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Original Article

Effect of *Zingiber officinale* (Ginger) Extract on Acetaminophen-Induced Hepatotoxicity in Mice

Samia Elzwi*

Department of Phamacology, University of Benghazi, Benghazi, LIBYA.

ABSTRACT

Objective: To evlalate hepatoprotective effects of *Zingiber officinale* extract against acetaminophen- induced hepatotoxicity. **Methods:** *B. preparation* of *Zingiber officinale* extract. **Maceration Method:** In this method fresh ginger rhizome was cut into small peices, dried and then pulverized into coarse powder and weighing about 400 g of powder. It was macerated in 1000 ml hydroalcoholic solution (70%) Ethanol, 30% distilled water) for seventy two hours. The extract was then shaked, filtered by using filter paper and the solution was evaporated in a rotatory evaporator under reduced pressure until dryness. In this experiment mice of either sex weighing 25-30g were divided into three groups, each consisting of seven mice. The animals were fasted for twelve hours prior to the experiment with free access to water. 1. Control group: given normal saline containing 0.5 % Tween-80 (orally) in a dose of 1ml each mice. 2. Extract group: given hydroalcoholic extract of ginger in a dose of (300mg/kg ip) for 14 days followed by acetaminophen (300mg/kg i.p) on the 15th day from starting of the extract. 3. Acetaminophen group: given acetaminophen in single (i.p) injection of 300mg/kg. By the end of 24hr following the injection of acetaminophen, the number of death in each group was calculated, all animals were fasted for 18 hrs. before sacrifice. The collected blood used for measurement of liver transaminases and the livers were isolated, fixed in 10% formalin for histopathological analysis. **Results:** As present in this figure the levels of AST where 142± 8.95, 90.66±16.54, 471±80.84 unit/ml in control, *Zingiber officinale*+ acetaminophen and acetaminophen treated group, whereas the level of ALT were 57.2±4.61, 31.66±9.36, 402±105.19 unit/ml in animal receiving the previously mentioned treatment respectively. By using one way ANOV and Post Hoc analysis, the level of AST and ALT was higher in acetaminophen treated group compared to the other group p≤ 0.001. Histological studies also provided evidence for the biochemical analysis . The control and *Zingiber officinale* treated groups showed the normal hepatocytes, portal tracts and central vein figure (A). Centrizonal necrosis accompanied by fatty changes were observed in the hepatocytes in the livers of mice in acetaminophen treated group figure (B).(C). The cellular necrosis was almost completely disappearing in the group treated with *Zingiber officinale* + acetaminophen groups figure (D).

Key words: Acetaminophen, Hepatotoxicity, Hepatoprotective effect, *Zingiber officinale*, Ginger extract mice.

Correspondence
Dr: Samia Elzwi, (MD)
Lecture Assistance, Department of Pharmacology, University of Benghazi, Public University in Benghazi, LIBYA.
Phone no: +218 0927088053
E-mail: Samia.alzwi@uob.edu.ly
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INTRODUCTION

Ginger (*Zingiber officinale*) is a medicinal plant that has been widely used in Chinese and Tibb Unani herbal medicines all over the world, since antiquity, for a wide array of unrelated ailments that include muscular aches, sore throat, constipation, arthritis, indigestion, vomiting and infectious diseases.

Currently, there is a renewed interest in ginger and several scientific investigations aimed at isolation and identification of active constituents of ginger, scientific verification of its pharmacological actions and of its constituents and verification of the basis of the use of ginger in several diseases and conditions.[1]

- Ginger is a perennial plant that grows in India, China, Mexico and several other countries. The rhizome is used as both spice and in herbal medicine.
- Ginger grows best in tropical and subtropical areas, which have good rainfall with hot and humid conditions during the summer season.
- It is a member of *Zingiberaceae* family originated in Southeast Asia and has been introduced to many parts of the globe where it proliferates in suitable environment. Belief in the medicinal properties of ginger existed in ancient Indian and oriental cultures where ginger has been used alone or as a component in herbal remedies. This practice continues today in many areas of the world including Africa, Brazil, China and Mexico. Ginger has introduced to Europe and other areas by Dutch, Portuguese Arab and Spanish explorers or traders from around the 13th to 16th centuries.

