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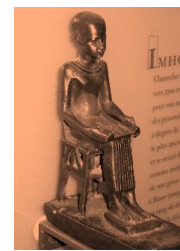
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## Original Article

# Study of The Protective Effect of Garlic Water Extract on Dexamethasone-Induced Hepatotoxicity and Insulin Resistance in Adult Male Albino Rats

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## ABSTRACT

### Article information

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**Background:** The liver has an essential role in the metabolism and detoxification of various metabolites and drugs so it is liable to injury. Long-term use of dexamethasone may cause hepatic injury and insulin resistance. Garlic contains a variety of effective compounds that exhibit antioxidant, hypocholesterolemic, hypoglycemic, antithrombotic, antibiotic, anticancer, as well as hypotensive activities.

**Objective:** To study the effect of garlic water extract on hepatic toxicity and insulin resistance induced by dexamethasone in adult male albino rats.

**Materials and Methods:** Twenty-four adult male albino rats of a local strain were divided into three equal groups, group 1 [control group], group 2 [dexamethasone-treated group], and group 3 [dexamethasone and garlic-treated group]. After two weeks from the onset of the experiment serum was isolated from blood samples for assessment of Alanine Transaminase [ALT], Aspartate Transaminase [AST], serum albumin, Alkaline Phosphatase [ALP], total bilirubin, fasting blood glucose [FBG], and Fasting insulin level. Homeostasis Model Assessment for Insulin Resistance [HOMA-IR] was then calculated. Samples of the liver were taken for histopathological studies.

**Results:** There was a significant elevation in ALT, AST, ALP, and total bilirubin and a significant reduction in serum albumin in the dexamethasone-treated group when compared with the control group. ALT, AST, ALP, and total bilirubin significantly improved in the dexamethasone and garlic extract-treated group. Also, there was a significant elevation in FBS, insulin level, and HOMA-IR in the dexamethasone-treated group when compared with the control group. These parameters were significantly decreased in the dexamethasone and garlic extract-treated group when compared with the dexamethasone-only treated group.

**Conclusion:** Garlic water extract showed a potential protective effect against dexamethasone-induced liver injury and insulin resistance.

**Keywords:** Garlic water extract; Dexamethasone; Hepatotoxicity; Insulin resistance.



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## INTRODUCTION

The liver has an essential role in the metabolic pathways of carbohydrates, lipids, and proteins. Furthermore, the detoxification and biotransformation of various metabolites and drugs occur mainly in the liver, hence, it is susceptible to the toxicity of these agents [1]. Continuous exposure of the liver to harmful metabolites, poisons, and drugs can lead to various acute and chronic liver diseases [2].

Glucocorticoids are important anti-inflammatory and immunosuppressive therapy. Various acute and chronic inflammatory and immune-mediated diseases are widely treated with glucocorticoids. Furthermore, many organ transplants and many malignancies such as leukemia are also using glucocorticoids as part of their therapeutic regimens. Long-term use of glucocorticoids may lead to metabolic disease, osteoporosis, and cardiovascular disorders [1].

Dexamethasone is an effective immune-suppressive and anti-inflammatory agent however, its use may have several side effects, for example, hepatic injury, skeletal muscle atrophy, and insulin resistance. Dexamethasone increases the production of free radicals which in turn increases oxidative stress-mediated tissue damage [3].

Insulin resistance is reduced responsiveness in insulin-targeting tissues to high physiological insulin levels and is considered the pathogenic driver of many diseases, including metabolic syndrome, nonalcoholic fatty liver disease [NAFLD], atherosclerosis, and T2DM. In the prediabetic condition, insulin levels increase to meet normal insulin requirements leading to chronic hyperinsulinemia, hyperglycemia-induced  $\beta$ -cell failure, and eventually T2DM [4].

Continuous exposure of the liver to harmful environmental and pharmacological agents may lead to liver diseases. The prevalent obesity and sedentary lifestyle are key determinants in insulin resistance and its subsequent metabolic disorders. Therefore, the optimization of pharmacotherapy, search and study of new drugs which can protect the liver and enhance tissue sensitivity to insulin is a topical issue of pharmacy and medicine. Phytotherapy has several advantages over traditional therapy including being low-toxic, can be used for long periods without significant side effects, being

well combined with synthetic drugs, and having a complex activity through many biologically active compounds [5].

Since ancient times, people have utilized garlic [*Allium sativum*] as a remedy. Garlic will probably find a position as a complement to existing methods of illness prevention and treatment even though it is not yet accepted as a viable replacement to these treatments. Garlic includes a number of potent chemicals that have anti-inflammatory, anti-platelet, anti-coagulant, antibacterial, anti-cancer, and hypotensive properties [6]. The first scientific studies on garlic were reported by Louis Pasteur, who attributed the plant as having anti-bacterial properties. Studies have also reported that garlic extracts have anti-inflammatory, anti-microbial, anti-asthmatic, and anti-cancer effects [7]. Garlic also known to contain natural antioxidants that can remove reactive oxygen species [ROS] [8].

## THE AIM OF THE WORK

This work aimed to study the effect of garlic water extract on hepatic toxicity and insulin resistance induced by dexamethasone in adult male albino rats.

## MATERIALS AND METHODS

Animal models for this study were 24 adult male albino rats of a local strain. They were 8 weeks old, weighing between 110 and 140 grams. They were housed at room temperature with a natural light-dark cycle in adequate cages [42x26x16 cm for every 4 rats]. Before beginning the experiment, they were held for 10 days to allow for acclimatization to the new surroundings. There were three equal groups of animals, each with eight rats [n = 8].

➤ **Group 1 [control group]:** eight rats were treated with saline at a dose of 2ml/kg body weight via intraperitoneal injection daily for two weeks.

➤ **Group 2 [dexamethasone-treated group]:** eight rats were treated with dexamethasone sodium phosphate [manufactured by Amriya Pharmaceuticals Industries, Alexandria, Egypt] at a dose of 1 mg/kg body weight via intraperitoneal injection daily for 2 weeks [9].

➤ **Group 3 [dexamethasone and garlic treated group]:** eight rats were treated with

dexamethasone sodium phosphate at a dose of 1 mg/kg body weight via intraperitoneal injection daily and treated with garlic water extract at a dose of 500mg/kg body weight via intraperitoneal injection daily for 2 weeks [6].

Fresh garlic bulbs that were easily accessible locally were used to make aqueous garlic extract. On a bed of crushed ice, the garlic bulbs were peeled. In 70 ml of cold, sterile 0.9% NaCl with some broken ice, 50 grams of peeled garlic that had been chopped into little pieces. In a blender, homogenization was done in 20-second bursts over the course of 30 seconds [the total time of homogenization was about ten minutes]. Three separate passes through cheesecloth were made with the homogenized mixture. The clear supernatant from the centrifuged filtrate was then diluted to a volume of 100 ml with ordinary saline. Based on the weight of the starting material [50 g/100 ml], it was determined that this garlic preparation had a 500 mg/ml concentration. Small aliquots of the aqueous garlic extract were kept at -20°C [6].

Blood samples were taken from the retro-orbital venous plexus under ether anesthesia two weeks after the experiment started and following an overnight fast using a heparinized capillary tube that was placed in the medial canthus. EDTA-containing centrifuge tubes with clean graduations were used to store the obtained blood samples. To separate the serum, the blood was centrifuged for around 15 minutes at 5000 rotations per minute. Serum was drawn out into Eppendorf tubes and kept frozen at -20°C until it was needed to measure:

- Alanine transaminase [ALT] [U/L]
- Aspartate transaminase [AST] [U/L]
- Serum albumin [g/dL]
- Alkaline phosphatase [ALP] [U/L]
- Total bilirubin [mg/dL]
- Fasting blood glucose [FBG] [mg/dL]
- Fasting insulin level [micro U/ml]
- Homeostasis Model Assessment for Insulin Resistance [HOMA-IR]: was calculated according to the formula: fasting insulin [micro U/ml] x fasting glucose [mMol/L]/22.5 [10]. FBG in mMol/L equals FBG in mg/dl divided by 18.018018.

