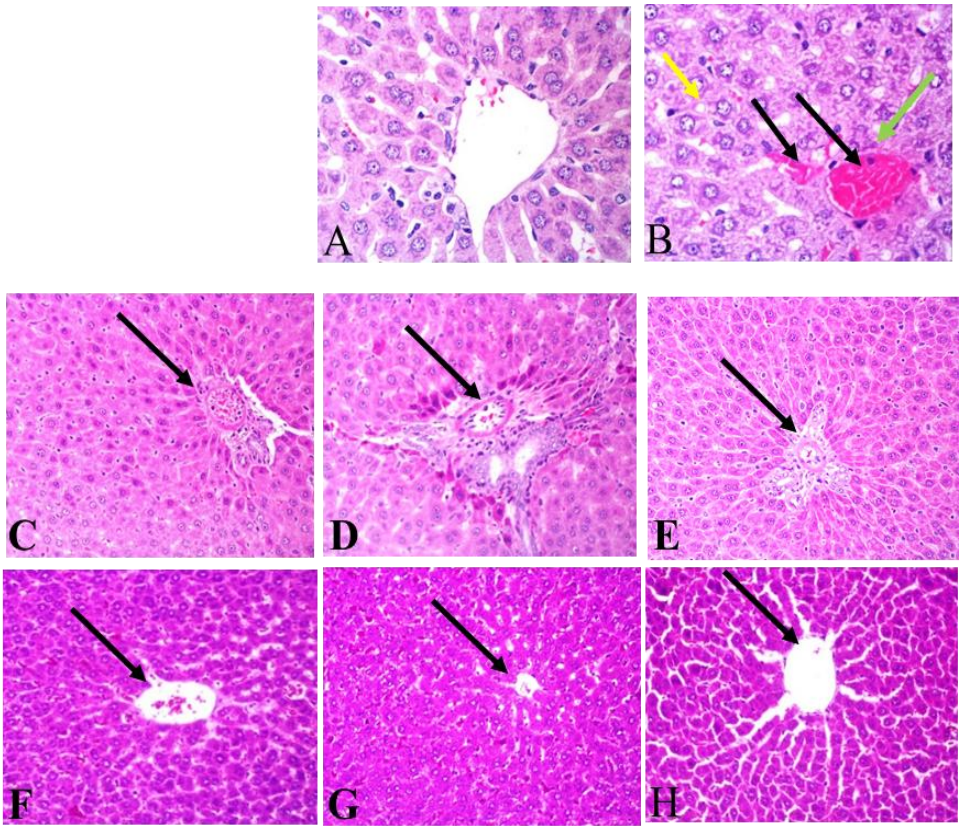

Figure 1: Rat Liver Cross Section. (A) Control Group: Hepatocytes display a healthy morphology with pink-stained cytoplasm and well-defined nuclei, arranged radially from the central vein (H&E, 40× magnification). (B) MTX Group: Marked central venous dilation and congestion, along with sinusoidal expansion (↑). Increased presence of activated Kupffer cells (↑) (H&E, 40× magnification. Pronounced dilation and congestion within the portal space (↑), accompanied by fatty changes (↑) (H&E, 40× magnification). (C) MTX + 100 mg/kg Garlic Extract: Mild reduction in congestion within the central vein and sinusoids (H&E, 20× magnification). (D) MTX + 250 mg/kg Garlic Extract: Moderate decline in congestion within the central vein and sinusoids (H&E, 40× magnification). (E) MTX + 500 mg/kg Garlic Extract: No pathological lesions observed. The liver parenchyma lacks inflammatory cells and necrosis, maintaining a nearly normal histological structure (H&E, 20× magnification). (F) MTX + 30 mg/kg Mountain tea Extract: Mild reduction in congestion within the central vein and sinusoids (H&E, 40× magnification). (G) MTX + 50 mg/kg Mountain tea Extract: Moderate decline in congestion within the central vein and sinusoids (H&E, 20× magnification). (H) MTX + 70 mg/kg Mountain tea Extract: No pathological lesions observed. The liver parenchyma lacks inflammatory cells and necrosis, maintaining a nearly normal histological structure (H&E, 40× magnification).