Constituents

1. Carbohydrates: Starch is major constituents up to 50%.

2. Oleo-Resin: Gingerol homologues (Major, about 33%) include derivatives with methyl side chain, shogaol homologues (Dehydration products of gingerols), zingerone (Degradation product of gingeorls), 1- dehydrogingerdione and 6- gingersulfonic acid.[2]

3. Lipids 6-8%: They include free fatty acids e.g palmitic acid,oleic acid, linoleic acid, caprylic acid, capric acid, lauric acid, myristic acid, pentadecanoic acid, heptadecanoic acid, stearic acid, linolenic acid, arachidonic acid, triglycerides, phosphatidic acid, lecithins and gingerglycolipids A, B and C.[3]

4. Volatile Oil: They constitute 1-3% they are complex predominately.

Hydrocarbons, zingiberene (Major components) and B-bisabolene.

Other sesquiterpenes include zingiberol, zingiberenol.

B- sesquiphellandrol arcurcumene, B-sesquiphellandrene, (Cis-trans). Numerous monoterpene hydrocarbons, alcohols and aldehydes.

B-sesquiphellandrol (e.g phellandrene, camphene, geraniol, neral, linalool and d-nerol) are also present.

5. Other Constitutes: Include amino acids as arginine, aspartic acid, cystine, glycine, isoleucine, leucine, serine, threonine and valine.

Proteins consistute about 9%. Diterpenes (Galanolactone), vitamins especially nicotinic acid (Niacin) and vitamin A as well as minerals are also present.[4]

MATERIALS AND METHODS

Experimental Animals

Albino mice of either sex weighing 20-30 g and male Wistar strain rats weighing 200-250 g were maintained in the animal house of Faculty of Medicine – Al Arab Medical University, Benghazi, Libya. The mice andrats were bred in the faculty animal house. All animals were housed in standard polypropylene cages (48×35×22 cm) and kept under controlled room temperature (20±5°C; relative humidity 60-70%) in a 12 h light-dark cycle. The animals were given a standard laboratory diet and free water

Food was withdrawn 12 h before and during the experimental hours.

B. Preparation of Zingiber officinale Extract Maceration Method

In this method fresh ginger rhizome was cut into small peices, dried and then pulverized into coarse powder and weighing about 400 g of powder. It was macerated in 1000 ml hydroalcoholic solution (70% Ethanol, 30% distilled water) for seventy-two hours. The extract was then shaked, filteredby using filter paper and the solution was evaporated in a rotatory evaporator under reduced pressure until dryness. Evaporation and removal of the solvent give hydroalcoholic extract of gingerout of 400 g of crude plant, 8 g of hydroalcoholic extract of ginger were obtained and kept for use in pharmacological experiments Iranian Herbal pharmacopeia.[5]

In this experiment mice of either sex weighing 25-30g were divided into three groups, each consisting of seven mice. The animals were fasted for twelve hours prior to the experiment with free access to water.

1. Control group: Given normal saline containing 0.5 % Tween-80 (orally) in a dose of 1ml each mice.

2. Extract group: Given hydroalcoholic extract of ginger in a dose of (300mg/kg ip) for 14 days followed by acetaminophen (300mg/kg i.p) on the 15th day from starting of the extract.

3. Acetaminophen group: Given acetaminophen in single (i.p) injection of 300mg/kg.

By the end of 24hr following the injection of acetaminophen, the number of death in each group was calculated, all animals were fasted for18 hrs. Before sacrifice. The collected blood used for measurement of liver transaminases and the livers were isolated, fixed in 10% formalin for histopathological analysis.

RESULTS

Compared to the control group that showed no death of animals, the acetaminophen treated group showed 2 deaths out of seven mice. This was reduced to 1 death of seven in the *Zingiber officinal*+ acetaminophen treated group.[6]

As present in this figure the levels of AST where 142± 8.95, 90.66±16.54, 471±80.84 unit/ml in control, *Zingiber officinale*+ acetaminophen and

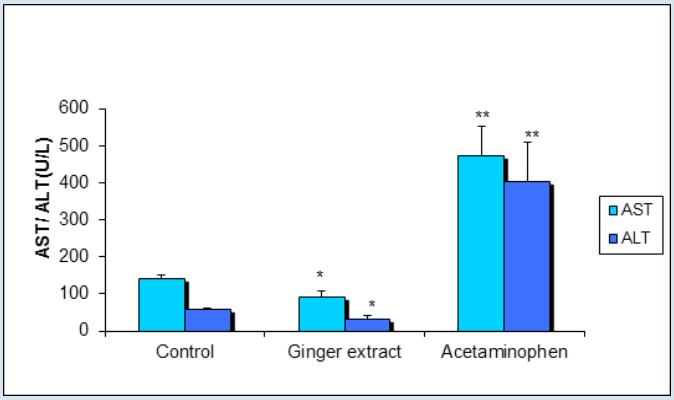

Figure 1: Effect of ginger extract on acetaminophen induced hepatotoxicity in mice