The midline abdominal incision was carried out right away following the ether inhalation anesthesia of the rats and blood sampling. The abdominal cavity was quickly opened up to

reveal the liver. Following initial fixation in 10% buffered formalin for 72 hours, liver samples were dehydrated in escalating grades of ethyl alcohol, cleared in xylene, impregnated, and embedded in paraffin wax to create paraffin blocks. Sections of 5 µ thickness were cut using a rotary microtome, mounted on spotless glass slides, and stained with hematoxylin and eosin [H&E]. The general histological makeup of the liver was examined with concern on hepatic architecture, hepatocellular degeneration, infiltration by inflammatory cells, presence of fibrosis and its extension.

All the ethical protocols for the experimental use of laboratory animals were carried out after the approval of the Faculty of Medicine [Boys] Institutional Research Board, Al-Azhar University, Cairo, Egypt [Approval Certificate number: Pat. 3Med. Research 000004]. The principle of reducing waste, reusing and recycling resources and products [RRR principle] was followed.

**Data analysis:** SPSS version 25 was used to analyze the collected data. If the data were normally distributed, the "Shapiro-Wilk" test, one-way analysis of variance [ANOVA], and post hoc "Tukey" test were performed to determine whether the distribution was normal. In the absence of normally distributed data, the "Kruskal Wallis" and "Mann Whitney U" tests were employed to compare means. The linear relationship between the variables under study was assessed using Spearman's correlation coefficient [ $\rho$ ]. P 0.05 was regarded as statistically significant, and data were reported as means and SD.

## RESULTS

Table [1] showed the means  $\pm$  SD of studied parameters in different groups of the study.

When comparing the dexamethasone-treated group 2 with the control group 1, there was a significant elevation in both ALT and AST levels [ $P < 0.0001$ ]. When comparing the dexamethasone and garlic extract-treated group 3 with the dexamethasone-treated group 2, there was a significant improvement in ALT and AST levels [ $P < 0.0001$ ]. However, ALT and AST levels were higher in the dexamethasone and garlic extract-treated group 3 when compared to the control group 1 [ $P < 0.005$  for ALT and  $P < 0.012$  for AST] [Figure 1].

Regarding bilirubin and ALP, their levels were higher in the group 2 when compared with group 1 [ $P < 0.0001$ ]. When comparing the group 3 with group 2, the levels of bilirubin and ALP was significantly lower [ $P < 0.0001$ ]. On the other hand, the levels of these parameters were significantly higher in group 3 when compared to group 1 [ $P < 0.0001$  for ALP and  $P < 0.038$  for bilirubin]. There was a significant difference in serum albumin level when comparing group 1 with the group 2 where it was lower in this group than in the control group [ $P < 0.0001$ ]. Serum albumin level was higher in group 3 when compared with group 2 however the difference was insignificant [Figure 2].

When comparing the dexamethasone-treated group [2] with the control group 1, there was a significant elevation in FBS, insulin levels, and HOMA-IR [ $P < 0.0001$ ]. When comparing the dexamethasone and garlic extract-treated group 3 with the dexamethasone-treated group 2, there was a significant improvement in the three parameters [ $P < 0.0001$ ]. Similarly, when comparing the dexamethasone and garlic extract treated group [3] with the control group [1], FBS, insulin levels and HOMA-IR were significantly higher [ $P < 0.0001$  for FBS and HOMA-IR and  $P < 0.005$  for insulin]; meaning that treatment with garlic extract causes improvement in these parameters but is still significantly higher than the control group [Figure 3].

There was a significant positive correlation between ALT and HOMA-IR with correlation factors “ $\rho$ ” 0.842 [ $P < 0.0001$ ]. Also, there was a significant positive correlation between AST and HOMA-IR with correlation factors “ $\rho$ ” 0.816 [ $P < 0.0001$ ] [Figure 4].

There was a significant positive correlation between ALP and HOMA-IR with correlation factors “ $\rho$ ” 0.838 [ $P < 0.0001$ ]. Also, there was

a significant positive correlation between bilirubin and HOMA-IR with correlation factors “ $\rho$ ” 0.801 [ $P < 0.0001$ ] [Figure 5]. On the other hand, there was a significant negative correlation between HOMA-IR and albumin level with correlation factor “ $\rho$ ” -0.529 [ $P < 0.008$ ] [Figure 6].

There was a significant positive correlation between FBS and insulin level with correlation factor “ $\rho$ ” 0.882 [ $P < 0.0001$ ] [Figure 7].

There was a significant positive correlation between FBS and HOMA-IR with a correlation factor of 0.958 [ $P < 0.0001$ ]. Also, there was a significant positive correlation between insulin level and HOMA-IR with a correlation factor of 0.934 [ $P < 0.0001$ ] [Figure 8].

### Histopathological examination [routine Hematoxylin & Eosin [H & E] staining technique]

Normal rat liver tissue stained with H&E contains a normal hepatic lobule and a thin-walled central vein, hepatic cords radiating to the periphery alternating with hepatic sinusoids lined by Kuepfer cells and endothelial cells.

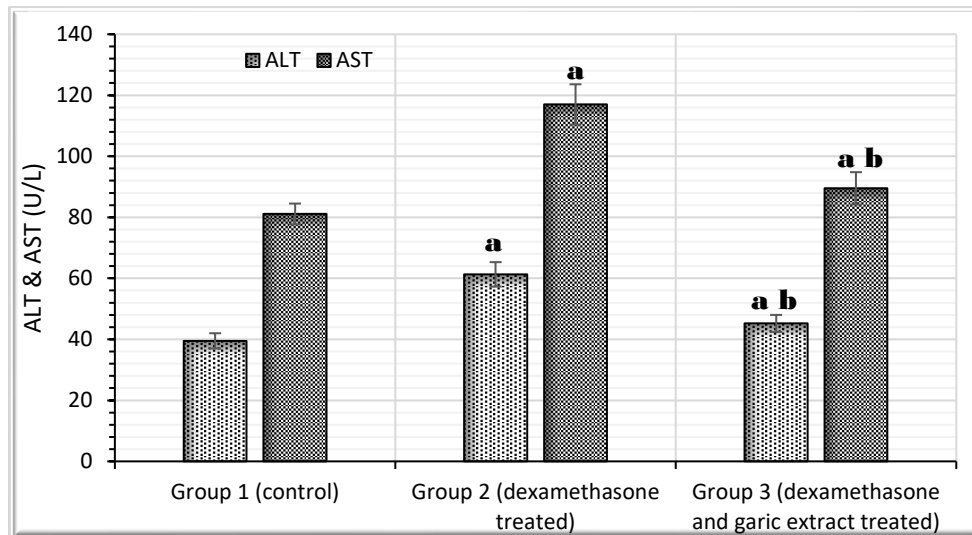
The liver tissues of the dexamethasone-treated group showed sinusoidal wall and portal fibrosis and loss of normal hepatic architecture and inflammatory cells infiltration mainly lymphocytes. There is mild bile ductular proliferation with minimal cellular and canalicular cholestasis in the parenchyma with marked macro-micro vesicular steatosis and marked feathery degeneration in some areas [figures 10-12] compared to the normal control group [Figure 9].

Liver tissues in the dexamethasone and garlic water-treated group showed preservation of normal architecture of the liver tissue, with no fibrosis or steatosis [figures 13 & 14].

