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RESEARCH

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Origanum majorana L. extract alleviates dexamethasone-induced hepatotoxicity, oxidative stress and pathological alterations in vivo

Howida Sayed Abou- Seif[1,2*] and Walaa Gamal Hozayen[3]

Abstract

Background *Origanum majorana* (*O. majorana*) is one of the most widely used herbs in Egypt due to its antioxidant, anti-inflammatory, anti-genotoxic, antimutagenic, anticoagulant and beneficial properties. Our study's main goal is to determine how well *O. majorana* leaf extract can reduce hepatotoxicity and oxidative stress produced by dexamethasone (DXM). Thirty female rats were divided into three groups of ten. Animals in group1 received distilled water daily for eight weeks and served as control. Those in group 2 exposed subcutaneously to 0.1 mg/kg body weight of DXM three times per week for eight weeks and served as the toxic group, while those in group 3 were treated daily and orally with 100 mg/kg of *O. majorana* aqueous extract + 0.1 mg/kg of DXM three times per week for eight weeks and served as treated group.

Results Due to DXM treatment, the activities of liver function markers were significantly elevated ($P < 0.0001$), whereas *O. majorana* pretreated animals improved or reduced the elevated liver function enzyme activities. Dexamethasone administration considerably enhancing oxidative stress which rose ($P < 0.0001$) MDA concentration and attenuated the antioxidant defense system by decreasing the activities of GST, GSP, GSR, and CAT significantly in liver homogenate when compared to control animals. The results further demonstrated that pretreatment with *O. majorana* boosted the antioxidant defenses against the damaging effects of DXM.

Conclusion It can be said that dexamethasone exposure induced- hepatotoxicity and oxidative stress in rats that repaired by *O. majorana* aqueous extract which had the ability to reduce the impact of hepatic damage. To evaluate the health benefits and safety of *O. majorana* in individuals, more clinical research is needed.

Keywords Dexamethasone, *O.marjorana*, Reactive oxygen species, Lipid peroxidation, Antioxidant defense system

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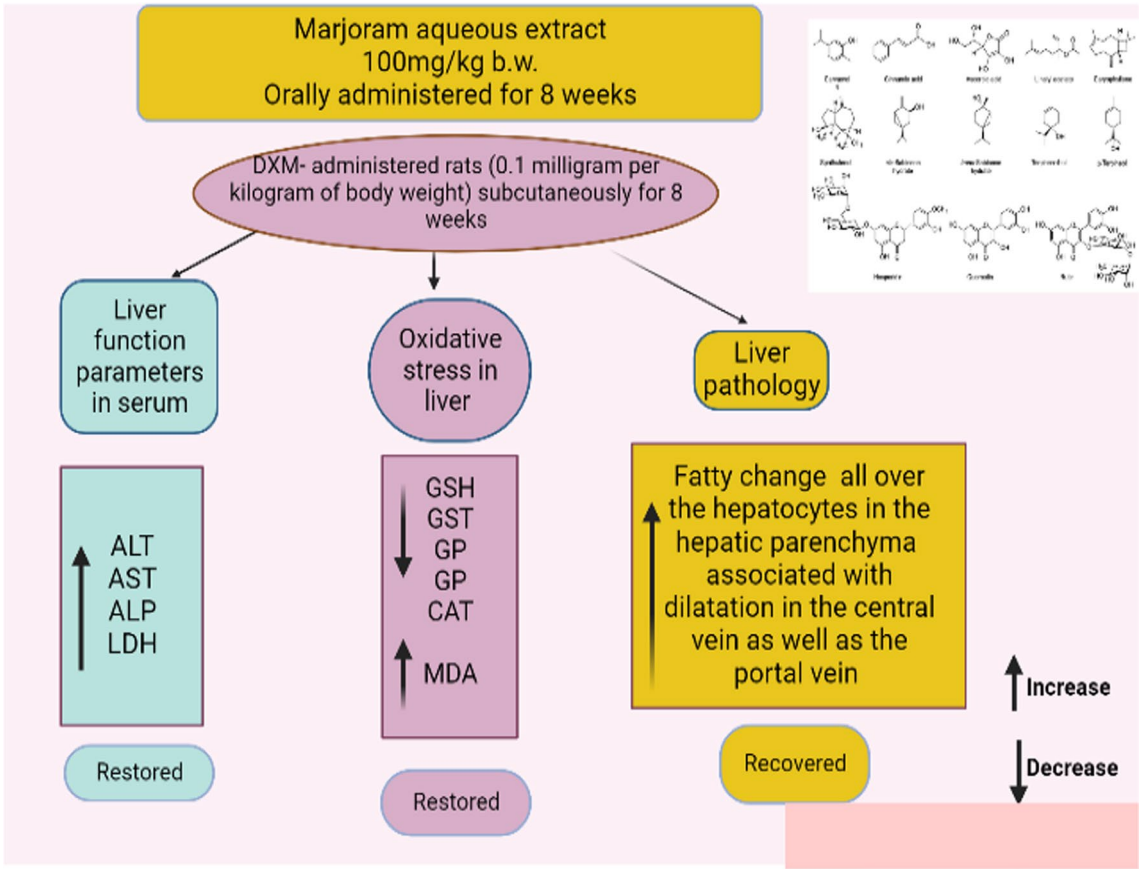
Graphical abstract



