Pathological Comparative Studies on Aqueous and Ethanolic Extracts of *Zingiber officinale* on Antioxidants and Hypolipidemic Effects in Rats

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Abstract: Objectives: This study was designed to evaluate the effect of *Zingiber officinale* extract on oxidative stress and plasma lipid profile in rats through antioxidant enzymatic activities, some selective biochemical analysis and histopathological examination on liver, kidney and stomach in rats through pathological investigation by histpathological and ultra structure lesions. **Methods:** Thirty male albino rats of body weight 150-200 gm, were divided randomly into 5 equal groups as follow: **Group I;** normal control, **Groups; II & III;** received aqueous extract of *Zingiber officinale* (200 & 400 mg/kg b wt.) respectively. **Groups; IV & V** received *Zingiber officinale* ethanol extract (200 & 400 mg/kg b wt.) respectively. The extracts were orally administered daily for 30 days. At the end of experiment period, tissues specimens were obtained from all groups and were fixed in 10% neutral buffered formalin for histopathological and ultra structure examination. **Results:** GSH level revealed significant increase in all *Zingiber officinalis* treated groups, compared to the control. SOD showed significant increase and MDA decrease in group **IV** only compared to the control group. Serum Triglycerides level reveled significant decrease in *Zingiber officinalis* treated groups (**II, IV, V**) compared to the control. Serum total cholesterol and cholesterol -LDL levels showed significant decrease in all *Zingiber officinalis* treated groups compared to the control. Liver transaminase activities and urea serum level showed significant increase in higher dose of ethanol extract **(Gp. V)** compared to control group. The pathological lesions were observed only in higher dose of *Zingiber officinale* ethanol extract, mild vacuolar degeneration of hepatocytes. The renal lesions were observed by marked granularity of the cytoplasm renal tubules, also ultra structures approved multiple cytoplasmic vacuoles with heterochromatic nucleus, moreover tunica intima of renal artery fused with tunica media. The gastric examination showing sloughing of gastric mucosa with leukocytes infiltration. **Conclusion:** Although *Zingiber officinale* extracts have been documented an effective in hypolipidemic effects and exerting antioxidant effect by enhance antioxidant activities and reduce oxidative stress. The present results conclude that, the *Zingiber officinale* aqueous extract more safe in compare with ethanol extract and more further studies are recommended to evaluate *Zingiber officinale* side effect regarding to the type of extracts, doses and duration administration.

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1. Introduction

Natural products and their active principles as sources for new drugs and treatment of diseases have attracted attention in recent years. Ginger, the rhizome of *Zingiber officinale*, is one of the most widely used food species of the ginger family. Ginger is primarily used to treat nausea, but it is also used as an anti-inflammatory, antioxidant and a cholesterol-lowering herb (Grant and Lutz, 2000).

Ginger contains a number of pungent constituents and active ingredients. Steam distillation of powdered ginger produces ginger oil, which contains a high proportion of sesquiterpene hydrocarbons, predominantly zingiberene (Govindarajan, 1982[a]). The major strong compounds in ginger, from studies of the lipophilic rhizome extracts, have yielded potentially active gingerols, which can be converted to shogaols, zingerone and paradol. The compound 6-gingerol appears to be responsible for its characteristic taste. Zingerone and shogaols are found in small amounts in fresh ginger and in larger amounts in dried or extracted

products.(Govindarajan, 1982[b]). The analyzed chemical composition of aqueous extracts of Ginger root *(Zingiber officina)* were polyphenols, vitamin C, B, C, β carotene, flavonoids and tannins (Shirin and Jammuna, 2010). While the HPLC analysis of *Zingiber officinale* ethanolic extracts were shogaol and gingrol, moreover, based on recent observations that 6-shogaol may have more potent bioactivity than 6-gingerol (Bak *et al*., 2012).

Several studies documented antioxidant effect of *Zingiber officinale extracts* , in rats fed a high fat diet, intoxicated rats by paracetamole, radiation and arsinic, where ginger supplementation provide significant, raising tissue concentrations of superoxide dismutase, catalase, and GPX as well as reducing gluatathione (Jeyakumar *et al.,* 1999, Ghada *et al.,* 2009, Asmah *et al.*, 2010, Debrup *et al.,* 2012) respectively.

Moreover, the hypolipdemic effect of *Zingiber officinale* extracts have been investigated in high fat feed diet rats by Atta *et al.* (2010) and Srinivas *et al.* (2009) and documented by lowering blood level of cholesterol, triglycerides, while HDL was not significantly change when compared with high-fat diet-fed.

Regarding to side effect of ginger, the acute LD_{50} of ginger in rats is greater than 5 grams of ginger oil per kilogram of body weight (Mascolo *et al.,* 1989). At normal doses, in human (up to 2 grams daily), ginger does not interfere with blood clotting or any individual coagulation parameter (Janssen *et al.,* 1996). In the lymphocyte proliferation assays and mixed lymphocyte culture dried homogenized ginger was consistently immunosuppressive (Wilasrusmee *et al.*, 2002). On the other hand, very large doses of 6 grams (intra-gastric infusion) may lead to gastric irritation and loss of protective gastric mucosa in volunteers (Desai *et al.,* 1990). It was concluded that; single dose of ginger powder 2500 mg/kg b wt can be toxic to a cardio vascular by causing severe hypotension and bradycardia with induction of prenecrotic changes in cardiac tissue (*Elkhishin and Awwad, 2009).*

This study was designed to compare the antioxidant and hypolipidemic effect of ethanol and aqueous extracts of *Zingiber officinale* in rats. As well as to compare the side effects of ethanolic and aqueous extracts of *Zingiber officinale* regarding to liver, kidney and stomach lesions.