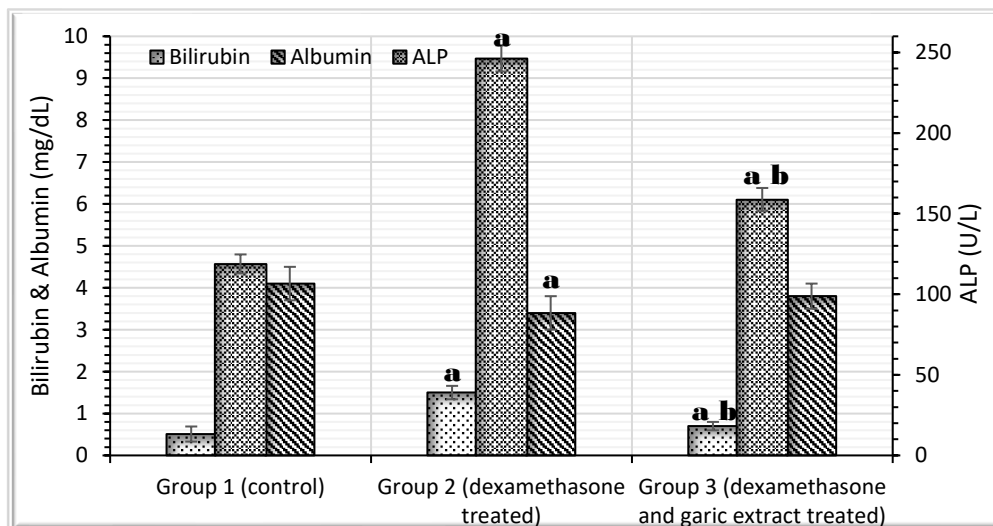
**Table [1]:** Mean and SD of studied parameters in different groups

Parameters	Group 1 (control)	Group 2 (dexamethasone-treated)	Group 3 (dexamethasone and garlic extract treated)
ALT (U/L)	39.5 ± 2.5	61.3 ± 4	45.2 ± 2.8
AST (U/L)	81.1 ± 3.4	117 ± 6.6	89.5 ± 5.3
ALP (U/L)	118.8 ± 5.9	246.3 ± 8.1	158.7 ± 7.2
Bilirubin (mg/dL)	0.51 ± 0.18	1.5 ± 0.16	0.7 ± 0.1
Albumin (g/dL)	4.1 ± 0.4	3.4 ± 0.4	3.8 ± 0.3
FBG (mg/dL)	88.3 ± 7	195.1 ± 12	137.9 ± 7.3
Insulin (micro U/L)	9.7 ± 0.6	13.4 ± 0.9	11 ± 0.7
HOMA-IR	2.1 ± 0.18	6.4 ± 0.57	3.7 ± 0.27

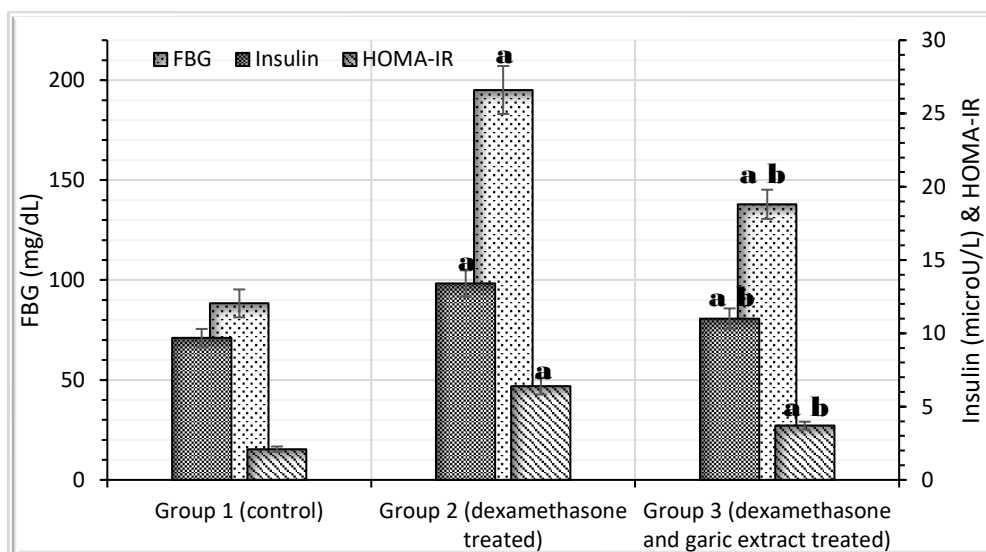




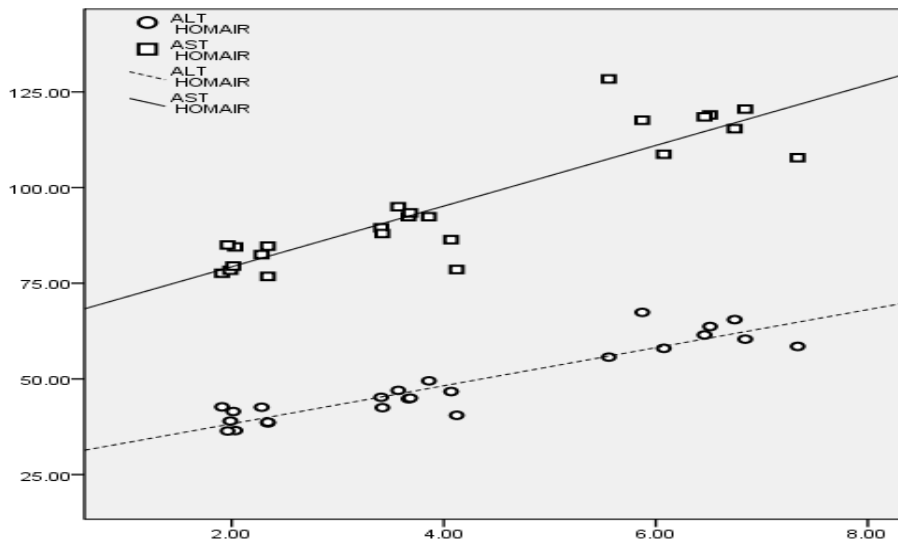
**Figure [1]:** ALT and AST levels in studied groups; a = significant difference when compared with group 1; b=significant difference when compared with group 2



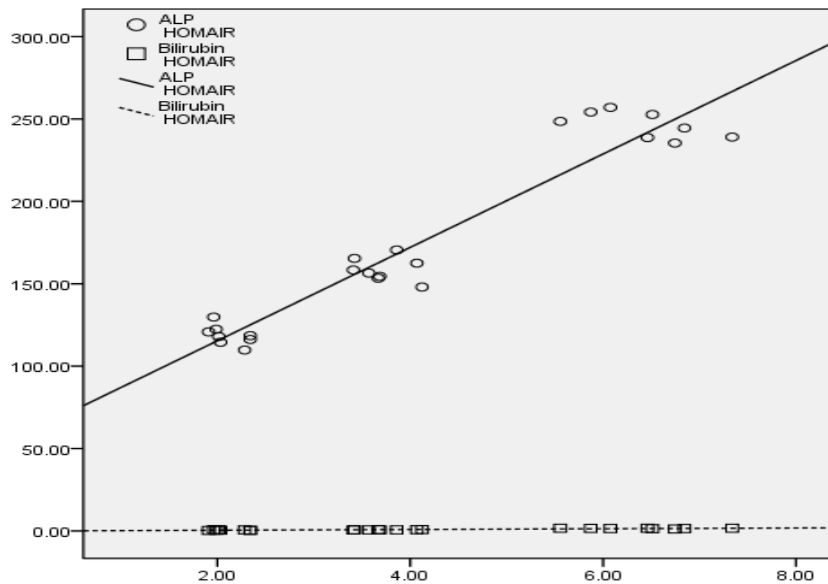
**Figure [2]:** Bilirubin, Albumin, and ALP levels in studied groups; a = significant difference when compared with group 1; b = significant difference when compared with group 2