Background

Metabolism is one of the liver main functions as it is responsible not only for protein, lipid and carbohydrate metabolism, but also drug and metabolite transformation and detoxification (Bastway et al. 2008; Rui 2014). Due to the harmful effect of drugs on the vital organs as liver, brain tissue, lung and heart, FDA decided to non-approval and withdrawal of it (Iorga et al. 2017). The liver also sensitive to toxicity and corticosteroids which alter the hepatocellular biological process and homeostasis (Hazra et al. 2008). Synthetic glucocorticoids (GCs) are used widely as anti-inflammatory drug, but it is inefficient in many tumor and auto- immune diseases (Coutinho and Chapman 2011). Although it is still doubtful, GCs used to treat many liver disorders. In spite of the beneficial effects of GCs as anti-inflammatory drug in cholestatic patients, it may attenuate the patient's defenses against the harmful effects of biliary component buildup. Dexamethasone is a long-acting anti-inflammatory synthetic GC (Courtois et al. 1999; Kubitz et al. 1999; Turncliff et al. 2004). Dexamethasone overdose-induced hyperglycemia, hyperlipidemia, steatosis development, and fatty liver (Hasona et al. 2017; Yin et al. 2017). Dexamethasone damages DNA and causes oxidative stress to have an anti-cancer effect (Motafeghi et al. 2022). Malonaldialdehyde is known as oxidative stress marker increased according to dexamethasone toxicity. Oxidative stress defined as an unbalance between cellular defense mechanism and free radical production (Pascussi et al. 2000).

Herbal medicines have been used traditionally since the ancient times for treating many diseases by improving the immunity. It is used also as dietary supplement to promote health (Babich et al. 2020, Pelvan et al. 2022). *Origanum majorana* L. (*O. majorana*), an aromatic plant from the Lamiaceae family. *O. majorana*, which is frequently used as a spice or seasoning, has a variety of pharmacological activities, including hepatoprotective, antibacterial, anti-inflammatory, cardioprotective, anti-platelet, antiulcer, antitumor, gastroprotective,

antimetastatic, antiatherosclerosis and antifungal, antiprotozoal and anticholinesterase inhibitory activities (Villalva et al. 2018; Arranz et al. 2019). *O. majorana* aerial component extracts in water, essential oil, and ethyl acetate have remarkable antioxidant activity (Triantaphyllou et al. 2001; Al-Howiriny et al. 2009; Hussain et al. 2011; Mossa and Nawwar 2011; Erenler et al. 2016). Other sweet *O. majorana* extracts, such as ethanolic, n-hexane, and hydroalcoholic extracts, have also been said to possess antioxidant effects (Vagi et al. 2005). The antioxidant effect is caused by phenolic compounds, such hydroxycinnamic acid and flavonoids, ursolic acid, carnosic acid, carnosol, rosmarinic acid, and caffeic acid (Triantaphyllou et al. 2001; Heo et al. 2002; Vagi et al. 2005; Hossain et al. 2014). The most frequent flavonoids found in sweet *O. majorana* are hesperetin, catechin, quercetin, kaempferol, naringenine, eriodictyol, diosmetin, luteolin, and apigenin. Flavonoid glycosides identified in sweet *O. majorana* include kaempferol-3-O-glucoside, quercetin-3-O-glucoside, narigenin-O-hexoside, and rutin (Al-Howiriny et al. 2009; Kozlowska et al. 2010; Queralt et al. 2015). When compared to the lead acetate-treated group, *O. majorana* alcoholic, aqueous, and essential oil extracts and essential oil significantly improved kidney and liver histology while lowering serum urea and creatinine levels and serum liver enzyme activities (El-Ashmawy et al. 2005). Cadmium altered lipid peroxidation levels may be successfully enhanced or decreased by *O. majorana* extract, which has protective and therapeutic properties that lessen the kidney and liver antioxidant activities against toxicities brought on by cadmium (Shati 2011).

Therefore, the current study's designed to study *O. majorana* protective role against hepatotoxicity and other harmful effects during dexamethasone treatment by boosting the immune system through the antioxidant defense mechanism, consequently attenuating oxidative stress and restoring the hepatocellular biomarkers toward normal in albino rats.

Methods

Study animals

30 female Wistar rats from the Giza, Egypt-based from Ophthalmology Research Center animal house, weighing between 120 and 150 g were used in the study. They were kept for 14 days under observation in conventional cages with access to food and cool, room-temperature water. The regular 12:12 h light–dark cycles were likewise maintained for them. The National Institutes of Health (NIH) and Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) criteria for the handling and use of experimental animals were followed in all animal operations. All experiments were performed in line with the ethical guidelines approved by the Medical Research Ethics Committee of the National Research Centre, El Dokki, Egypt of Experimental Animals (No. 20286).

Chemicals

In Egyptian Tec Pharmaeutical industries, dexamethasone was purchased from Sigma—S. A. E.

Plant materials

The Sekem Co. provided the Egyptian sweet *O. majorana* leaves for the medicinal plant (Cairo, Egypt). An ecologist (Dr. Kaled Elsayed, assistant professor) from the Plant Biotechnology, Botany Department, Faculty of Science, Beni- Suef University, Egypt, identified the plant material used in the current study and deposited a voucher specimen in a public herbarium.

Origanum majorana L. aqueous extract preparation

Ramadan et al. (2012) technique states that to make *O. majorana* leaf aqueous extract, 100 mg/kg of body weight of the herb was dissolved in 0.5 ml of boiling distilled water (equal to three cups of *O. majorana* tea, respectively), covered and allowed to stand for 10 min at room temperature. The extract was then filtered and administered to the animals immediately.

Doses and treatment

To include an increase in the frequency of hepatotoxicity and oxidative stress, dexamethasone (DXM) was previously reported in mammalian systems (Feng et al. 2013). Subcutaneously and for eight weeks (three doses weekly), 0.1 mg/kg DXM dose was dissolved in sterilized water. In our study *O. majorana* dose were adjusted to 100 mg/kg b.wt. for 8 weeks (Ramadan et al. 2012).

Study design

Three groups (ten animals each) were divided into three groups (Fig. 1):

1. *Group 1*: Rats received distilled water daily for eight weeks and served as control.
2. *Group 2*: Rats received DXM subcutaneously three doses weekly (0.1 mg per kilogram of body weight) for eight weeks (Feng et al. 2013) and served as toxic group.
3. *Group 3*: Rats received subcutaneously 0.1 mg/kg. b. wt. of dexamethasone three times per week together with 100 mg/kg body weight *O. majorana* aqueous extract (orally) for eight weeks (Ramadan et al. 2012) and served as treated group.