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Discussion

MTX is a folic acid antagonist used to treat malignant disorders and autoimmune diseases, which is known due to the toxic effects and oxidative reactions that occur during the liver metabolism, and therefore liver toxicity, which is one of the major side effects of treatment with MTX, it limits the therapeutic effect of the drug(Armagan et al., 2015). The present study investigates the role of oxidative stress in liver damage induced by MTX, as well as clarifying the protective effect of garlic extract and tea tea against this toxicity. The results of this study indicate that MTX leads to oxidative tissue damage by increasing the lipid peroxidation and, consequently, inflammation in the liver tissue and decreasing the level of oxidative enzymes. Active oxygen species are involved in MTX-induced hepatotoxicity. MTX not only causes significant increases in oxidative stress biomarkers, but also significantly reduces the antioxidant enzymes(Tawfik, 2015). Our findings support the hypothesis that oxidative stress plays an important role in MTX-induced hepatotoxicity. The results of this study indicate that MTX leads to oxidative tissue damage by increasing the lipid peroxidation and, consequently, inflammation in the liver tissue and decreasing the level of oxidative enzymes(Cao et al., 2019; Mahmoud et al., 2020; Swayeh, Abu-Raghif, Qasim, & Sahib, 2014). MDA is a free radical metabolite that causes the lipid peroxidation cascade. It is commonly known as an oxidative stress marker and it eliminates lipid layers . Methotrexate, by significantly increasing the amount of MDA, increases the lipid peroxidation by free oxygen radicals, which is thought to be a major cause of damage to the cell membrane and as a major contributor to the development of MTX-induced tissue damage(Kose et al., 2012). On the other hand, MTX significantly reduced amount of the GSH, CAT, SOD and TAC. This is consistent with previous findings(Fouad, Hafez, Hamouda, & toxicology, 2020; Mahmoud et al., 2020). When MTX reduces the level of GSH, redox cell status is impaired and the cell becomes more sensitive to active oxygen metabolites. One of the mechanisms that may be related to reducing GSH is that it reduces the availability of NADPH due to inhibitory effects of MTX on glucose 6-phosphate dehydrogenase. The reduction of GSH by MTX leads to a reduction in the effectiveness of the antioxidant enzyme system. Therefore, under these conditions, endogenous antioxidant enzymes are likely to cause detoxification systems, the use of antioxidants, and the lack of re-antioxidants in the tissues due to the excessive production of free oxygen radicals(Moghadam et al., 2015). The present study showed that the administration of garlic extract and mountain tea significantly decreased the amount of MDA and increased the levels of GSH, CAT, SOD and TAC, due to the antioxidant properties of garlic and mountain tea. It has been reported that the consumption of garlic increased activity The enzymes increase CAT and SOD and GSH and also reduce MDA levels(Yüncü et al., 2006). In a study done in the body, it was shown that mountain tea also has a protective role against oxidative stress due to the presence of flavonoids and antioxidant properties(Rahzani et al., 2013). A study also showed that mountain tea is rich in monoterpene and sesquiterpene compounds(Pirbalouti & Mohammadi, 2013).Oxidative damage, along with the production of free radicals and lipid peroxidation, is the main cause of tissue damage caused by MTX as a result of the imbalance between oxidants and antioxidants that is beneficial for oxidants. If this balance is not maintained in the tissue, pathological changes that occur with cell damage occur(Hafez et al., 2015). Histopathologic studies of the liver tissue using hematoxylin -eosin stained staining are hepatocyte swelling, decreased cellular space, and cytoplasm of the acidophilic cell and progress to necrosis. Histopathologic results showed that liver therapy with garlic extract and mountain tea helps to heal liver cells, which may be due to garlic organo-sulfur compounds and flavonoid compounds of mountain tea that can rejuvenate the liver tissue (fig1).

Conclusion

The results of this study indicate that MTX leads to oxidative tissue damage by increasing lipid peroxidation and subsequent inflammation in the liver tissue and weakening antioxidant defense system. The results show that the hydroalcoholic extract of garlic and mountain tea improved oxidative stress markers. Reducing lipid peroxidation and enhancing the antioxidant defense system suggests that garlic extract and mountain tea can reduce free radicals production, which may be due to the high antioxidant activity of the extract due to organosulphur compounds in garlic and flavonoid compounds Mountain tea. Considering the effects of doses of 100, 250 and 500 mg / kg of garlic extract, a dose of 500 mg / kg, as well as doses of 30, 50 and 70 mg / kg of mountain tea extract, a dose of 70 mg / kg The reason for having the most significant difference with the MTX group is the highest dose of protection against MTX-induced hepatotoxicity.

Conflict of Interest

None

Acknowledgment

None

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