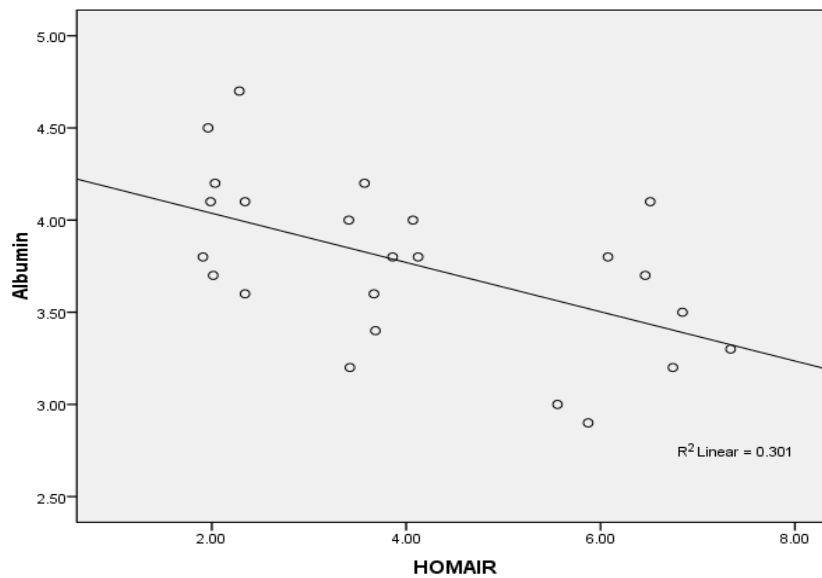
**Figure [3]:** FBG, Insulin, and HOMA-IR levels in studied groups; a = significant difference when compared with group 1; b = significant difference when compared with group 2