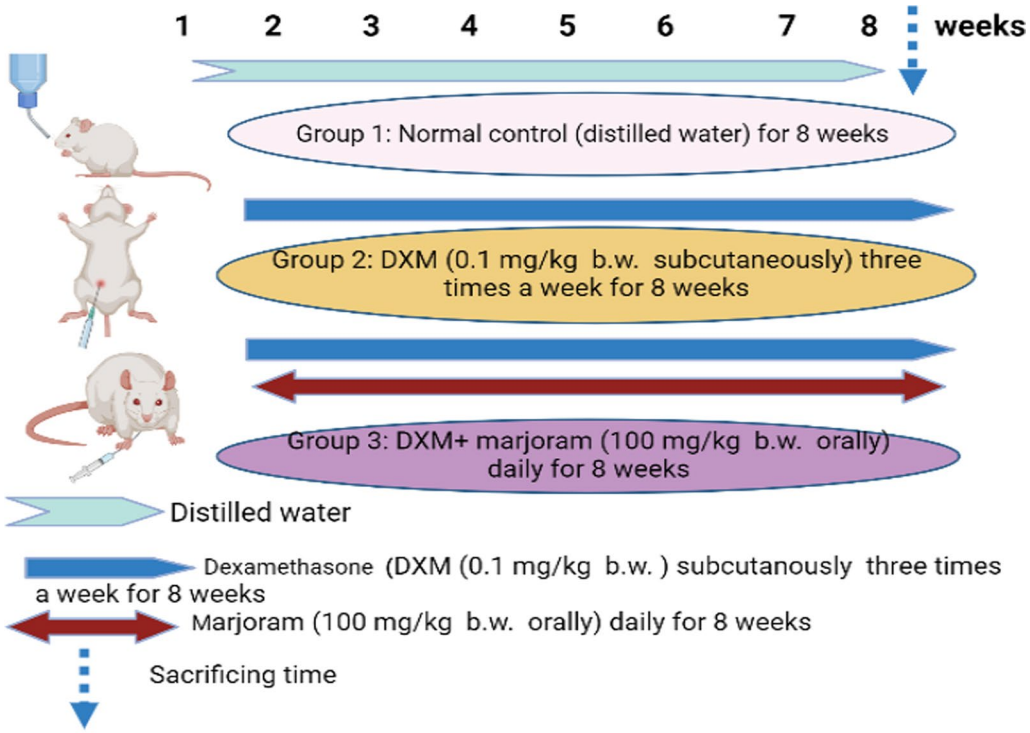


Fig. 1 A diagrammatic description of the study design and animal classification

Sampling

In the morning, at the end of the experiment and under light ether anesthesia. Animals were sacrificed by cervical decapitation; 5 ml of blood were collected from the jugular vein (Lucas et al. 2004), then centrifuged for 15 minutes to separate serum and kept frozen at −20 °C for biochemical analyses.

Liver marker enzymes

Regarding Rosalki et al. (1993), serum alkaline phosphatase (ALP) was kinetically estimated. Lactate dehydrogenase (LDH) kit was bought from Stanbio Laboratories in Texas, USA, and estimated using the Buhl and Jackson (1978) method. Reitman and Frankel (1957) methods were used to measure serum alanine transferase (ALT) and aspartate aminotransferase (AST) activity using kits supplied from Biodiagnostic (Egypt).

Hepatic antioxidant enzymes analyses and oxidative stress

Each animal's liver was quickly sampled after dissection and cleaned in saline solution. 0.5 g of liver tissue was homogenized in 5 ml of saline solution using a Teflon tissue homogenizer. Measurements of antioxidant enzymes were performed using the clear supernatant. For the estimation of reduced glutathione (GSH) and lipid peroxidation (MDA) using Ohkawa et al. (1979) approach and Beutler et al. (1963). According to Paglia and Valentine (1967), the activity of the enzyme glutathione peroxidase (GPx) was estimated. The GST activity was measured using a technique developed by Habig et al. (1974). Glutathione reductase (GR) and catalase (CAT) activity were evaluated using the techniques developed by Goldberg and Spooner (1983) and Aebi (1984), respectively.

Histopathological study

Liver specimens were cleaned in saline solution and then kept in 10% formalin solution in accordance with the Banchroft et al. (1996) technique. Paraffin wax was used to compare the morphologies of liver tissues. After dehydration, 5- µm thick liver slices were deposited with hematoxylin and eosin (H& E).

Statistical analysis

Using graph Pad Prism 5 software, analyzed data were presented as mean ± SEM (San Diego, Calif., USA). Remarkable data were considered when $P < 0.05$. The statistical comparisons were made by ANOVA (one-way analysis of variance) according to Tukeye Kramer methods, post-hoc analysis.

Table 1 *O. majorana* aqueous extract preventative role of on serum activities of ALT, AST, ALP and LDH against DXM treatment

Parameters Treatments	Serum ALT IU/L	% change	Serum AST IU/L	% change	Serum ALP IU/L	% change	Serum LDH IU/L	% change
G1 Control	55.9 ± 1.8	–	173.7 ± 2.18	–	183.0 ± 3.6	–	2481.0 ± 16.4	–
G2 DXM	77.9 ± 4.0***	39.4	264.0 ± 5.5 ***	51.99	303.2 ± 3.5 ***	65.57	2563 ± 21.7 ***	3.3
G3 DXM + *O. majorana*	54.2 ± 2.2 ***	− 30.4	234.0 ± 3.2***	− 11.36	180.0 ± 2.3 ***	− 40.59	2278 ± 9.3 ***	− 11.1
F-Probability	$P < 0.0001$	–	$P < 0.0001$	–	$P < 0.0001$	–	$P < 0.0001$	–