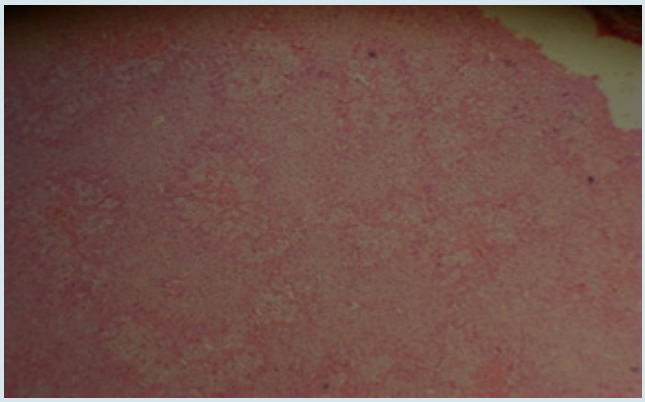

Figure 2: Histological studies of Acetaminophen Treated liver with Centrizonal Necrosis.

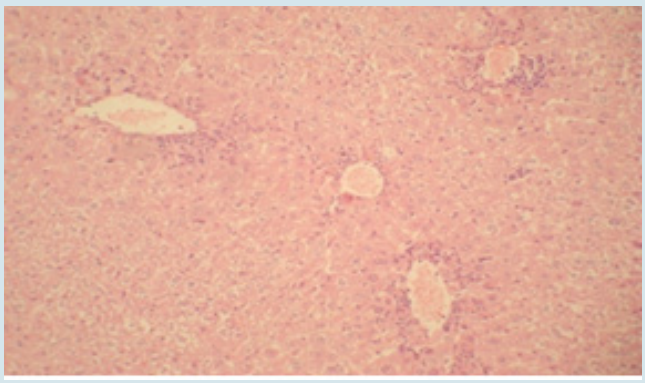

Figure 1a: Histological studies of Normal Liver.

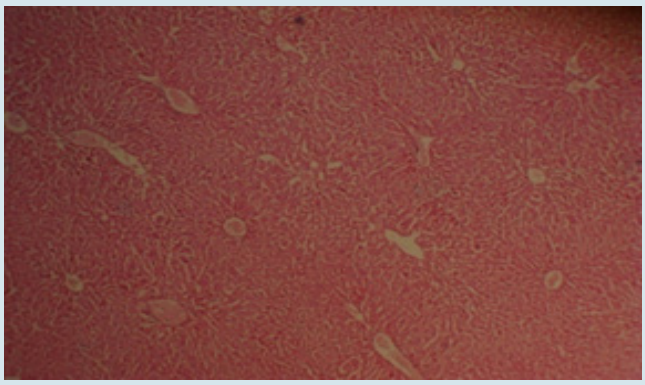

Figure 3: Histological studies of Acetaminophen Treated Liver with Fatty Changes.

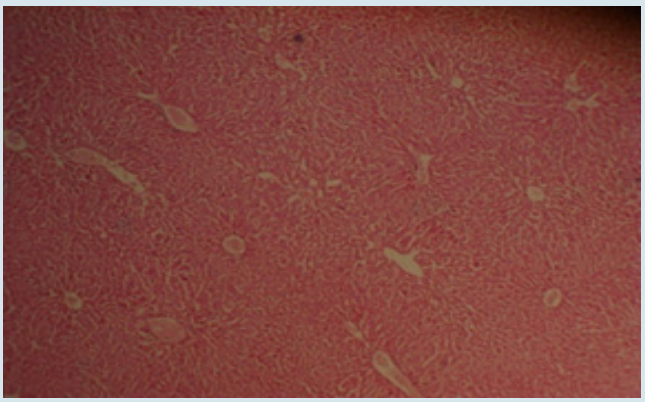

Figure 4: Histological studies of Ginger Treated Liver with no Changes.

acetaminophen treated group, whereas the level of ALT were 57.2±4.61, 31.66±9.36, 402±105.19 unit/ml in animal receiving the previously mentioned treatment respectively.