**Figure [4]:** Correlation between ALT & HOMA-IR and AST & HOMA-IR



**Figure [5]:** Correlation between ALP & HOMA-IR and bilirubin & HOMA-IR



**Figure [6]:** Correlation between albumin & HOMA-IR



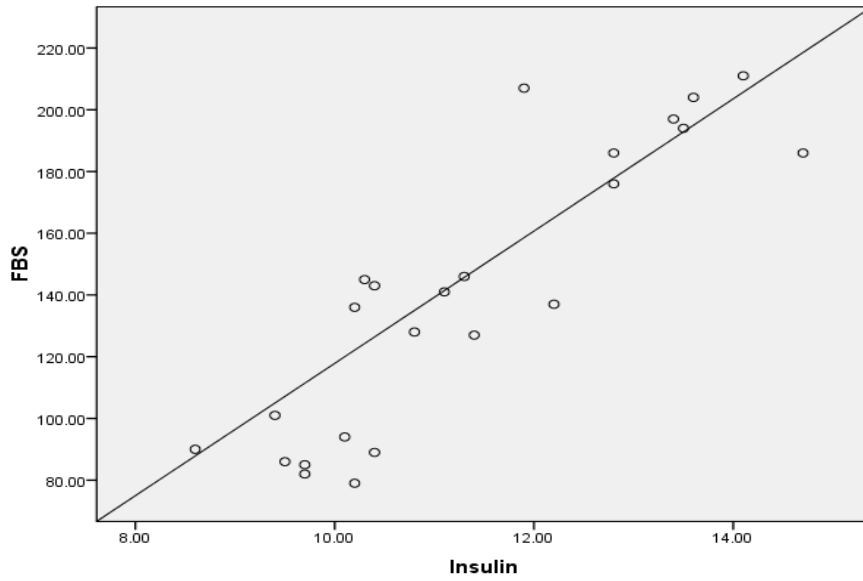


Figure [7]: Correlation between FBS & insulin

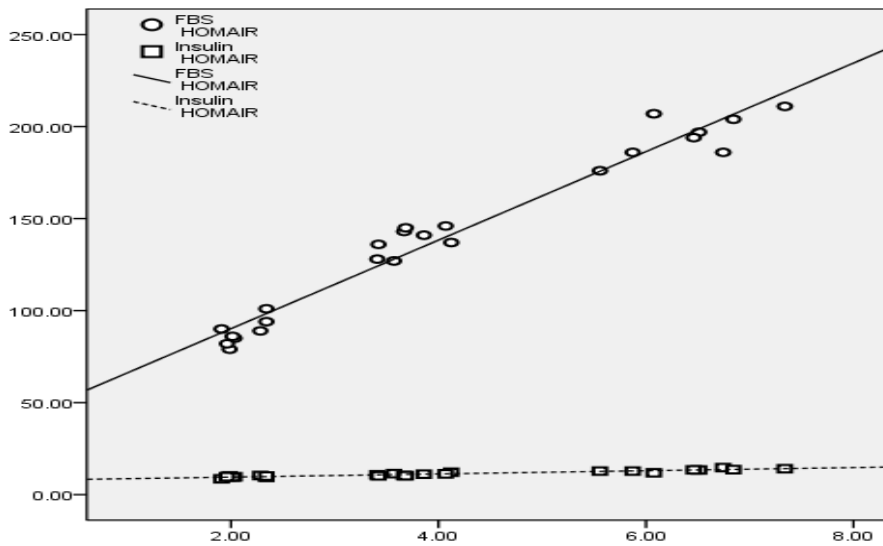


Figure [8]: Correlation between FBS & HOMA-IR and insulin & HOMA-IR

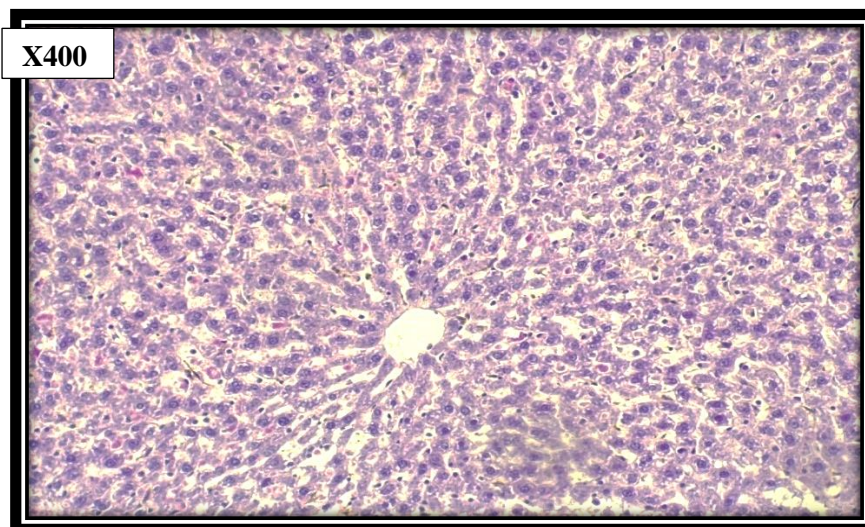
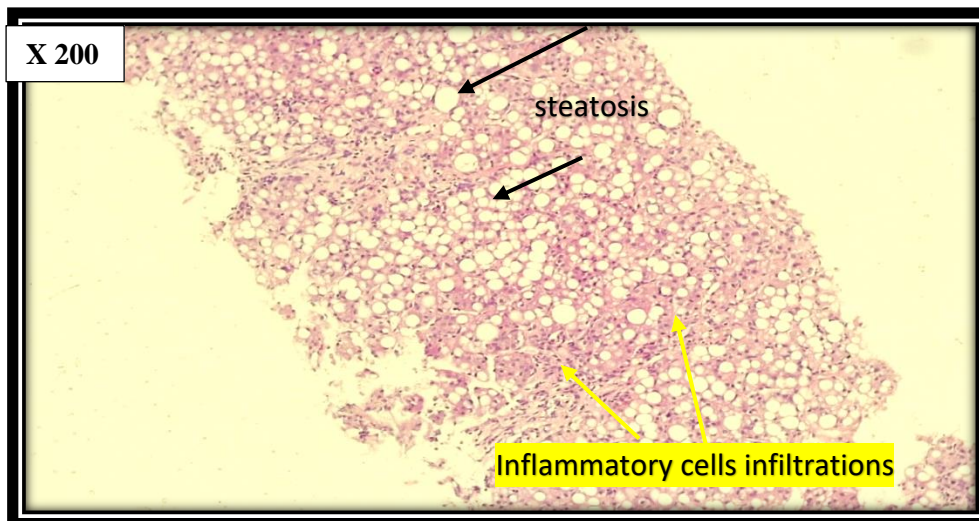
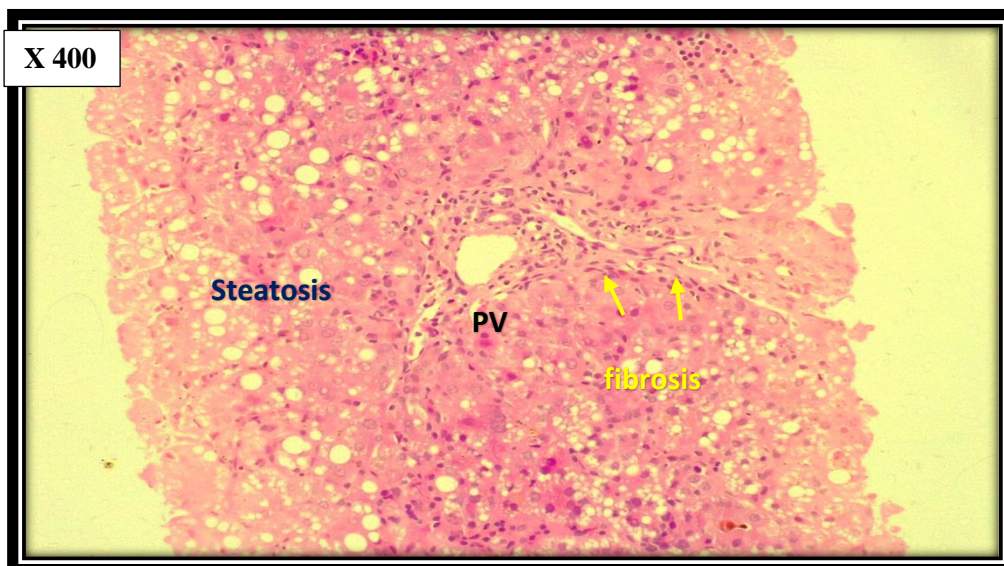


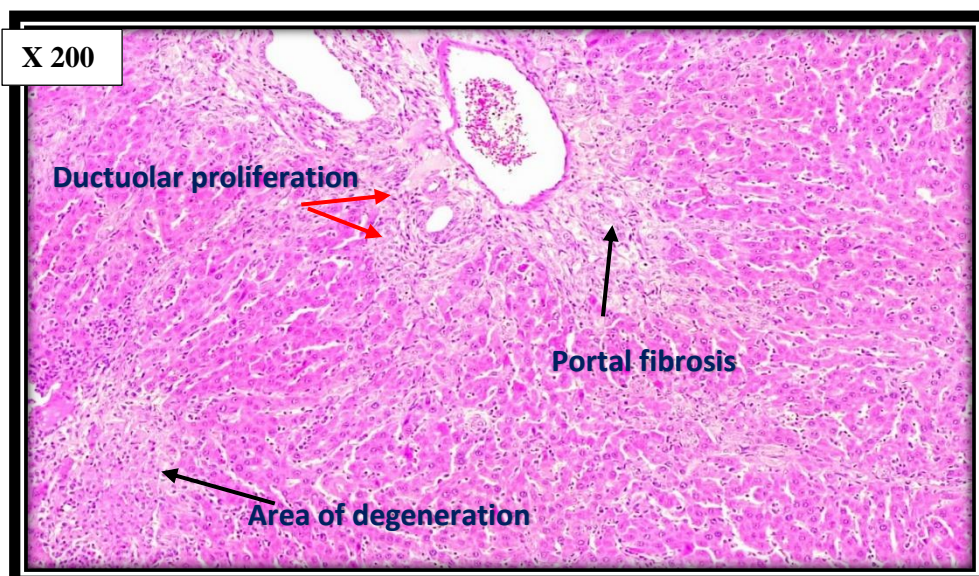
Figure [9]: A photomicrograph of a section in normal rat liver. showing cords of hepatocytes radiating from the central vein which appeared with normal and normal blood sinusoids (H & E)



**Figure [10]:** A photomicrograph of a section in dexamethasone-treated rat liver tissue showing steatosis with inflammatory cells infiltrations (H & E)

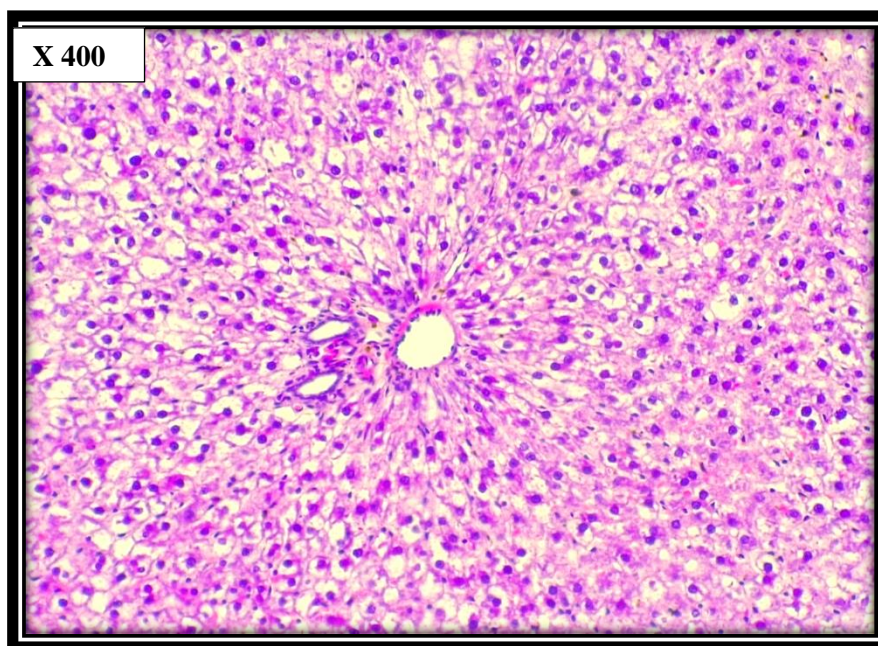


**Figure [11]:** A photomicrograph of a section in dexamethasone-treated rat liver tissue. The Figures show steatosis with portal area fibrosis extension (H & E)