Data are mean ± SE, (n = 6), G1 compared to G2 and G3 compared to G2

DXM Dexamethasone

*, ** and ***Indicate significant change from control, DXM, and DXM + *O. majorana*, respectively, at $P < 0.0001$

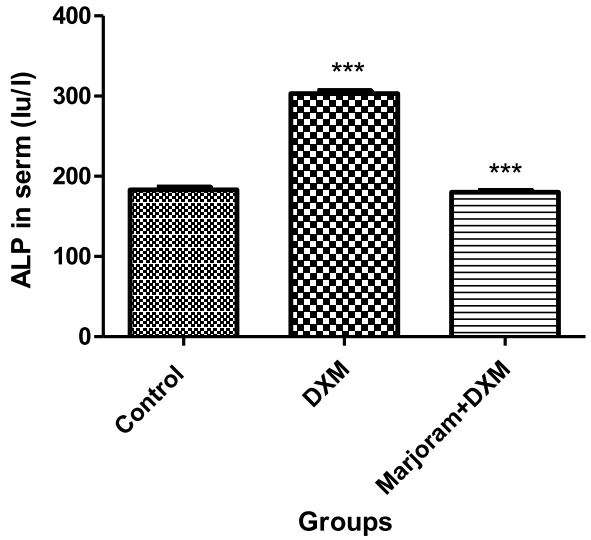


Fig. 2 *O. majorana* aqueous extract preventive role on serum activity of ALP against DXM treatment. *, ** and *** show significant variation from control, DXM and DXM + *O. majorana*, respectively, at $P < 0.0001$. DXM: Dexamethasone

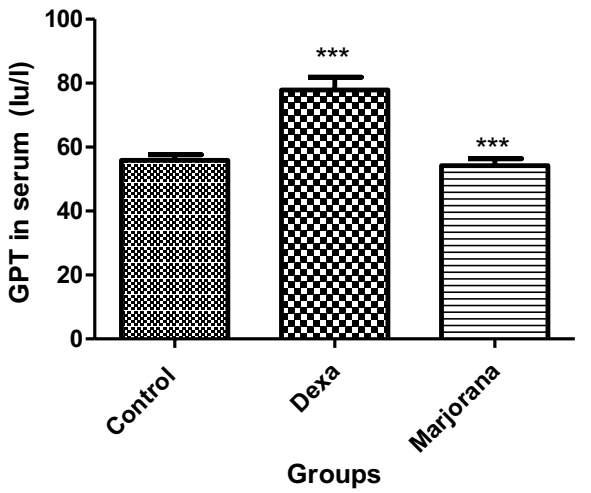


Fig. 3 *O. majorana* aqueous extract preventive role on serum activity of ALT against DXM treatment. *, ** and *** show significant variation from control, DXM and DXM + *O. majorana*, respectively, at $P < 0.0001$. DXM: Dexamethasone

Results

O. majorana alleviate Serum Liver Function Related Parameters in DXM treated rats

Table 1 illustrates liver damage which obviously appeared as a significant elevated activities ($P < 0.0001$) of circulating enzymes in serum (ALT, AST, ALP and LDH) after DXM treatment. Conversely, *O. majorana* pretreated animals successfully improved liver function markers which restored and/ or reduced these enzyme activities to normal level (Figs. 1, 2, 3, 4).

O. majorana prevents DXM-induced oxidative stress in rats

Table 2 clarifies that *O. majorana* pretreated group augmented the antioxidant defense system which elevated obviously ($P < 0.0001$) GSH level, CAT, GST, GPx plus GR activities in liver homogenate. In addition to that, *O. majorana* pretreatment suppressing oxidative stress

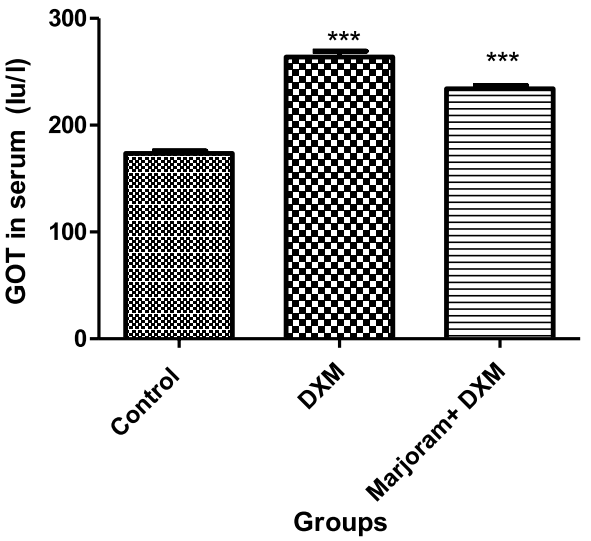


Fig. 4 *O. majorana* aqueous extract preventive role on serum activity of AST against DXM treatment. *, ** and *** show significant variation from control, DXM and DXM + *O. majorana*, respectively, at $P < 0.0001$. DXM: Dexamethasone

Table 2 *O. majorana* aqueous extract preventive role on the level of liver MDA, GSH, the activities of GST, CAT, GPx, and GR against DXM treatment

Parameters Treatments	MDA (nmol/g Tissue/hr)	% change	GSH (nmol/g tissue)	% change	GST IU/gm tissue	% change	CAT (IU/gm tissue)	% change	GPx (IU/gm tissue)	% change	GR (IU/gm tissue)	% change
G1 Control	13.1 ± 1.1	–	33.5 ± 3.7	–	4.1 ± 0.2	–	0.80 ± 0.004	–	171.5 ± 8.4	–	317.2 ± 12.6	–
G2 DXM	25.7 ± 1.7***	95.9	18.5 ± 1.4 **	− 44.8	2.3 ± 0.2 ***	− 43.2	0.213 ± 0.01 ***	− 73.4	81.6 ± 6.1***	− 52.4	180.1 ± 5.7***	− 43.2
G3 DXM + *O. majorana*	22.0 ± 0.1	− 14.4	31.8 ± 2.4 ***	72.2	3.6 ± 0.1 ***	55.6	0.363 ± 0.1 **	− 70.4	176.6 ± 4.0 **	116.5	267.8 ± 13.4***	48.7
F-Probability	P < 0.0001	–	P < 0.0020	–	P < 0.0001	–	P < 0.0001	–	P < 0.0001	–	P < 0.0001	–