2.Materials and Methods

Experimental Animals:

Thirty male albino rats of range body weight 150-200 gm were used in this study. Rats were obtained from Department of Biochemistry and Anatomy, Faculty of Medicine, UAQ, KSA. The animals were kept in metal cages under strict hygienic conditions. The animals were ensured free from any infection. The rats were maintained on standard laboratory diet and fresh water *ad libitum.*

Zingiber officinalis

The root of *Zingiber officinalis* were purchased from local market. They were identified by morphologic and microscopic comparison according to different standard texts by Botany Department, Mansoura University, Egypt.

2.Methods:

Zingiber officinalis extraction:

Aqueous extract:

The roots of *Zingiber officinale* was washed, peeled, cut into small pieces, dried at room temperature and crushed in electrical grinder and powdered. The aqueous extract powder (500 g) was soaked in 2 liters of distilled water for two days. The mixture was filtered, frozen and dried by using lyophilizer for 72 hours, then froze at -30 ^{o}C. The powder was taken and weighted for26 g which dissolved in 520 ml distilled water (Lemhadri *et al.,* 2004).

Ethanol extract:

The ethanol extract powder (200 g) was mixed with one liter of 99.9 % ethanol. The mixture was kept on water bath at 37 ^{o}C for two days with intermittent shaking. The mixture was centrifuged at 2000 rpm for 10 min and the supernatant was collected. Solvent in the pooled supernatant was evaporated at room temperature, then frozen. The residue obtained (8.75 g) was dissolved in 175 ml of distilled water (Mirsa *et al.,* 2009).

Experimental Design:

Treatment regimen was as follow:

Thirty rats were divided randomly into five equal groups.

Group I: Negative control.

Group II: *Zingiber officinalis* aqueous extract was orally given at a dose of 200 mg/kg *B wt***,** daily for 30 days.

Group III: *Zingiber officinalis* aqueous extract was orally given at a dose of 400 mg/kg *B wt***,** daily for 30 days.

Group IV: *Zingiber officinalis* ethanol extract was orally given at a dose of 200 mg/kg *B wt***,** daily for 30 days.

Group V: *Zingiber officinalis* ethanol extract was orally given at a dose of 400 mg/kg *B wt***,** daily for 30 days.

2.2.3. Sampling:

Blood samples:

At the end of the experiment, six rats were picked up randomly from each group and blood was collected from retro-orbital venous plexus for serum

chemistry. All the samples were analyzed in duplicated.

Serum biochemical analysis:

Antioxidant markers, malondialdehyde (MDA), reduced glutathione (GSH), and superoxide dismutase (SOD) were determined from undiluted serum samples using commercially available ELISA Kits (Cayman Chemical Co.). The plates were read at 450 nm and a correction wavelength of 550 nm was measured on a computerized automated microplate ELISA reader**.** Total triglycerides, total cholesterol, cholesterol- HDL, cholestrol- LDL, AST (Human, Diagnostic Co. Germany), and ALT, ALP, total protein, albumin, glucose, uric acid, urea and creatinine (Cresent Diagnostic Co. KSA) were estimated spectrophotometeic according to enclosed pamphlet.

Tissue specimens:

Specimens from stomachs, liver and kidney were collected from rats of all experimental groups at the end of the experimental period.

Histopathological Examination:

Small tissue specimens from stomach and kidney of rats in different groups were collected and immediately fixed in 10% formalin. After proper fixation, the specimens were dehydrated in ethyl alcohol, cleared in xylol, embedded and casted in paraffin. Thin paraffin sections were prepared and stained with hematoxylin and eosin stain according to Bancroft *et al.,* (1990). The histological examination was done in pathology lab faculty of medicine Umm Alqura university, Saudi Arabia.

Ultra Structure

Transmission Electron Microscopy examination was done in histology lab faculty of medicine Zagazig University, Egypt. From the remaining part of the strip, the tissue samples that were free of grossly visible lesions were removed. Small specimens were fixed in Karnovsky's liquid for 3 hr at room temperature and postfixed in 1% OsO4 in 0.1 M phosphate buffer (pH 7.2) for 90 min at room temperature. After dehydration in a graded series of acetone and embedding in Araldite resin, semithin sections were cut parallel to the plane of the section. Semithin sections were examined with the aim of selecting sections in which the surface epithelium was not disrupted and the thickness of the mucosa was preserved. Thin sections, approximately 80 nm thick and examined with a Zeiss 109 electron microscope (kriz *et al.,* 2005).

Statistical Analysis:

Serum biochemical parameters were analyzed by analysis of variance, one way (ANOVA) using SPSS. 20 for window. The mean and standard error were calculated for each variable. Pearson omnibus normality test was used to assess the normality of data distribution. Data were normally distributed; therefore, post hoc LSD multiple comparison was used to assess statistical differences among different groups. For all statistical examinations, results were considered significant at $p < 0.05$.