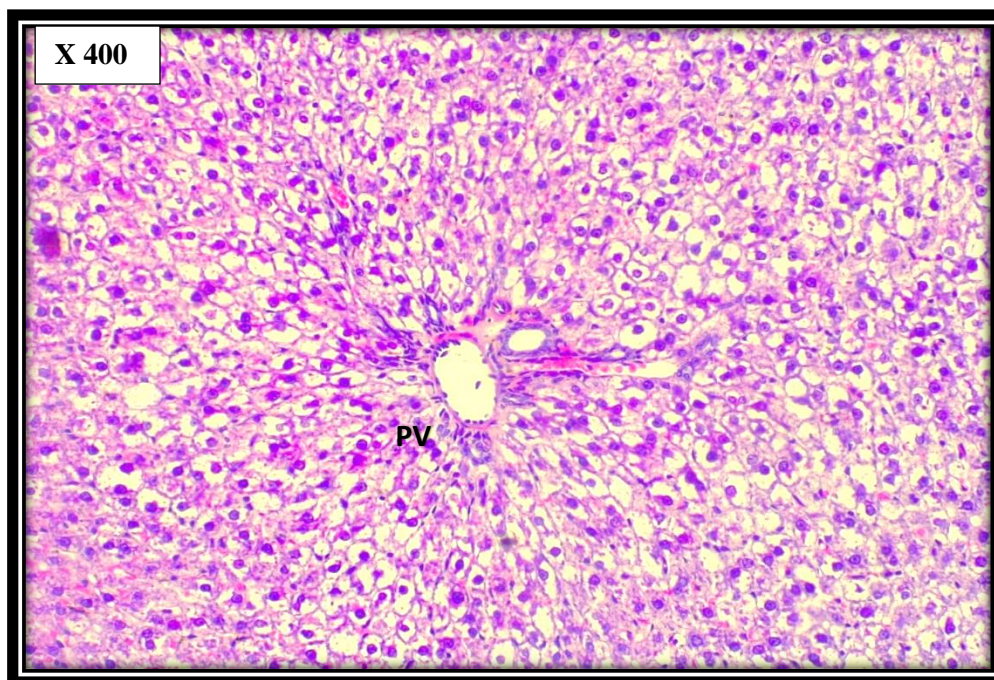


**Figure [12]:** A photomicrograph of a section in dexamethasone-treated rat liver tissue showing degeneration with portal area fibrosis and mild bile duct proliferation (H & E)





**Figure [13]:** A photomicrograph of a section in garlic water-treated rat liver tissue. The figure showed a more or less normal central vein, with the restoration of normal hepatic architecture & radiating regenerated cords of hepatocytes with the reappearance of open-face nuclei and normal blood sinusoids but there is still a presence of infiltration by inflammatory cells around the portal vein and mild steatosis (H&E)



**Figure [14]:** A photomicrograph of a section in garlic water-treated rat liver tissue. The figure showed more or less normal central vein, with the restoration of normal hepatic architecture & radiating regenerated cords of hepatocytes with the reappearance of open face nuclei and normal blood sinusoids but there is still presence of mild fat cells infiltrations and blood inside and around the portal vein and mild parenchymal steatosis (H&E)

## DISCUSSION

Dexamethasone is frequently used as an immunomodulatory and anti-inflammatory drug. Clinical doses of dexamethasone usually do not exceed 8 mg per day. Its dose may reach up to 40mg/day if pulse steroid therapy is needed such as during exacerbation of immune

diseases but this continues for short duration ranging from 3 to 5 days. When steroids are indicated for clinical use, they are usually used for long duration which will precipitate toxic effects in various tissues. The protracted administration and/or overdose of dexamethasone may have negative side effects, such as insulin resistance, development of diabetes

and hypertension, liver and renal affection, osteoporosis, immunosuppression and super-imposed infections [11].

Our study showed that treatment with dexamethasone caused a significant elevation in liver enzymes; ALT and AST also the levels of ALP & bilirubin were elevated whereas the level of albumin was significantly lower. All these changes indicated the liver injury induced by dexamethasone. Similar results were reported by Zhu and coworkers [12] who noted that dexamethasone treatment dramatically elevated ALT, AST, and ALP activities, as well as a significant elevation of blood bilirubin levels indicated the onset of liver impairment.

**Nkono et al.** [13] reported that the administration of dexamethasone induced a significant increase in AST, ALT, ALP, and bilirubin levels. Similarly, **El-Sawy et al.** [14] reported that dexamethasone-treated rats showed a significant elevation in liver enzymes ALT, AST, and ALP and also in serum bilirubin when compared to the control ones.

The results of this study are also concordant with **Soliman et al.** [15] who reported that treatment of rats with dexamethasone was associated with hepatocyte injury leading to an increase in liver enzymes together with elevated bilirubin level. Dexamethasone also induces a decrease in protein synthesis and an increase in protein catabolism causing a decrease in serum albumin levels.

**Yamada et al.** [16] reported that dexamethasone has several effects on the metabolism of liver cells in the culture one of them is depression of albumin synthesis.

The metabolic profile of rats treated with dexamethasone showed an increase in amino acids that are implicated in the suppression of protein synthesis and protein breakdown [9].

Exposure to a high dosage of dexamethasone leads to an increase in reactive oxygen species production that results in mitochondrial dysfunction, elevated cytosolic calcium, and irreversible oxidative modifications of cellular lipids, proteins, and DNA eventually causing cellular injury [12].

Our study showed that the group treated with dexamethasone concomitantly with garlic

extract showed significantly lower levels of ALT, AST, ALP, and bilirubin levels when compared with the group treated with dexamethasone alone indicating a protective effect of garlic extract against dexamethasone-induced hepatocyte injury.

It has been validated in many reports that oxidative stress induced by glucocorticoids played a crucial role in the pathophysiology of cellular dysfunction. According to this concept, assortments of natural remedies and antioxidants have been used to hinder dexamethasone-induced cellular injury. Some antioxidants from natural sources can effectively scavenge free radicals and ROS, thus reducing or eliminating oxidative stress [17].

The antioxidant properties of garlic have been reported in many previous studies [6, 18-21] and many other reports. The advantages of natural antioxidants against drug-induced toxicity have received more attention. To restore the oxidant/antioxidant equilibrium and stop or lessen oxidative assaults, a potential source of natural antioxidants can be used [22].

**Tavares et al.** [23] reported that garlic contains bioactive compounds such as organosulfur, phenols, and saponins with many biological activities, including antioxidant, hepatoprotective, anti-diabetic, anti-obesity, and many other activities.

The current study showed that dexamethasone caused a significant elevation in FBS, insulin level, and HOMA-IR when compared to the control. These findings are consistent with other reports [5, 24, 25].

In line with the hyperglycemic impact of dexamethasone and an increase in insulin levels linked with dexamethasone therapy both in vivo and in vitro, **Shittu et al.** [9] observed a significant rise in blood glucose levels in dexamethasone-treated rats. They stated that an adaptive reaction of the pancreatic islet to hyperglycemia results in elevated insulin levels.

When a larger insulin dose is necessary to have the same effects on glucose storage, this is known as insulin resistance. As a result, the liver, muscles, and adipose tissues absorb and use less glucose, while the liver produces more glucose, which causes hyperglycemia [26].



Numerous researchers have confirmed the reliability of HOMA-IR in predicting insulin resistance in rodents. Since HOMA-IR and insulin resistance are correlated, a rise in HOMA-IR denotes insulin resistance while a reduction in HOMA-IR denotes insulin sensitivity [27]. In all insulin-sensitive organs, glucocorticoids are strong inducers of insulin resistance. They are hormones that promote catabolism and alter the primary anabolic insulin pathway. Multiple molecular pathways, including the insulin receptor and transcription factors, are involved in doing this [26].

The current study showed that FBS, insulin level, and insulin sensitivity improved with garlic extract treatment. The hypoglycemic and insulin-sensitizing effects of garlic extract were reported by **Supakul et al.** [28]. Allicin included in garlic extract may improve insulin sensitivity. This substance's metabolites have been demonstrated to enhance glucose absorption and utilization by turning on multiple insulin signaling cascade stages [28].

