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Ameliorative effects of *Zingiber officinale* extracts against experimentally-induced hepatotoxicity in rats

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ABSTRACT

The ameliorative effects of Zingiber officinale extracts against paracetamol induced hepatotoxicity in rats was experimentally investigated. Fifty- four (54) adult male albino rats comprising of nine normal and forty-five paracetamol hepatotoxic rats were used. Paracetamol hepatotoxicity was induced by single administration of paracetamol at 750mg/kg ip on the first day of the experiment. The biochemical parameters assessed were determined before the start of the study and subsequently monthly for the duration of the study. Blood samples were collected from the rat through the retro orbital plexus for analysis and serum was obtained by centrifugation (5000rpm for 10mins) and stored at -20^{o}C prior to analysis. The ameliorative effects of duration and increasing dosages (200, 300 and 450mg/kg) of Z. officinale extracts produced a duration dependent significant ($p < 0.05$) reductions in the alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH) and total serum bilirubin (TSB) of paracetamol hepatotoxic rats after the duration of study when compared with those of the paracetamol, normal and silymarin control rats. Z. officinale reduced alanine aminotransferase, total serum bilirubin and lactate dehydrogenase levels in a dose dependent fashion whereas it reduced aspartate aminotransferase and alkaline phosphatase levels in a dose independent manner. It was evident that Z. officinale showed potent hepatoprotective properties as it ameliorated significantly all the elevated biochemical parameters due to paracetamol hepatotoxicity. Given the findings of this study, the clinical relevance of Z. officinale in hepatoprotection and its nutraceutical role in human nutrition could be pursued in future studies.

Key words: *Zingiber officinale*, paracetamol, ameliorative effects, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total serum bilirubin.

INTRODUCTION

In spite of tremendous strides in modern medicine, there are few drugs that stimulate liver function, offer protection to hepatotoxicity or help regeneration of hepatic cells [1]. Natural resources such as plants are always considered and used in the search for new molecules to be used as hepatoprotective agents. Numerous medicinal plants and their formulations are used for hepatotoxicity in ethnomedical practice as well as traditional system of medicine [2]. Plant-based therapeutic agent like silymarin from *Silybum marianum* (milk thistle) is accepted and used worldwide as hepatoprotective agents [3, 4, 5]. *Z. officinale* is one of the most widely used members of the family

Zingiberaceare and is a common condiment for various foods and beverages. *Z. officinale* has a long history of medicinal use for conditions such as headaches, nausea, rheumatism and cold [6]. It has been reported to warm the body and treat cold extremities, improve a weak and tarchy pulse, address a pale complexion and strengthen the body after blood loss [7]. The compounds 6-gingerol and 6-shogaol from *Z. officinale* have been shown to have a number of pharmacological activities, including antipyretic, analgesic, antitussive and hypotensive effects [8]. *Z. officinale* extracts exhibit inhibition of platelet aggregation and thromboxane synthesis *in vitro* [9, 10] which has led to concerns *Z. officinale* extracts may prolong bleeding, however, several European studies using *Z. officinale* orally did not find any significant anticoagulant effects *in vivo* [11]. It has been established that *Z. officinale* has antidiabetic and hypolipidaemic effects in rats [12, 13], closely related spices like *A. cepa* and *A. sativum* has been established by previous works to be hepatoprotective [14, 15]. The management of hepatotoxicity with plant-derived compounds which are accessible and do not require laborious pharmaceutical synthesis is highly attractive and hence the need to embark on this study. This present study was designed to determine the ameliorative effects of increasing dosage of *Z. officinale* (ginger) extracts against paracetamol induced hepatotoxicity in rats viz-a- viz biochemical parameters such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH) and total serum bilirubin (TSB) levels of paracetamol induced hepatotoxic rats.

EXPERIMENTAL SECTION

Plant Materials

Z. officinale used for the study was bought from the Ogige market, Nsukka, Enugu state, Nigeria. The plants were identified to species level [16] at the Herbarium Unit, Department of Plant Science and Biotechnology, University of Nigeria, Nsukka, Enugu State, Nigeria.

Animal Model

Fifty- four (54) adult white wistar strain male albino rats (*R. norvegicus*) weighing 180 to 200g were used for the study. They were fed *ad libitum* with 18% crude protein (Guinea feed) commercial feed and allowed to acclimatize for two weeks under standard photoperiodic condition in a clean rat cage with three rats per cage in the research laboratory. All animals were maintained under the standard laboratory condition for temperature (26 ± 2^oC), humidity ($50 \pm 5\%$) and light (12 hours day length) and were allowed free access to food and water.