3.Results

Oxidative Stress Parameters

The obtained results regarding some selective oxidative stress parameters 30 days post treatment with *Zingiber officinalis* extracts are presented in table (1). SOD activity revealed highly significant increase in ZO treated group (IV, aqueous, 400 mg) compared to the control.

Table 1. Some selective oxidative stress markers (Mean ± SE) four weeks post treatment with *Zingiber officinalis* extracts.

Groups	SOD U/ml	GSH U/ml	MDA mmol/dl
Control	65.72^{b} ±2.16	54.98^{c} ±2.19	17.85^{a} ±0.92
ZO aqueous (200 mg/K.b wt)	68.10^{b} ±3.22	59.50^{b} ±1.26	16.82^{a} ±1.52
ZO ethanol (200 mg/K.b wt)	67.38^{b} ±3.45	60.17^{b} ±2.54	16.99^{a} ±1.43
ZO aqueous (400 mg/K.b wt)	72.32^{a} ±2.14	68.42^{a} ±1.31	14.10^{b} ±0.86
ZO ethanol (400 mg/K.b wt)	68.26^{b} ±3.34	$56.86^{c,b}$ ±2.75	17.16^{a} ±1.12

ZO(*Zingiber officinalis*), **MDA** (Malnoaldhyde), **SOD** (Superoxide dismutase), **GSH** (Reduced Glutathione). The same column is not followed by the same letter differ significantly ($p<0.05$).

Table 2. Lipid profile (Mean ± SE) four weeks post treatment with *Zingiber officinalis* extract.

Groups	TG mg/dl	TC mg/dl	HDL-C mg/dl	LDL-C mg/dl
Control	32.35 [a] ±1.82	71.56 [a] ±3.42	52.12[a] ±1.72	13.10 [a] ±1.84
ZO aqueous (200 mg/K.b wt)	26.82[b] ±1.92	61.18[b] ±2.28	53.01[a] ±1.68	3.98 [b] ±0.42
ZO ethanol (200 mg/K.b wt)	31.78[a] ±2.15	60.91[b] ±3.05	50.17[a] ±2.11	4.52 [b] ±0.74
ZO aqueous (400 mg/K.b wt)	24.84[b] ±2.88	63.32[b] ±2.54	54.10[a] ±1.92	4.92 [b] ±0.61
ZO ethanol (400 mg/K.b wt)	26.94[b] ±1.94	59.91[b] ±3.29	51.95[a] ±1.82	3.51 [b] ±0.82

ZO (*Zingiber officinalis*), TG (Triglycrides), TC(Total Cholesterol), HDL-C (High Density Lipoprotein-Cholesterol), LDL-C (Low Density Lipoprotein- Cholesterol). The same column is not followed by the same letter differ significantly ($p< 0.05$).

Table 3. Some selective biochemical parameters (Mean ± SE) four weeks post treatment with *Zingiber officinalis* extract.

Groups	ALT IU/L	AST IU/L	ALP IU/L	T. Protein g/dl	Albumin g/dl	Glucose mg/dl
Control	41.2[b] ±2.95	52.80[b] ±1.46	118.20[a] ±5.11	7.56[a] ±0.72	3.72[a] ±0.15	82.54[a] ±4.78
ZO aqueous (200 mg/K.b wt)	40.51[b] ±2.42	51.40[b] ±1.74	116.00[a] ±4.94	7.84[a] ±0.98	3.68[a] ±0.19	81.42 [a] ±3.72
ZO ethanol (200 mg/K.b wt)	42.24[b] ±2.12	53.20[b] ±1.58	121.82[a] ±5.19	7.84[a] ±0.83	3.78[a] ±0.20	83.12[a] ±2.32
ZO aqueous (400 mg/K.b wt)	42.01[b] ±2.83	50.48[b] ±1.92	122.60[a] ± 5.32	7.62[a] ±0.68	3.84[a] ±0.18	79.92[a] ±4.15
ZO ethanol (400 mg/K.b wt)	48.92[a] ±1.84	59.94[a] ±1.56	125.92[a] ±5.14	7.41[a] ±0.79	3.55[a] ±0.23	86.13[a] ±4.52

ZO (*Zingiber officinalis*), The same column is not followed by the same letter differ significantly ($p< 0.05$).

Table 4. Some selective serum biochemical parameters (Mean ± SE) four weeks post treatment with *Zingiber officinalis* extract

Groups	Urea mg/dl	Creatinine mg/dl	Uric Acid mg/dl
Cont.	46.52[b] ±1.01	0.48[a] ±0.01	0.92[a] ±0.06
ZO aqueous (200 mg/K.b wt)	45.82[b] ±1.18	0.49[a] ±0.01	0.90[a] ±0.04
ZO ethanol (200 mg/K.b wt)	47.12[b] ±1.46	0.50[a] ±0.01	0.94[a] ±0.06
ZO aqueous (400 mg/K.b wt)	44.96[b] ±1.92	0.47[a] ±0.02	0.95[a] ±0.05
ZO ethanol (400 mg/K.b wt)	54.81[a] ±1.62	0.54[a] ±0.02	0.99[a] ±0.08

ZO (*Zingiber officinalis*), The same column is not followed by the same letter differ significantly ($p< 0.05$).