By using one-way ANOV and Post Hoc analysis, the level of AST and ALT was higher in acetaminophen treated group compared to the other group $p \leq 0.00$.

The statistical analysis showed that the levels of AST and ALT in the *Zingiber officinale* + acetaminophen treated group were not significantly changed compared with control group.[7]

Histological studies also provided evidence for the biochemical analysis. The control and *Zingiber officinale* treated groups showed the normal hepatocytes, portal tracts and central vein (Figure 1).

Centrizonal necrosis accompanied by fatty changes were observed in the hepatocytes in the livers of mice in acetaminophen treated group (Figure 2, 3).

The cellular necrosis was almost completely disappearing in the group treated with *Zingiber officinale* + acetaminophen groups (Figure 4).[8]

Light photomicrographs (10× magnifications) of hematoxylin and eosin –stained sections of liver.

DISCUSSION

In acute parenchymal liver disease there is sudden widespread liver damage in which variable number of hepatocytes undergo necrosis.

These episodes are mainly due to hepatitis virus or drug. Alanine Aminotransferase (ALT). Cytoplasmic enzyme and Aspartate Aminotransferase (AST), present both in cytoplasm and mitochondria, are the two important aminotransferase. Normal plasma contain low activities of both enzymes. ALT occur in much higher concentration in the liver than elsewhere and consequently increased in serum ALT activity reflects hepatic damage more specifically.

ALT and AST are liberated into the blood whenever liver cells are damaged and increased plasma enzyme activity in sensitive index of hepatic damage.

Acetaminophen causes cellular damage through induction of oxidative stress, a consequence of depletion of reduced glutathione (GSH) and significant elevation in the levels of N- acetyl – p- benzoquineimine occur, resulting in oxidative stress, cell damage and death.[9]

Hepatic damage due to acetaminophen produce particularly high activities of ALT and AST 100 to 500 times the normal values.

Several years ago suggested that GST formed part of a general adaptive response against cellular stress.

The result of our paper indicated that (*Zingiber officinale*) ginger has hepatoprotective effect through antioxidant properties.[10]

In support of our paper study by.[11] For effect of ginger on acetaminophen – induced hepatotoxicity. In this study aqueous ethanolic extract of *Zingiber officinale* was evaluated against single dose of acetaminophen-induced (3glkg p.o) acute hepatotoxicity in rat.

Administration of single dose of aqueous extract of *Zingiber officinale* (200 and 400 mglkg p.o) prior to acetaminophen significantly declines the activities of serum transaminase. Further hepatic oxidative status in the liver such as activities of superoxide dismutase, catalase, gluathione peroxidase and gluthione –s- tranferase and levels of reduced gluthione (GSH) was enhanced in the ginger plus acetaminophen treated group than control.[12]

CONCLUSION

In acute parenchymal liver disease there is sudden widespread liver damage in which variable number of hepatocytes undergo necrosis. ALT and AST are liberated into the blood whenever liver cells are damaged and increased plasma enzyme activity in sensitive index of hepatic damage Acetaminophen causes cellular damage through induction of oxidative stress, a consequence of depletion of reduced glutathione (GSH) and significant elevation in the levels of N- acetyl – pbenzoquineimine occur, resulting in oxidative stress, cell damage and death The result of our paper indicated that (*Zingiber officinale*) ginger has hepatoprotective effect through antioxidant properties.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

AST: Aspartate Aminotransferase; **ALT:** Alanine Amniotranferase; **p.o:** Per Oral Route; **GSD:** Reduced Gluthatione; **ANOVA:** Analysis of Variance.

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SUMMARY

- Ginger (*Zingiber officinale*) is a medicinal plant that has been widely used in Chinese and Tibb Unani herbal medicines all over the world, since antiquity, for a wide array of unrelated ailments that include muscular aches, sore throat, constipation, arthritis, indigestion, vomiting and infectious diseases.
- Currently, there is a renewed interest in ginger and several scientific investigations aimed at isolation and identification of active constituents of ginger, scientific verification of its pharmacological actions and of its constituents and verification of the basis of the use of ginger in several diseases and conditions.
- It has many pharmacological effect like anti-inflammatory, analgesic activity and gastropropective. effects in addition to antioxidant and hepatoprotective effects.