Data are mean ± SE, (n = 6), G1 compared to G2 and G3 compared to G2

DXM Dexamethasone

*, ** and *** Indicate significant change from control, DXM, and DXM + *O. majorana*, respectively, at $P < 0.0001$

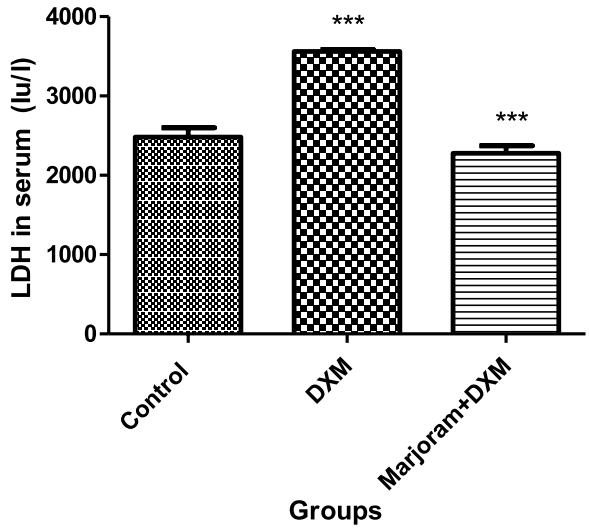


Fig. 5 *O. majorana* aqueous extract preventive role on serum activity of LDH against DXM treatment*, ** and *** show significant variation from control, DXM and DXM + *O. majorana*, respectively, at $P < 0.0001$. DXM: Dexamethasone

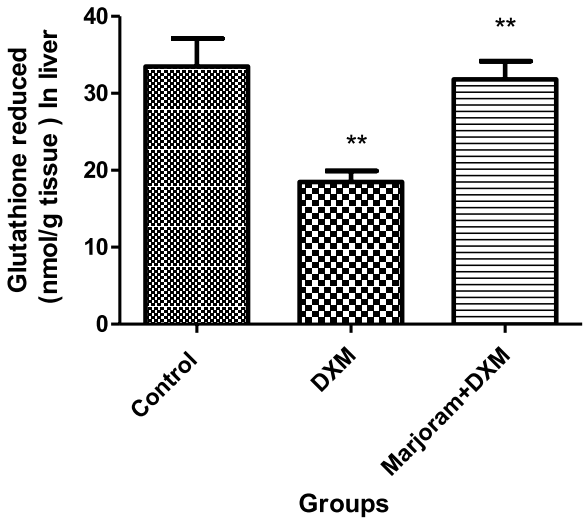


Fig. 7 *O. majorana* aqueous extract preventive role on liver GSH level against DXM treatment. *, ** and *** show significant variation from control, DXM and DXM + *O. majorana*, respectively, at $P < 0.0001$. DXM: Dexamethasone

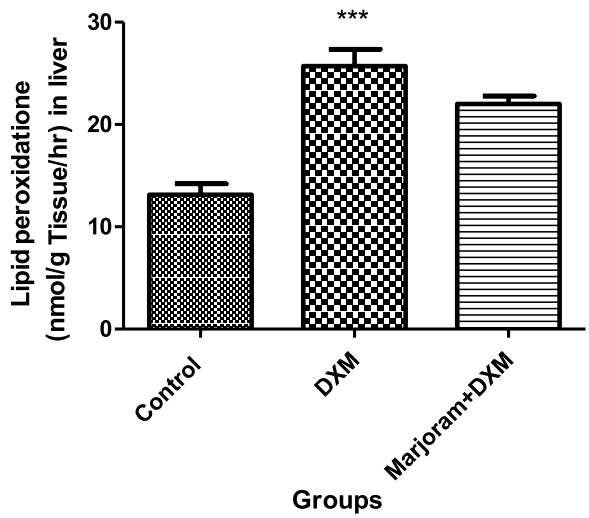


Fig. 6 *O. majorana* aqueous extract preventive role on liver MDA level against DXM treatment. *, ** and *** show significant variation from control, DXM and DXM + *O. majorana*, respectively, at $P < 0.0001$. DXM: Dexamethasone

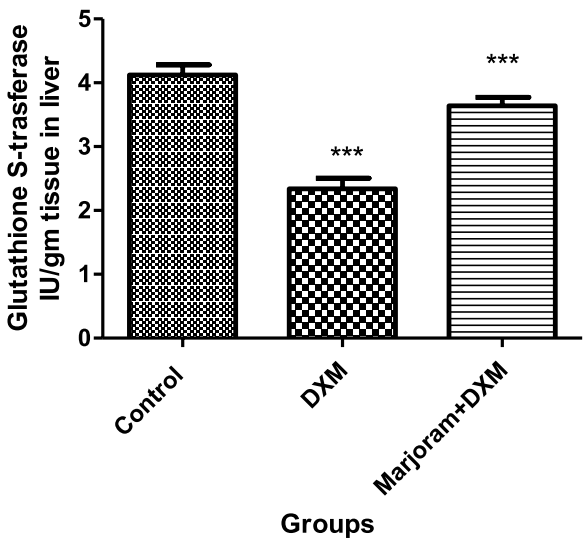


Fig. 8 *O. majorana* aqueous extract preventive role on liver activity of GST against DXM treatment. *, ** and *** show significant variation from control, DXM and DXM + *O. majorana*, respectively, at $P < 0.0001$. DXM: Dexamethasone

by lowering lipid peroxidation (LPO) in comparison with DXM administered animals. When compared to the normal control group, DXM impaired the antioxidant defense system and decreased the activities of GSH, CAT, GST, GPx& GR. Also, DXM treated rats boosted the oxidative stress which raised LPO level remarkably ($P < 0.0001$) in liver homogenate when compared with the control levels (Figs. 5, 6, 7, 8, 9, 10, 11).