On the other hand, no significant change was noticed in ZO treated groups (II, III, V) compared to the control. GSH level revealed highly significant increase in all ZO treated groups (GP. II, III, IV, V) compared to the control. In ZO treated group (IV, aqueous, 400 mg), GSH level showed significant increase compared to the other ZO treated groups (I, II, IV). Serum MDA level reveled significant decrease in ZO treated group (IV, aqueous, 400 mg) compared to the control. No significant change was observed in ZO treated groups (II, III, V) compared to the control.

Lipid Profiles Results

Lipid profile parameters 30 day post treatment with *Zingiber officinalis extracts* and their controls are presented in table (2).Serum Triglycerides level reveled significant decrease in *Zingiber*

officinalis treated groups (II, IV, V) compared to the control. No significant change was observed in *Zingiber officinalis* treated group (III) compared to the control. Serum total cholesterol and LDL -cholesterol levels showed significant decrease in all *Zingiber officinalis* treated groups compared to the control. No significant changes was recorded in HDL-Cholesterol level between all experimental group.

Biochemical Results

The obtained results regarding some serum biochemical parameters 30 days post treatment with *Zingiber officinalis* extracts and their controls are presented in tables (3& 4). Regarding to the liver function test, the activities of liver enzymes, ALT& AST showed significant increase in ZO treated group (V, ethanol, 400 mg) compared to control one.

Regarding to kidney function test, a significant increase in serum urea level was seen in ZO treated group (V, ethanol, 400 mg) compared to the control one.

Alkaline phosphatase activity, total protein, albumin, glucose, uric acid and creatinine serum levels, showed no significant changes between all experimental groups.

Gross examination

No gross pathological lesions were observed between all investigated groups compared with control groups.

Histopathological Examination:

Liver : Microscopically, liver of rat from group 1 (control) showed the normal histology of hepatic lobule which consists of central vein and around it concentrically hepatocytes (Figure.1). Conversely, liver of rat from group (V) revealed vacuolar degeneration of hepatocytes (Figures.2&3). Meanwhile, liver of rat from groups (II, III&IV) showed no histopathological changes (Figure. 4).

Stomach*:* Microscopically, Stomach of control rats and rats treated with ethanolic extract of ginger at 200 mg\ Kg BW, as well as aqueous extract 200 & 400 200 mg\ Kg BW, showing normal histological structure in gastric glands lamina propria (Figure 5) compared to stomach of rats treated with 400 mg of ethanolic extract of ginger showing slightly decreased the cell reaction (edema) in lamina propria glandular stomachs and mononuclear cells infiltration. (Figure 6).

Kidneys: Microscopically, kidneys of rat from group I (control) showed the normal histology of renal parenchyma (Figure. 7). However kidneys sections from rats in groups (II, III&IV) revealed apparent normal renal parenchyma with no histopathological changes (Figure.8) Conversely proteinaceous cast in the lumen and granularity of the cytoplasm of some renal tubules was noticed in kidneys of rat from group V (Figures. 9&10).

Kidney Ultra Structure

An electron micrograph of right kidney in control rats (Figure 11) showing normal basal infoldings and few lysosomes with euchromatic nucleus and mesangial matrix X 10000. Also, An electron micrograph of renal artery in control rats showing tunica intima, thick tunica media, internal elastic lamina X7000 (Figure 13). Meanwhile the higher doses treated rat with ethanolic extracts 400 mg/ Kg BW, the right kidney showing multiple lysosomes and multiple cytoplasmic vacuoles with heterochromatic nucleus. X 10000 (Figure 12). Also, an electron micrograph of renal artery in rats treated with high dose of ginger ethanolic extract showing tunica intima of renal artery limited externally and fused with tunica media X6000 (Figure 14).

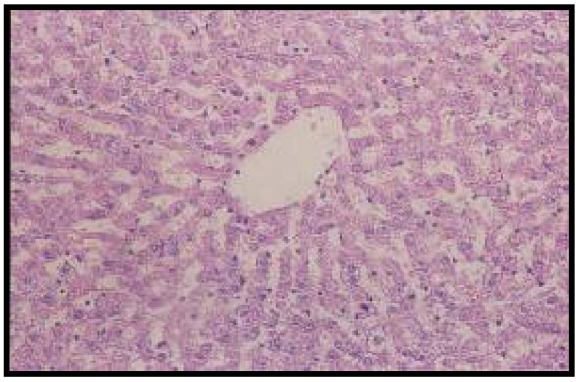

Fig. 1 Liver of rat from group I(control) showing normal histology of hepatic lobule. (H & E X 200).