Preparation of Extracts

Fresh healthy *Z. officinale* were washed, cut into small pieces and homogenized in a warring blender. The resulting mixture was soaked in two litres of 80% methanol. The mixture was allowed to stand for twenty four hours with intermittent shaking. Following filtration, the filtrate obtained was concentrated to dryness at 40^oC using a rotary evaporator under reduced pressure. The dried extracts were weighed and then stored in a refrigerator.

Induction of Paracetamol Hepatotoxicity in Rats

The minimum dose of paracetamol that causes death in rats is 1060mg/kg and the median lethal dose (LD_{50}) is 765mg/kg [17]. Paracetamol hepatotoxicity was induced by single administration of solution of paracetamol at 750mg/kg intraperitoneally. After 4 days only rats with ALT levels above 65U/l were considered hepatotoxic and used for the study. Several researchers have induced hepatotoxicity in rats by single administration of solution of paracetamol on rats at 750mg/kg ip [18, 19, 20].

Experimental Design

This study was carried out on paracetamol- induced hepatotoxic rats for twelve weeks. The experimental design was the three by three Latin square design. Fifty-four rats used were divided into two major groups:

Group I: Nine non-hepatotoxic rats (Normal control)
Group II: Forty-five paracetamol induced hepatotoxic rats.

The group I rats were three rats each in three different cages and each received 1ml/kg of 5% methanol solution daily throughtout the duration of the study. The Group II rats (paracetamol induced hepatotoxic rats) were divided into three subgroups (IIa, IIb, IIc). The subgroup IIa was the paracetamol control, three rats in a cage, and was replicated thrice and had 3 rats each which received 750mg/kg of paracetamol only [21, 22]. Subgroup IIb was divided into 3 replicates (IIb_1, IIb_2, and IIb_3) respectively each replicate had 3 rats and received 200 mg/kg, 300

mg/kg or 450 mg/kg of *Z. officinale* extracts orally daily. The subgroup IIc, three rats each in a cage, and replicated thrice received the standard drug silymarin at 100mg/kg [23]. The biochemical parameters (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase and total serum bilirubin) assessed were determined first before the start of the experiment and subsequently monthly for the duration of the study. Blood samples were collected from the rat through the retro-orbital plexus monthly for analysis. Serum was obtained by centrifugation (5000rpm for 10 mins) and stored at -20^{o}C prior to analysis.

Evaluation of Biochemical Parameters

Serum alanine aminotransferase and aspartate aminotransferase levels were determined by colorimetric method of [24] and absorbance was read at 505nm using spectrophotometer. Alkaline phosphatase level in serum was determined by the method of [25]. Serum was incubated with disodium phenylphosphate as substrate buffered at P^H 10 for 15 minutes at 37^{o}C. The hydrolytic products, phenol was condensed with 4-amino antipyrine and then oxidized with alkaline ferrcyanide and the red complex developed was read at 510nm using spectrophotometer. Lactate dehydrogenase level was estimated by the method of [26],the reduction of nucleoside derived amino acids (NAD) was coupled with the reduction of tetrazolium salt and the produced formazan was measured using spectrophotometer at 503nm. Total serum bilirubin was determined following the method of [27]. Diazotised sulphonilic acid reacts with bilirubin in diluted serum and forms purple colored azobilirubin which was read at 540nm using spectrophotometer.

Data Analysis

The data collected was pooled and analyzed for their central tendencies using descriptive statistic, values were given as mean ± standard deviation of the observations. Analysis of variance and LSD was employed to test the significant differences ($P < 0.05$) among treatment means. All analyses were performed using SPSS for windows statistical software package version 20. The resulting outputs were presented in Tables and Figures.

RESULTS AND DISCUSSION

Alanine Aminotransferase Level

Z. officinale extracts treatment produced a duration dependent significant ($p < 0.05$) reductions in the alanine aminotransferase levels of paracetamol hepatotoxic rats after the duration of the study when compared with those of paracetamol and silymarin control rats. Alanine aminotransferase levels were significantly higher in paracetamol control groups throughout the duration of the study compared to all other treatment groups whereas it was significantly higher in all groups at the same period compared to the normal group. *Z. officinale* reduced alanine aminotransferase level in a dose dependent fashion across the duration of the study with *Z. officinale* at 200mg/kg reducing alanine aminotransferase level by 20.58%, at 300mg/kg it was reduced by 21.94% whereas at 450mg/kg it was lowered by 22.23% after the duration of treatments when compared to paracetamol control at week 4. Silymarin reduced alanine aminotransferase level by 30.15% after the duration of treatment compared with paracetamol control at week 4 (Table 1). Normal control had no significant effect on alanine aminotransferase level whereas the paracetamol treated control raised alanine aminotransferase level by 8.19%.