Histological study

Figure 12 demonstrates rat liver in normal control group that have no pathological variations. But, fatty change was detected all over the hepatocytes in the hepatic parenchyma (Fig. 12B) associated with dilatation in the central vein as well as the portal vein in dexamethasone treated group. *O. majorana* pretreated group showed

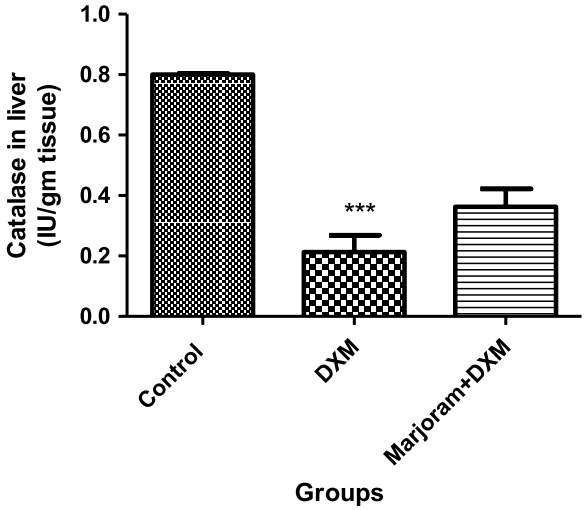


Fig. 9 *O. majorana* aqueous extract preventive role on liver activity of CAT against DXM treatment. *, ** and *** show significant variation from control, DXM and DXM + *O. majorana*, respectively, at $P < 0.0001$. DXM: Dexamethasone

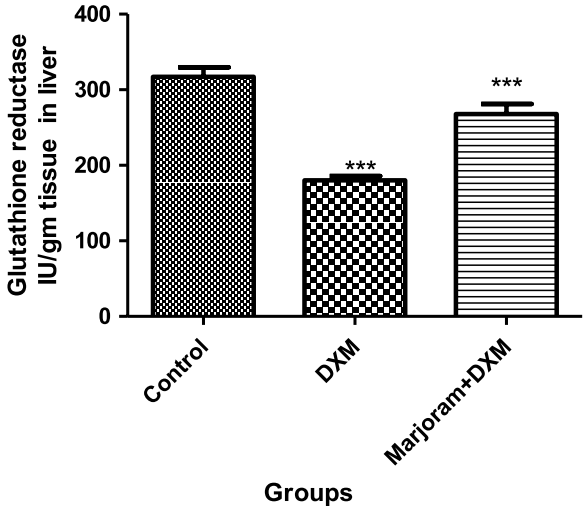


Fig. 11 *O. majorana* aqueous extract preventive role on liver activity of GR against DXM treatment. *, ** and *** show significant variation from control, DXM and DXM + *O. majorana*, respectively, at $P < 0.0001$. DXM: Dexamethasone

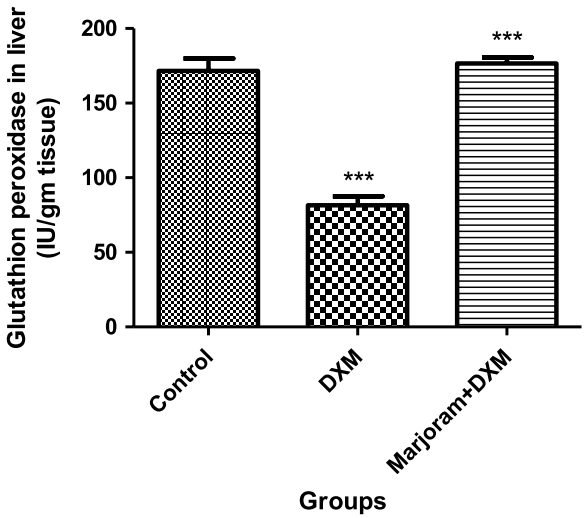


Fig. 10 *O. majorana* aqueous extract preventive role on liver activity of GPx against DXM treatment. *, ** and *** show significant variation from control, DXM and DXM + *O. majorana*, respectively, at $P < 0.0001$. DXM: Dexamethasone

edema and newly formed bile ductules in the portal area (Fig. 12C).

Discussion

The present work showed the hepatic damage in dexamethasone treated animals that was elicited by the elevated serum circulating enzymes (ALT, AST, ALP& LDH) activities obviously which ameliorated by *O. marjorana* pretreatment. These findings are in agreement with Hasona and Morsi (2019) who found that dexamethasone caused hepatotoxicity which elevated liver function activities significantly (ALT, AST& ALP). Increased liver marker enzymes were found in the serum of rats exposed to dexamethasone (Hasona et al. 2017). These enzymes' activities are sensitive indicators of hepatic damage and are directly correlated with the severity of the damage (Bastway et al. 2008). Generally, increased liver marker activities may reflect hepatocellular and bile canalicular destruction (Ha et al. 2001; Ahmed et al. 2014).