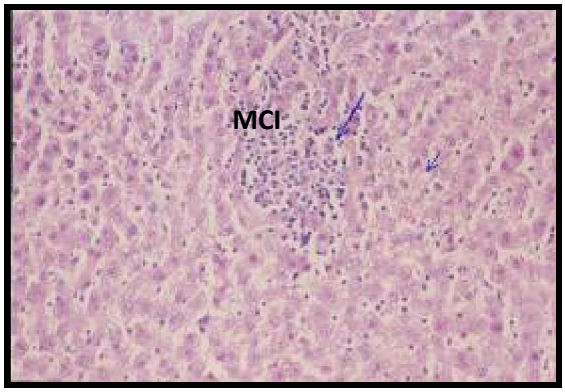

Fig. 2 Liver of rat from group (V) showing vacuolar degeneration of hepatocytes with mononuclear cells infiltration (MCI). (H& E X 200)

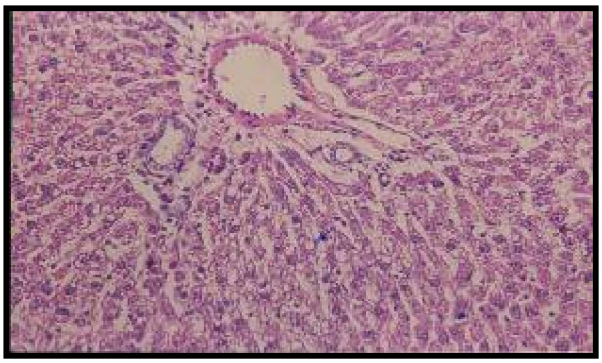

Fig. 3 Liver of rat from group (V) showing vacuolar degeneration of hepatocytes. (H and E X 200).

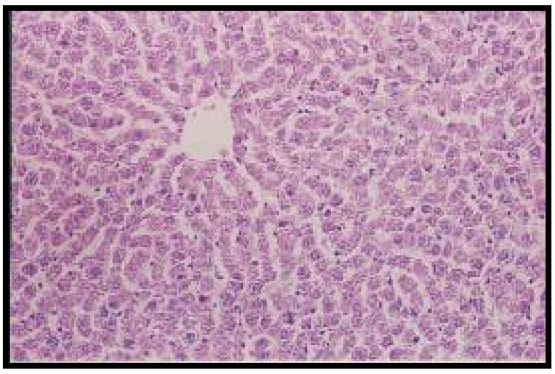

Fig. 4 Liver of rat from group(IV) showing no histopathological changes (H and E X 200)

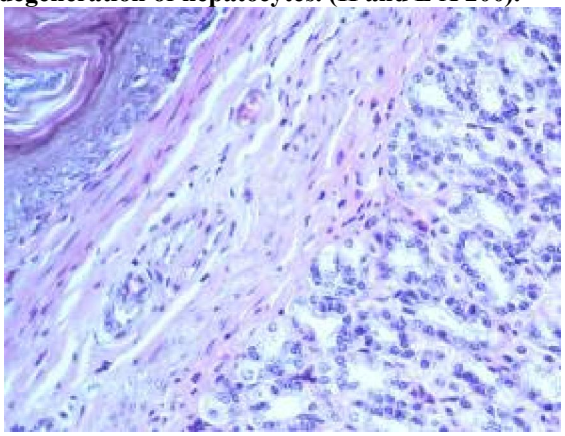

Fig. 5 Stomach of rat from group (I) showing the normal histological structure in gastric glands and normal arrangement of gastric layers. (H & E x200)

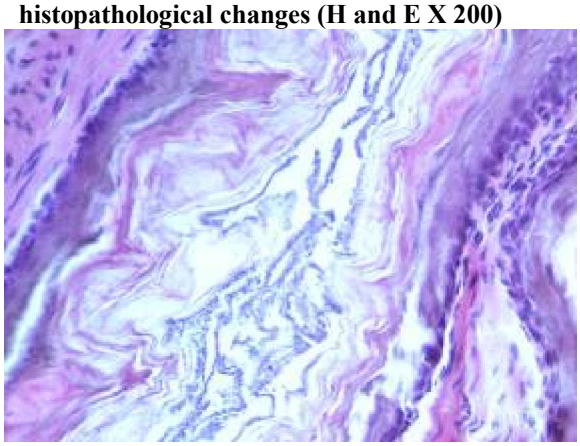

Fig. 6 Stomach of rat from group (V) showing disarrangement of gastric layers, edema in lamina propria and mononuclear cells infiltration. (H &E x200)

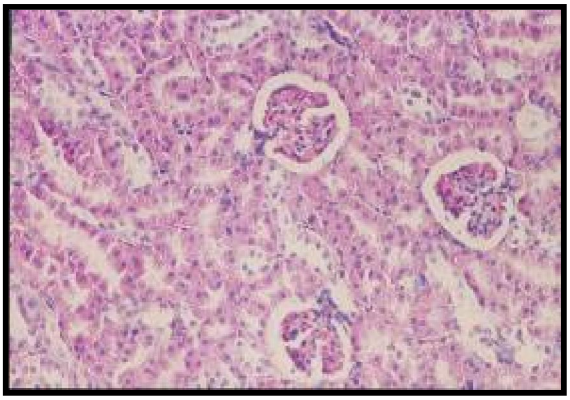

Fig. 7 Kidney of rat from group (I) (control) showing the normal histology of renal parenchyma (H and e x 200)