Garlic is one of the most widely accepted anti-diabetic plants. The presence of volatile Sulphur compounds such as alliin, allicin, diallyl disulfide, diallyl trisulfide, diallyl sulphide, S-allyl cysteine, ajoene, and allyl mercaptan is primarily responsible for garlic's favorable impact on diabetes mellitus. Due to allicin and its metabolites, garlic extracts have been shown to be useful in lowering insulin resistance and raising insulin sensitivity [29]. Garlic is advantageous for lowering HbA1c, fasting insulin, FBS, and insulin resistance [30].

In a recent clinical trial study, 50 T2DM patients with dyslipidemia were divided into two groups: one group received traditional therapy along with hypolipidemic and hypoglycemic medications as the control, and the other group received traditional therapy along with the herbal compound as the intervention [300 mg garlic]. After 12 weeks of therapy, the intervention group's HbA1c levels considerably dropped, although fasting blood sugar levels remained unaffected [31].

Liver sections from healthy [control] mice stained with HE in microscopic specimens showed the typical and consistent architecture of hepatocytes and portal space. Due to the liver toxicity brought on by dexamethasone, there was severe steatosis, hepatic inflammation,

mononuclear cell infiltration around the hepatic veins, partial destruction of the nearby hepatocytes, and portal fibrosis. On the other hand, using garlic water extracts to treat the condition decreased the inflammatory response, reduced the amount of steatosis and portal fibrosis, and restored normal hepatocyte and portal space architecture.

These findings are concomitant with **Bhat et al.** [32] and **Feng et al.** [33] who reported that in liver tissues of dexamethasone-treated rats, steatosis was the main histological problem so it is considered one of the causes of nonalcoholic fatty liver. **Abou-Seif et al.** [3] stated that administration of dexamethasone for an extended period of time or at a high dose by any method can seriously change the liver's structure and consequently its functioning.

The drug-induced liver injury is a wide title that describes how can drugs affect the liver and induce injury through different mechanisms, which may be dose or duration related or may be idiosyncratic [34].

Corticosteroids at low doses are thought to be safe for hepatic function, but excessive doses and/or prolonged usage of the medication can cause steatohepatitis. The main mechanism of corticosteroid-induced hepatotoxicity is thought to be increased oxidative stress. Additionally, steroid-induced hepatic steatosis may be attributed to metabolic peculiarities brought on by abnormal hepatic metabolism of corticosteroids [35].

Dexamethasone induced hepatocytes injury will subsequently lead to fatty infiltration of hepatocytes [steatosis] and then degeneration and inflammation of liver tissue [steatohepatitis] and this explains other histopathological complications such as inflammatory cells infiltration and fibrosis [35].

Many agents were used as hepatoprotectives, but garlic specially recorded significant success in protecting the liver tissue from many injurious agents including steroids, acetaminophen, phenobarbital, and ethanol [36].

**Conclusion:** Garlic water extract showed a protective effect against dexamethasone-induced liver injury and insulin resistance owing to the antioxidant and insulin-sensitizing properties of its chemical constituents. Garlic

could be used; as a complement to the established method; to relieve the hazards of glucocorticoid therapy and to help control metabolic syndrome taking advantage of traditional pharmacological agents of being natural, has minimal side effects, cheap and available.

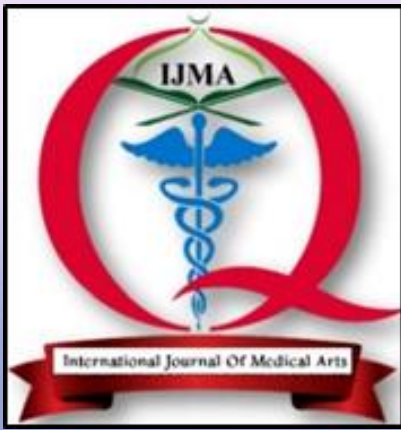
**Conflict of Interest:** None

## REFERENCES

- Hasona N, Morsi A. Grape Seed Extract Alleviates Dexamethasone-Induced Hyperlipidemia, Lipid Peroxidation, and Hematological Alteration in Rats. *Indian J Clin Biochem.* 2019 Apr;34[2]: 213-218. doi: 10.1007/s12291-018-0736-z.
- Fahim NF, Sathi ZS. Assesment of hepatoprotective activity of roots and barks of *Achyranthes aspera* in carbon tetrachloride-induced hepatotoxicity in rats. *Malays J Halal Res.* 2018;1[2]:23-26. doi: 10.26480/mjhr.02.2018.23.26.
- Abou-Seif HS, Hozayen WG, Hashem KS. Thymus vulgaris extract modulates dexamethasone induced liver injury and restores the hepatic antioxidant redox system. *Beni-Suef University J Basic Applied Sci.* 2019 Dec;8[1]:1-9. doi: 10.1186/s43088-019-0021-0.
- Lee SH, Park SY, Choi CS. Insulin Resistance: From Mechanisms to Therapeutic Strategies. *Diabetes Metab J.* 2022 Jan;46[1]:15-37. doi: 10.4093/dmj.2021.0280.
- Savych A, Marchyshyn S, Basaraba R, Lukanyuk M. Antihyperglycemic, hypolipidemic and antioxidant properties of the herbal mixtures in dexamethasone-induced insulin resistant rats. *PharmacologyOnLine.* 2020 Aug 30;2:73-82.
- Shalaby A, El-Feki S, Alkot A, Mahmoud AM. Effect of garlic [*Allium Sativum*] water extract and vitamin E on alloxan-nicotinamide adult male diabetic rats. *Al-Azhar Med J.* 2015;44[4]: 497-510. doi: 10.12816/0023145.
- Abe K, Hori Y, Myoda T. Volatile compounds of fresh and processed garlic. *Exp Ther Med.* 2020 Feb;19[2]:1585-1593. doi: 10.3892/etm.2019.8394.
- Jang HJ, Lee HJ, Yoon DK, Ji DS, Kim JH, Lee CH. Antioxidant and antimicrobial activities of fresh garlic and aged garlic by-products extracted with different solvents. *Food Sci Biotechnol.* 2017 Dec 12;27[1]:219-225. doi: 10.1007/s10068-017-0246-4.
- Shittu ST, Lasisi TJ, Shittu SA, Adeyemi A, Adeoye TJ, Alada AA. *Ocimum gratissimum* enhances insulin sensitivity in male Wistar rats with dexamethasone-induced insulin resistance. *J Diabetes Metab Disord.* 2021 Jul 13;20[2]:1257-1267. doi: 10.1007/s40200-021-00850-y.
- Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia.* 1985 Jul;28[7]:412-9. doi: 10.1007/BF00280883.
- Yi J, Zhu R, Wu J, Wu J, Xia W, Zhu L, et al. In vivo protective effect of betulinic acid on dexamethasone induced thymocyte apoptosis by reducing oxidative stress. *Pharmacol Rep.* 2016 Feb;68[1]:95-100. doi: 10.1016/j.pharep.2015.07.003.
- Zhu L, Yi X, Zhao J, Yuan Z, Wen L, Pozniak B, et al. Betulinic acid attenuates dexamethasone-induced oxidative damage through the JNK-P38 MAPK signaling pathway in mice. *Biomed Pharmacother.* 2018 Jul;103:499-508. doi: 10.1016/j.biopha.2018.04.073.
- Nkono BL, Sokeng SD, Désiré DD, Kamtchouing P. Antihyperglycemic and antioxidant properties of *Alstonia boonei* De wild.[Apocynaceae] stem bark aqueous extract in dexamethasone-induced hyperglycemic rats. *Int. J. Diabetes Res.* 2014;3[3]:27-35.
- El-Sawy AE, El-Maddawy ZK, Ashoura NR. Role of Silymarin in Restoring the Deleterious Effects induced by Dexamethasone in Male Rats. *Alex J Vet Sci.* 2018 Oct 15;59[2]:125-135. doi: 10.5455/ajvs.5950.
- Soliman HA, El-Desouky MA, Hozayen WG, Ahmed RR, Khaliefa AK. Hepatoprotective effects of parsley, basil, and chicory aqueous extracts against dexamethasone-induced in experimental rats. *J Intercult Ethnopharmacol.* 2016 Jan 27;5[1]:65-71. doi: 10.5455/jice.20160124113555.
- Yamada S, Otto PS, Kennedy DL, Wayne TF Jr. The effects of dexamethasone on metabolic activity of hepatocytes in primary monolayer culture. *In Vitro.* 1980 Jul;16[7]:559-70. doi: 10.1007/BF02618379.
- Hasona NA. Grape seed extract attenuates dexamethasone-induced testicular and thyroid dysfunction in male albino rats. *Andrologia.* 2018 Jun;50[5]:e13002. doi: 10.1111/and.13002.
- Kim ID, Park YS, Park JJ, Dhungana SK, Shin DH. Physicochemical and antioxidant properties of garlic [*A. sativum*] prepared by different heat treatment conditions. *Korean J Food Sci Technol.* 2019;51[5]:452-8. doi: 10.9721/KJFST.2019.51.5.452.
- Fitrotin U, Hidayah BN. Investigation of Antioxidant Properties on Some Garlic Varieties