In the existing results, DXM also attenuated the immune system by increasing lipid peroxidation level remarkably and reducing the antioxidant defense markers significantly (GSH, GST, CAT, GPx & GR) and consequently confirmed by pathological disorders including fatty change all over the hepatocytes in the hepatic parenchyma, associated with dilatation in the central vein as well as the portal vein. *O. marjorana* boosted the immune system which enhanced the antioxidant defense system (elevated GSH, GST, CAT, GPx& GR) and attenuated the oxidative stress (reduced LPO). The current results are in agreement with Kamanli et al. (2004) who stated that corticosteroid therapy for liver damage causes increased liver function enzymes. DXM, which produces cell membrane oxidative damage leading to fatty liver alteration, may be responsible for increased inflammatory cell infiltration in the portal area, which is accompanied with liver injury. DXM-induced inflammatory cells infiltration, severe hepatocyte degeneration and necrosis (Safaei et al. 2012). Dexamethasone can severely altered hepatocytes

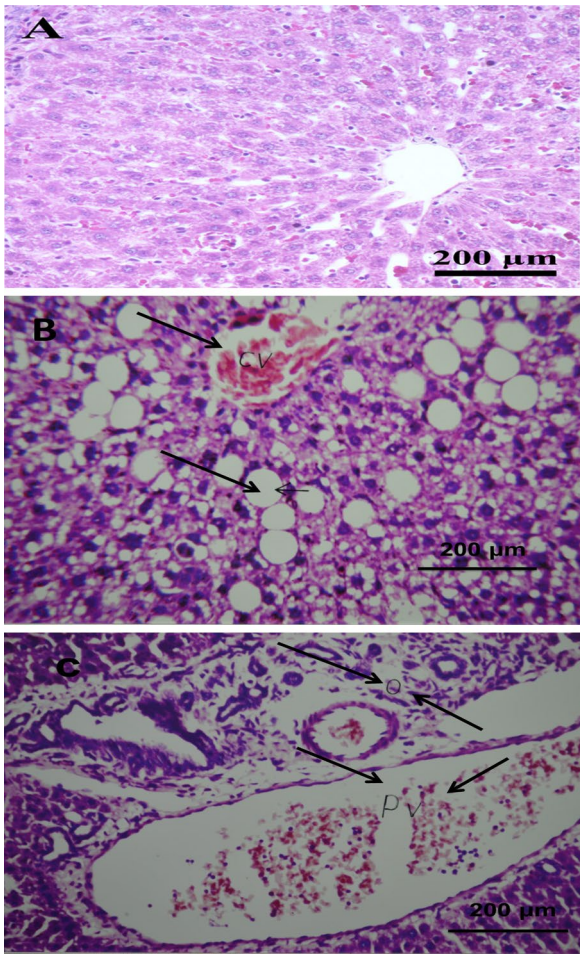


Fig. 12 **A** Normal control rat liver transverse section presenting a central vein (CV), hepatic cords (h) and sinusoids in between. x 400. **B** In the hepatic parenchyma fatty change was detected all over the hepatocytes associated with the central and the portal veins dilatation in dexamethasone treated group. x 400 **C** Hepatocytes of *O. majorana* pretreated group showing edema (o) and newly formed bile ductules in the portal area. x 400

function in long-term administered with high-dose as it is metabolized mainly in the hepatocytes via cytochrome P450 3A (Pascussi et al. 2001). Consequently, dexamethasone attenuates hepatocyte regeneration capacity after reducing hepatocyte proliferation activity which affected liver stored lipids and glycogen, subsequently leading to degeneration of glycogen and lipid in hepatocytes. Dexamethasone decreasing proliferation of liver cells to a lesser extent and apoptosis (Kimura et al. 2011). Concerning oxidative stress, the existing data coincided with Hasona et al. (2017) who stated that the principal cause of dexamethasone-induced liver injury is oxidative stress caused by the excessive production of free radicals. Dexamethasone significantly lowered the actions of entire antioxidant capacity as well as superoxide dismutase, resulting in oxidative stress by raising the volumes of peroxide hydrogen plus malondialdehyde (Miguel 2010). After exposure to dexamethasone, malondialdehyde levels in the plasma, liver and kidney were significantly elevated, indicating enhanced peroxidation and a breakdown of the antioxidant defense systems. The major cause of oxidative stress due to dexamethasone-induced liver injury is the free radicals excessive production (Airaodion et al. 2020).

Plants contain abundant phytochemicals with antioxidant which attenuated in vitro the agents of the oxidative stress (Iuchi et al. 2003). Antioxidants assist in preventing oxidation, which can harm cells and speed up aging. Antioxidants could improve immune response and lower the risk of cancer, heart disease, and infections. Foods include antioxidants in the form of vitamins, minerals, and other substances (Valko 2007). Increased MDA concentrations have been shown to decrease in the presence of antioxidants and phytochemicals (Airaodion et al. 2019a, b, c, d; Megwas et al. 2021). *O. marjorana* rich in flavonoids as quercetin, apigenin, naringenine, catechin, kaempferol, luteolin, eriodictyol, diosmetin, and hesperetin (Mossa et al. 2013, Villalva et al., 2018). Hydroxycinnamic acids and flavonoids, the watery extract of sweet *O. majorana* phenolic compounds have a significant ability in lipid oxidation slowing down (Triantaphyllou et al. 2001; El-Ashmawy et al. 2005). Ursolic acid from *O. majorana* decreased micromolar Abeta chance to enhanced oxidative cellular death (Heo et al. 2002). Quercetin and naringenine restored the liver function toward normal. Also, they offer protective effect on hepatocellular membrane against modifications or injury induced by diethylnitrosamine and acetylaminofluorene. These flavonoids might maintain hepatocytes by stabilizing membrane integral structures and thus prevent the release of these enzymes (Chen 2010; El-Denshary et al. 2015). The natural antioxidants protected the body from the dangerous chemicals known as free radicals (Devi et al. 2016). By the creation of reactive oxygen species, oxidative stress leads to the production of free radicals such as superoxide anions (O_2^-), hydrogen peroxide (H2O2), hydroxyl radicals (OH^-), nitric oxide (NO), and organic hydroperoxide [(ROOH) (ROS)] (Aly and Duk 2016; Devi et al. 2016). The most prevalent soluble antioxidant, glutathione is present in all cell compartments (Airaodion et al. 2019a, b, c, d). Liver glutathione production and antioxidant defense are essential for effective detoxification procedures in response to metabolic stressors (Chen et al. 2020). In addition to playing a significant role in the metabolism of xenobiotics, glutathione directly quenches ROS such lipid peroxides.