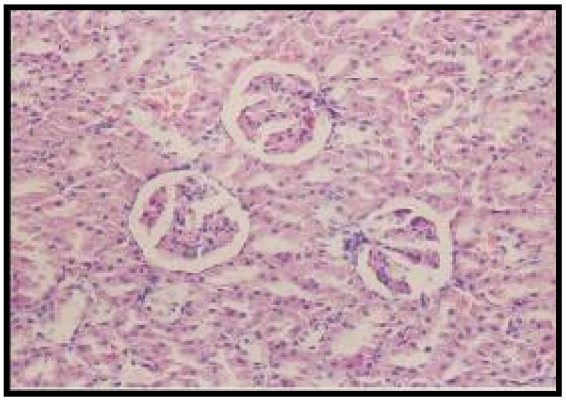

Fig. 8 Kidney of rat from group (III) showing no histopathological abnormalities (H and E X 200)

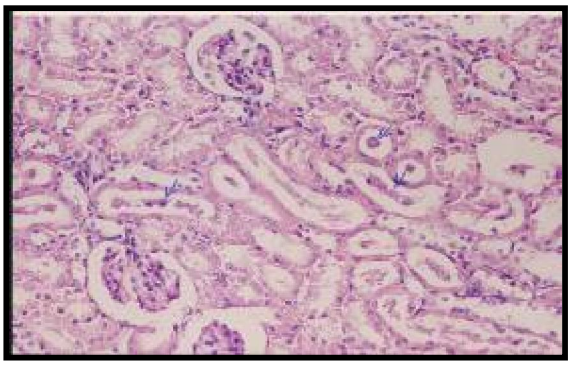

Fig. 9 Kidney of rat from group (V) showing proteinaceous cast in the lumen of some renal tubules (H and E X 200)

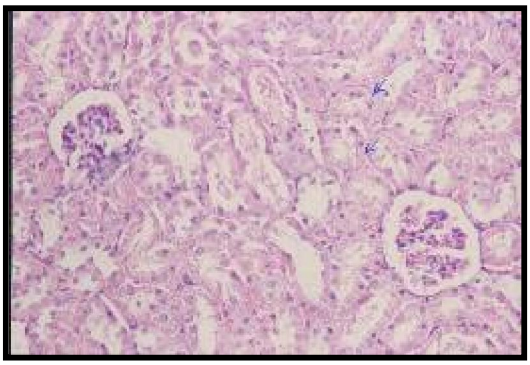

Fig. 10 Kidney of rat from group (V) showing granularity of the cytoplasm of epithelial lining renal tubules (H&E X200)

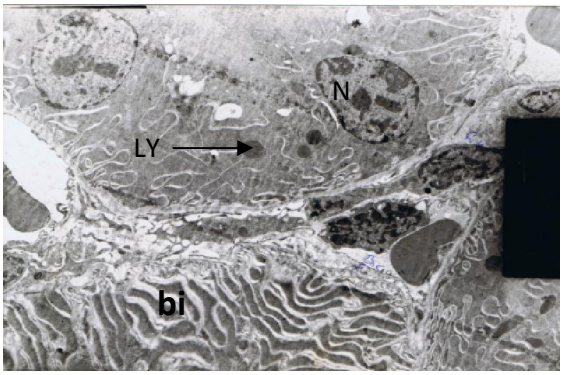

Fig. 11 An electron micrograph of right kidney in control rats showing normal basal enfolding (bi) and few lysosomes (ly arrow) with euchromatic nucleus (N) and mesangial matrix (mm). X 10000

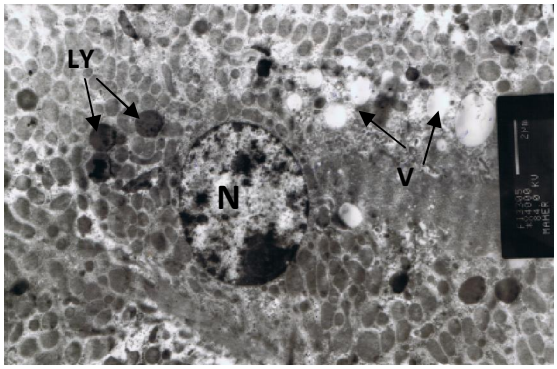

Fig. 12 An electron micrograph of right kidney in rats treated with high dose of *Zingiber officinale* ethanolic extract showing multiple lysosomes (ly arrows) and multiple cytoplasmic vacuoles (v) with heterochromatic nucleus (N). X 10000

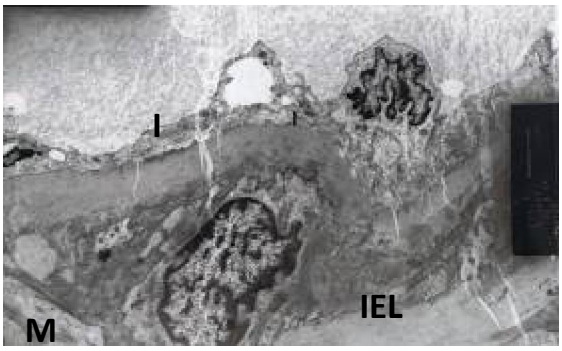

Fig 13. An electron micrograph of renal artery in control rats showing tunica intima (I), thick tunica media (M), internal elastic lamina (IEL), ×7000.