Table 1: Ameliorative Effects of *Z. officinale* extracts on alanine aminotransferase level of paracetamol induced hepatotoxic rats

Alanine Aminotransferase Level (U/L)						
TREATMENTS	DOSAGE	WEEK 0	WEEK 4	WEEK 8	WEEK 12	% change after 12weeks
ME	1.0ml/kg	49.70± 3.27^{1,a}	48.77± 3.10^{1,a}	51.00± 2.52^{1,a}	50.63± 3.30^{1,a}	-
PARA	750mg/kg	49.27± 3.15^{1,a}	72.41± 4.00^{2,b}	75.36± 4.52^{3,2,b}	78.34± 5.40^{4,b}	8.19
ZO	200mg/kg	51.62± 3.24^{1,a}	65.31± 2.09^{2,j,c}	59.27± 3.80^{3,2,h,c}	57.51± 2.31^{4,l,d,e,f,h}	-20.58
ZO	300mg/kg	51.69± 2.95^{1,a}	51.74± 2.70^{1,j}	62.33± 4.76^{3,l,c,g,h}	56.52± 3.58^{3,j,d,e,f,g,h,i}	-21.94
ZO	450mg/kg	51.01± 2.49^{1,a}	58.41± 4.20^{2,k,f}	58.50± 3.44^{2,j,c,h,i}	56.31± 2.45^{2,g,k,d,e,f,g,h,l,j}	-22.23
SL	100mg/kg	50.57± 3.83^{1,a}	52.41± 3.621^{1,g,j}	51.94± 2.18^{1,a}	50.58± 2.56^{1,a}	-30.15

Values given represents the Mean ±SD of 9 observations, mean values labeled with the same number superscripts (1 – 4) along the same row are not significantly different at 5% significance level (p < 0.05). Mean values labeled with the same alphabets superscripts (a – l) on the same column are not significantly different at 5% significance level (p < 0.05). ME = 5% Methanol solution represents the Non- hepatotoxic control, PARA = Paracetamol negative control, ZO = Z. officinale and SL= Silymarin representing hepatotoxic control. % change = % change from para treated at weeks 4 compared to all treatments groups at week 12. Negative % change denotes decrease, Positive % change denotes an increase.

Aspartate Aminotransferase Level

Z. officinale extracts produced a duration dependent significant ($p < 0.05$) reductions in the aspartate aminotransferase level of paracetamol hepatotoxic rats after the duration of treatment when compared with those of the paracetamol and silymarin control rats. Aspartate aminotransferase level were significantly higher in paracetamol control groups throughout the duration of the study compared to all other treatment groups whereas it was significantly higher in all groups at the same period compared to the normal group. *Z. officinale* reduced aspartate aminotransferase level in a dose independent fashion across the duration of study with *Z. officinale* at 200mg/kg reducing aspartate aminotransferase level by 59.72% at 300mg/kg it was reduced by 59.60% whereas at 450mg/kg it was lowered by 51.38% after the duration of the study when compared to paracetamol control at week 4. Silymarin at 100mg/kg reduced aspartate aminotransferase level by 62.26% after the duration of treatment compared with paracetamol control at week 4 (Table 2). Normal control had no significant effect on aspartate aminotransferase level whereas the paracetamol treated control raised aspartate aminotransferase level by 8.97%.

Table 2: Ameliorative Effects of *Zingiber officinale* extracts on aspartate aminotransferase level of paracetamol induced hepatotoxic rats

Aspartate Aminotransferase Level (U/L)						
TREATMENTS	DOSAGE	WEEK 0	WEEK 4	WEEK 8	WEEK 12	% change after 12weeks
ME	1.0ml/kg	86.76± 2.84^{1,a}	86.62± 2.49^{1,a}	86.32±2.68^{1,a}	87.10± 2.58^{1,a}	-
PARA	750mg/kg	87.17± 2.41^{1,a}	659.97± 12.00^{2,b}	688.42± 20.83^{3,b}	725.01± 12.09^{4,b}	8.97
ZO	200mg/kg	86.42± 2.70^{1,a}	388.71± 13.83^{2,i}	373.79± 13.57^{3,i}	265.84± 11.46^{4,I,j}	- 59.72
ZO	300mg/kg	87.17± 2.60^{1,a}	409.94 ± 9.82^{2,j}	391.78± 12.61^{3,j,k}	266.60 ± 7.91^{4,I,j}	- 59.60
ZO	450mg/kg	86.84± 2.64^{1,a}	428.84± 11.24^{2,k}	398.91± 14.75^{3,k}	320.88± 63.86^{4,k}	- 51.38
SL	100mg/kg	86.53± 2.63^{1,a}	278.68± 17.63^{2,l}	257.12± 10.03^{3,l}	249.09± 7.64^{3,l}	-62.26