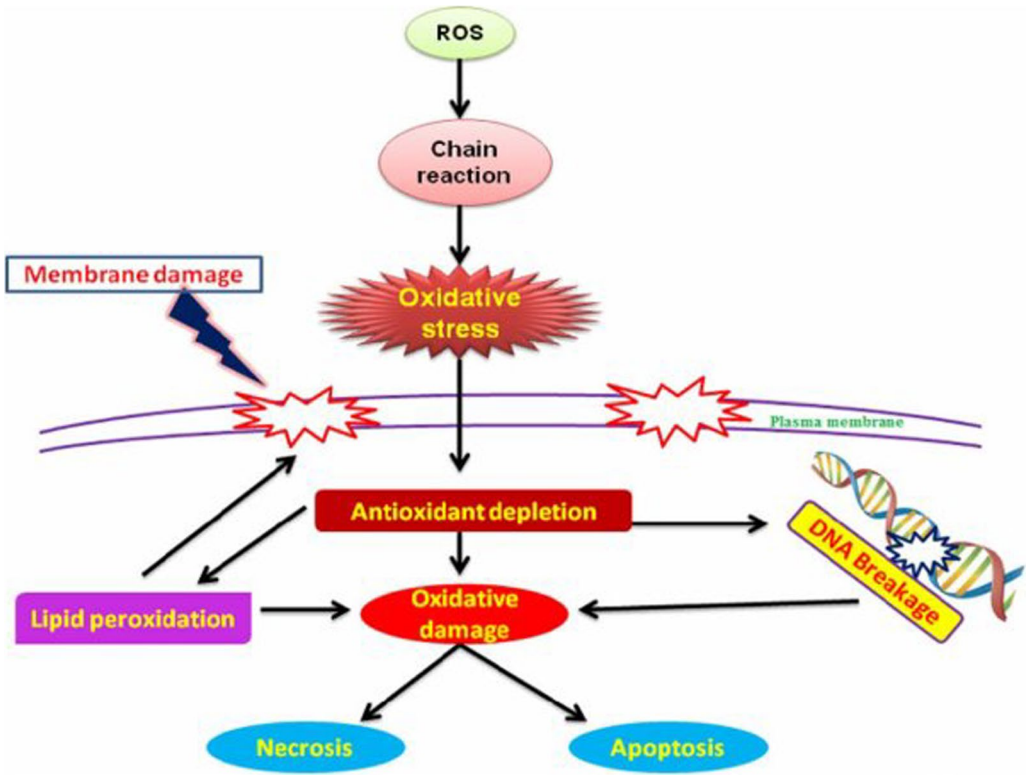


Fig. 13 Cellular damage induced by oxidative stress

Glutathione plays a crucial function in the metabolism of xenobiotics and directly suppresses ROS such lipid peroxides (Ogbuagu et al. 2019). Glutathione detoxifies hydrogen peroxide and lipid peroxide by providing hydrogen peroxide an electron, converting it to water and oxygen, and protecting macromolecules from oxidation, such as lipids (Airaodion et al. 2019a, b, c, d). It is interesting to note that the biological system has been set up with natural enzymatic antioxidants like catalase, superoxide dismutase, and glutathione reductase to counteract the harmful effects of free radicals (Singh and Jambunathan 2017). Superoxide dismutase, catalase and glutathione-s-transferase maintaining the balance between ROS and antioxidant enzymes. Dismutation of superoxide anion (O_2^-) to H_2O_2 and O_2 catalyzes by SOD. CAT catalyzes the decomposition of H2O2 to water because H_2O_2 is still harmful to cells and this mechanism is the important to avoid harm by oxidative stress (Al-Badr 2011). LPO had a significant effect to damage the cell membrane through altering its normal function (Fig. 13). An excess of reactive oxygen species was the source of an increase in oxidative stress (ROS). Consequently ROS have implicated in a number of disease processes, as liver injury, aging, diabetes, heart disease and cancer (Bokov et al. 2004, Giordano 2005, Mossa 2004, Mansour and Mossa 2010, Pelvana et al. 2022). Extreme doses of dexamethasone may increase the generation of free radicals, especially ROS. Free radicals cause cells to become more susceptible to apoptosis, mitochondrial malfunction, and permeability, which lower cellular energy production (Sato et al. 2010; Feng and Tang 2014).

Conclusions

Overall, the hepatotoxic effect of dexamethasone appeared clearly either by liver function markers elevation or antioxidant defense system attenuation as well as liver histological alterations. *Origanum majorana L.* (*O. majorana*) aqueous extract boosted the immune system, attenuated the oxidative stress and consequently protect the liver from the damaging effects induced by dexamethasone. To apply *O. majorana* as an important therapeutic strategy requires attention to assess its safety as well as benefits.

Abbreviations

DXM	Dexamethasone
GCs	Glucocorticoids
Cd	Cadmium
b.wt.	Body weight
ALP	Alkaline phosphatase

LDH	Lactate dehydrogenase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
GSH	Reduced glutathione
MDA or LPO	Lipid peroxidation
GPx	Glutathione peroxidase
GST	Glutathione-s-transferase
GR	Glutathione reductase
CAT	Catalase
H& E	Hematoxylin and eosin
ROS	Reactive oxygen species
SOD	Superoxide dismutase
SE	Standard error

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Author contributions
In this study WH and HA have conceived and planned the experiments. WH and HA carried out the experiments. HA analyzed the data. HA and WH discussed the results. HA prepared, edited, reviewed and finalized the manuscript. Both authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate
The National Institutes of Health (NIH) and Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) criteria for the handling and use of experimental animals were followed in all animal operations. All experiments were performed in line with the ethical guidelines approved by the Medical Research Ethics Committee of the National Research Centre, El Dokki, Egypt of Experimental Animals (No. 20286).

Consent for publication
Not applicable.

Competing interests
The authors do not declare any conflict of interest about this research.

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