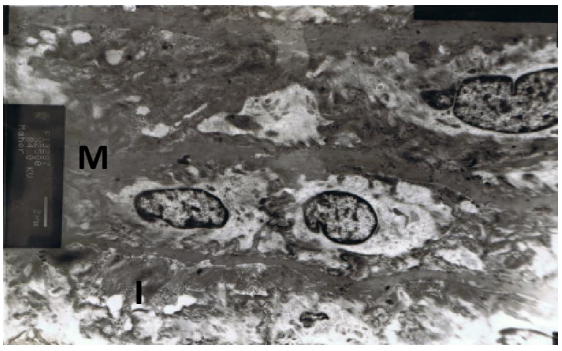

Fig. 14 An electron micrograph of renal artery in rats treated with high dose of *Zingiber officinale* ethanolic extract showing tunica intima (I), of renal artery limited externally and fused with tunica media (M), ×6000.

4. Discussion

Zingiber officinale Roscoe, commonly known as ginger, is one of the commonly used spices around the world. *Zingiber officinale* roots and the obtained extracts contain polyphenol compounds, which have a high antioxidant activity (Ghada *et al.,* 2009; Asmah *et al.,* 2010, Debrup *et al.,* 2012).

In our experiment the activities of GSH level show marked elevation at the end of the experiment in all *Zingiber officinale* treated groups compared to the control. This result agree with Ajith *et al.* (2007)and Chakraborty *et al.* (2012) who reported that a significant increase in hepatic GSH level in rats treated with *Zingiber officinale* extract after intoxicated with acetaminophen and arsenic respectively.

In the present study. SOD activity show significant elevation only *Zingiber officinale* treated group (aqueous, 400 mg/ Kg. b wt) compared to the control. In the same manner, Ajith *et al.* (2007), concluded that the hepatoprotective effect of aqueous ethanol extract of *Zingiber officinale* against acetaminophen-induced acute toxicity is mediated either by enhancing hepatic antioxidant (GSH and SOD) or due to its direct radical scavenging capacity. Treatment with gingerol along with arsenic intoxication rat showed lesser amount of ROS accumulation and significantly increased cell viability of hepatocyteets (Chakraborty *et al.*,2012). They concluded gingerol reduced the oxidative stress as revealed from the increased activity of antioxidant biomarkers like CAT, SOD, GPx and GSH.

Lipid peroxidation plays an important role in carcinogenesis Banakar *et al.* (2004) and may lead to the formation of several toxic products, such as malondialdehyde (MDA). Malondialdehyde level showed significant decrease in *Zingiber officinale* treated group (aqueous, 400 mg/ Kg. b wt) compared to the control. This result agrees with Blessy *et al.* (2009), who found that there was significant decrease in lipid peroxidation groups treated with *Zingiber officinale* when compared to animals treated with DMBA alone. The observed reduction in the level of lipid perioxidation in *Zingiber officinale* treated animals was presumably due to its ability to scavenge the hydroxyl and peroxyl radicals. Moreover, Stoilova *et al.* (2007) confirmed that, the ginger extract is a powerful free hydroxyl (OH^-) scavenger, resulting in inhibiting lipid peroxidation in linoleic acid model system.

Several studies defined the antioxidative and free radical scavenging potential of *Zingiber officinale* extracts as well as their particular components, i.e., gingerol, acid resins, vitamin C compounds, folic acid, inositol, chlorine, pathothenic acid, sesquiterpene, vitamin B3 & B6, volatile oils and bio trace elements. These bioactive components with antioxidative and antiproliferative activities are also constituents of the *Zingiber officinale* extract used in the present study. The antioxidant barriers of the *Zingiber officinale* extract's constituents plays a role on the inhibition of ROS generation, ROS neutralization, or the induction of endogenous antioxidants as obtained by **(**Ghada *et al.*,2009Asmah *et al.,* 2010, Debrup *et al.,* 2012).

Dyslipidaemia is the most important modifiable risk factor contributing to the development of metabolic diseases. Thus the importance of blood levels of triglycerides, cholesterol, LDL- cholesterol and phospholipids in the pathogenesis of lipid disorders have been extensively reviewed (Tan, 2007)

Triglycerides serum level showed significant decrease in *Zingiber officinale* treated group compared to the control. This result agrees with Akiko *et al.* (2009) & Atta *et al.* (2010) who found that there was significant decrease in triglycerides in high fat diets treated rats with *Zingiber officinale* when compared to controls group. It was also reported that consumption of 250 mg/day of ginger extract for 10 weeks resulted in the reduction of triglyceride level in mice (Fuhrman *et al.,* 2000). On the other hand, no significant difference was observed in the triglyceride serum level in hypecrholesterolmic rate treated with *Zingiber officinale* powder extract at a dose 5% and 10% for 6 weeks (Ajayi, 2011).