- and Influence of Farming Inputs on the Quality of Garlic. *Int J Biosci Biochem Bioinformatics*. 2019;9[3]:180-7. doi: 10.17706/ijbbb.2019.9.3.180-187.
20. Ruiz-Sánchez E, Pedraza-Chaverri J, Medina-Campos ON, Maldonado PD, Rojas P. S-allyl Cysteine, a Garlic Compound, Produces an Antidepressant-Like Effect and Exhibits Antioxidant Properties in Mice. *Brain Sci*. 2020 Aug;10[9]:592. doi: 10.3390/brainsci10090592.
  21. Marmitt DJ, Bitencourt S, da Silva GR, Rempel C, Goettert MI. Traditional plants with antioxidant properties in clinical trials-A systematic review. *Phytother Res*. 2021 Oct; 35[10]:5647-5667. doi: 10.1002/ptr.7202.
  22. Abd El-Galil MM, Alkot AMF. Impact of Crude Aloe Vera gel on Silver Nanoparticle-Induced Lung Cytotoxicity in Adult Male Albino Rats: Functional, Histological and Immunohistochemical Study. *Al-Azhar Med J*. 2022;51[1]: 563-604. doi: 10.21608/amj.2022.212647.
  23. Tavares L, Santos L, Noreña CP. Bioactive compounds of garlic: A comprehensive review of encapsulation technologies, characterization of the encapsulated garlic compounds and their industrial applicability. *Trend Food Sci Tech*. 2021 Aug 1;114:232-44.
  24. Fofié CK, Nguefack-Mbuyo EP, Tsabang N, Kamanyi A, Nguefack TB. Hypoglycemic Properties of the Aqueous Extract from the Stem Bark of *Ceiba pentandra* in Dexamethasone-Induced Insulin Resistant Rats. *Evid Based Complement Alternat Med*. 2018 Sep 16;2018:4234981. doi: 10.1155/2018/4234981.
  25. Rajasekhar C, Nagendranayak IM. Preventive Effects of *Enicostemma littorale* Blume Extract against Dexamethasone Induced Insulin Resistance in Wistar Rats. *J Krishna Inst Med Sci [JKIMSU]*. 2019 Jul 1;8[3].
  26. Beaupere C, Liboz A, Fève B, Blondeau B, Guillemain G. Molecular Mechanisms of Glucocorticoid-Induced Insulin Resistance. *Int J Mol Sci*. 2021 Jan 9;22[2]:623. doi: 10.3390/ijms22020623.
  27. Antunes LC, Elkfury JL, Jornada MN, Foletto KC, Bertoluci MC. Validation of HOMA-IR in a model of insulin-resistance induced by a high-fat diet in Wistar rats. *Arch Endocrinol Metab*. 2016 Apr;60[2]:138-42. doi: 10.1590/2359-39970000-00169.
  28. Supakul L, Pintana H, Apaijai N, Chattipakorn S, Shinlapawattayatorn K, Chattipakorn N. Protective effects of garlic extract on cardiac function, heart rate variability, and cardiac mitochondria in obese insulin-resistant rats. *Eur J Nutr*. 2014 Apr;53[3]:919-28. doi: 10.1007/s00394-013-0595-6.
  29. Hosseini A, Hosseinzadeh H. A review on the effects of *Allium sativum* [Garlic] in metabolic syndrome. *J Endocrinol Invest*. 2015 Nov;38[11]: 1147-57. doi: 10.1007/s40618-015-0313-8.
  30. Mahdavi A, Bagherniya M, Mirenayat MS, Atkin SL, Sahebkar A. Medicinal Plants and Phytochemicals Regulating Insulin Resistance and Glucose Homeostasis in Type 2 Diabetic Patients: A Clinical Review. *Adv Exp Med Biol*. 2021;1308:161-183. doi: 10.1007/978-3-030-64872-5\_13.
  31. Ghorbani A, Zarvandi M, Rakhshandeh H. A Randomized Controlled Trial of a Herbal Compound for Improving Metabolic Parameters in Diabetic Patients with Uncontrolled Dyslipidemia. *Endocr Metab Immune Disord Drug Targets*. 2019;19[7]:1075-1082. doi: 10.2174/1871530319666190206213420.
  32. Nitasha Bhat GM, Nayak N, Vinodraj K, Chandralekha N, Mathai P, Cherian J. Comparison of the efficacy of cardamom [*Elettaria cardamomum*] with pioglitazone on dexamethasone-induced hepatic steatosis, dyslipidemia, and hyperglycemia in albino rats. *J Adv Pharm Technol Res*. 2015 Jul-Sep;6[3]:136-40. doi: 10.4103/2231-4040.157981.
  33. Feng Z, Pang L, Chen S, Pang X, Huang Y, Qiao Q, et al. Didymin ameliorates dexamethasone-induced non-alcoholic fatty liver disease by inhibiting TLR4/NF- $\kappa$ B and PI3K/Akt pathways in C57BL/6J mice. *Int Immunopharmacol*. 2020 Nov;88:107003. doi: 10.1016/j.intimp.2020.107003.
  34. Andrade RJ, Chalasani N, Björnsson ES, Suzuki A, Kullak-Ublick GA, Watkins PB, et al. Drug-induced liver injury. *Nat Rev Dis Primers*. 2019 Aug;5[1]:58. doi: 10.1038/s41572-019-0105-0.
  35. Lee CC, Peng YJ, Lu CC, Chen HC, Yeh FC. Corticosteroid-Induced Liver Injury in Adult-Onset Still's Disease. *Medicina [Kaunas]*. 2022 Jan;58[2]:191. doi: 10.3390/medicina58020191.
  36. Pathak S, Catanzaro R, Vasan D, Marotta F, Chabria Y, Jothimani G, et al. Benefits of aged garlic extract in modulating toxicity biomarkers against p-dimethylaminoazobenzene and phenobarbital induced liver damage in *Rattus norvegicus*. *Drug Chem Toxicol*. 2020 Sep;43[5]: 454-467. doi: 10.1080/01480545.2018.1499773.





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