In our study the total cholesterol and LDL-cholesterol serum level show marked decrease at the end of the experiment in all *Zingiber officinale* treated groups compared to the control. This result agree with Akiko *et al.* (2009) and Srinivas *et al.* (2009) and Ajayi (2011), who reported that a significant decrease in total cholesterol level in high fat diet treated rats *Zingiber officinale*. Also decrease serum cholesterol level in hypercholesterlomic rats treated with *Zingiber officinale* extract recorded by Ajayi (2011). Srinivas *et al.* (2010) concluded the hypocholesterolmic effect of *Zingiber officinale* could be attributed to down-regulated of HMG-CoA reductase activity. Reduced cellular cholesterol biosynthesis is often associated with increased activity of LDL receptor, which in turn leads to the removal of cholesterol -LDL from plasma resulting in reduced plasma cholesterol concentration (Srinivas *et al.,* 2009). Earlier studies have demonstrated that *Zingiber officinale* through its activity on hepatic cholesterol-7α-hydroxylase, stimulates the conversion of hepatic cholesterol to bile acids (Ahmed and Sharma, 1997). More recently, Han *et al.* (2005) found that *Zingiber officinale* increased the fecal excretion of cholesterol, suggesting that ginger may block absorption of cholesterol in the gut. In conclusion, the mechanisms responsible for the observed lipid lowering effects of *Zingiber officinale* could be due a single or multiple effects of its active

components on potential sites of action leading to decreased intestinal fat absorption and/or decreased lipid biosynthesis and/or enhanced cholesterol elimination.

In the present study, the serum cholesterol-HDL none significant change in all *Zingiber officinale* treated groups compared with control. this result agree with Srinivasn and Sambaiah (1991) who reported no significant change in serum HDL cholesterol in high-fat diet rats, treated with *Zingiber officinale* extract at a dose 200&400 mg/ Kg.b wt compared to control group. On the other hand, the plasma HDL-cholesterol significantly increased in hyperchplesterlomic rat treated with *Zingiber officinale* powder 5% and 10% for 6 weeks (Ajayi, 2011).

In our experiment the slight increase serum activities of ALT and AST, were observed at high dose of ethanol extract (400 mg/ Kg. b wt.). Our results approved histopathologically by mild vacoular and hydropic hepatic degeneration. The hepatic damage in higher dose ethanolic extract could be attributed to the different in chemical ingredient of aqueous extract, (polyphenols, vitamin C, B, C, β carotene, flavonoids and tannins) than ethanolic extract, shogaol and gingrol (Shirin and Jammuna, 2010 & Bak *et al.,* 2012). The acute LD_{50} of ginger in rats is greater than 5 grams of ginger oil per kilogram of body weight (Mascolo *et al.,* 1989). The acute LD_{50} of ginger in rats is greater than 5 grams of ginger oil per kilogram of body weight (Mascolo *et al.,* 1989). It was reported that; the ginger powder at a dose 500 mg/kg b wt for 28 days can be toxic and produced degenerative changes in cardiac myocyte tissue in albino rat (Elkhishin and Awwad, 2009).

Regarding to the kidney function test, no significant change in serum creatinine in all groups treated with *Zingiber officinale* extract compared to control group. While mild elevation in serum urea level was recorded in high dose ethanol extract, 400 mg/ kg b wt compared to control. Also Renal histopathological finding in our results reveled, proteinaceous cast in the lumen and granularity of the cytoplasm of some renal tubules was noticed in kidneys of rat treated with high dose ethanol extract (400 mg/ Kg b wt). Also ultra-structure of renal tissues, showed multiple lysosomes and multiple cytoplasmic vacuoles with heterochromatic nucleus. We concluded that the renal damage in our study could be as result of the anti-inflammatory effects of *Zingiber officinale* extract. In our opinion, the renal damage could be attributed to anti-inflammatory effects of *Zingiber officinale* extract, with long administration period, 30 days. Recently, the anti-inflammatory effects of *Zingiber officinale* extract have been demounted by *(*Altman and Marcussen, 2001, Bak *et al.,* 2012*)*. The other two exploratory studies with ginger extracts (Bliddal *et al.,* 2000 & Wigler *et al.,* 2003) show a trend towards pain-relieving effects and are backed by three uncontrolled studies in which up to 50 g ginger/day for musculoskeletal pain were administered (Srivastava and Mustafa, 1989; Mustafa and Srivastava, 1990; Srivastava and Mustafa, 1992). In comparison, Ginger extracts with anti-inflammatory drugs, Ribel-Madsen *et al.* (2012) approved that Ginger extract is effective an anti-inflammatory agent as cortisol therapy (betamethasone) *in vitro* model. Renal damage induced by dexamethasone and hydrocortisone has been documented by Celsi *et al*. (1988).

The only gastric lesions were observed in higher doses of *Zingiber officinale* ethanolic extracts. In human ginger pretreatment (2000 mg) induced nausea and increased bradygastric activity (Lien *et al.,* 2003). Three exploratory clinical studies investigating the effect of ginger on nausea/emesis resulting from other causes could be acetonemia (Careddu, 1986) or cytostatics (Pace, 1987 & Meyer *et al.,* 1995). Moreover, Ginger may cause heartburn (Anonymous, 2003). In quantities higher than 6 g ginger may act as a gastric irritant (Desai *et al.,* 1990). Inhalation of dust from ginger may produce immunoglobulin E-mediated allergy (Van Toorenenbergen and Dieges, 1985).

In Conclusion; In conclusion, the *Zingiber officinale* extract showed remarkable hypolipidemic effects with antioxidant activities and can control the free radicals and the peroxidation of lipids. Basis on our study, the *Zingiber officinale* aqueous extract is more effective and safe compared to the ethanol extract. Further studies are recommended to evaluate side effect of *Zingiber officinale extracts* regarding to the doses and duration administration

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