Values given represents the Mean ± SD of 9 observations, mean values labeled with the same number superscripts (1 – 4) along the same row are not significantly different at 5% significance level (p < 0.05). Mean values labeled with the same alphabets superscripts (a – l) on the same column are not significantly different at 5% significance level (p < 0.05). ME = 5% Methanol solution represents the Non- hepatotoxic control, PARA = Paracetamol negative control, ZO = Z. officinale and SL= Silymarin representing hepatotoxic control. % change = % change from para treated at weeks 4 compared to all treatments groups at week 12. Negative % change denotes decrease, Positive % change denotes an increase.

Alkaline Phosphatase Level

Z. officinale extracts produced a duration dependent significant ($p < 0.05$) reductions in the alkaline phosphatase level of paracetamol hepatotoxic rats after the duration of treatment when compared with those of the paracetamol and silymarin control rats. Alkaline phosphatase level were significantly higher in paracetamol control groups throughout the duration of the study compared to all other treatment groups whereas it was significantly higher in all groups at the same period compared to the normal group. *Z. officinale* reduced alkaline phosphatase level in a dose independent manner with *Z. officinale* at 200mg/kg reducing alkaline phosphatase level by 54.63%, at 300mg/kg it was reduced by 56.90% whereas at 450mg/kg it was lowered by 56.85% after the duration of the study when compared to paracetamol control at week 4. Silymarin at 100mg/kg reduced alkaline phosphatase level by 75.70% after the duration of treatment compared with paracetamol control at week 4 (Table 3). Normal control had no significant effect on alkaline phosphatase level whereas paracetamol treated control raised alkaline phosphatase level by 6.00%.

Table 3: Ameliorative Effects of *Z. officinale* extracts on alkaline phosphatase level of paracetamol induced hepatotoxic rats

Alkaline Phosphatase Level (U/L)						
TREATMENTS	DOSAGE	WEEK0	WEEK4	WEEK8	WEEK12	% change after 12weeks
ME	1.0ml/kg	112.44 ±1.91^{1,a}	112.64± 1.86^{1,a}	112.07 ± 1.62^{1,a}	112.40± 1.72^{1,a}	-
PARA	750mg/kg	112.16± 2.02^{1,a}	904.34± 13.31^{2,b}	941.61 ± 13.83^{3,b}	958.60 ± 19.67^{4,b}	6.00
ZO	200mg/kg	112.22± 2.04^{1,a}	417.64± 13.60^{2,I,h,g,d}	410.29± 11.35^{3,2,I,h,g,d}	410.29± 11.36^{4,2,I,h,g,d}	-54.63
ZO	300mg/kg	112.69± 1.59^{1,a}	408.06± 6.82^{2,j}	389.78± 13.27^{3,j}	389.78± 13.27^{4,3,j}	-56.90
ZO	450mg/kg	112.42± 1.40^{1,a}	400.97 ± 7.89^{2,k,j}	400.97± 7.98^{3,2,k,I,h}	390.19± 7.82^{4,k,j}	-56.85
SL	100mg/kg	112.33± 1.80^{1,a}	249.69 ± 15.30^{2,l}	249.69± 15.29^{3,2,l}	219.78 ±10.25^{4,l}	-75.70

Values given represents the Mean ± SD of 9 observations, mean values labeled with the same number superscripts (1 – 4) along the same row are not significantly different at 5% significance level (p < 0.05). Mean values labeled with the same alphabets superscripts (a – l) on the same column are not significantly different at 5% significance level (p < 0.05). ME = 5% Methanol solution represents the Non- hepatotoxic control, PARA = Paracetamol negative control, ZO= Z. officinale and SL= Silymarin representing hepatotoxic control. % change = % change from para treated at weeks 4 compared to all treatments groups at week 12. Negative % change denotes decrease, Positive % change denotes an increase.

Lactate Dehydrogenase Level

Z. officinale extracts produced a duration dependent significant ($p < 0.05$) reductions in the lactate dehydrogenase level of paracetamol hepatotoxic rats after the duration of the study when compared with those of the paracetamol and silymarin control rats. Lactate dehydrogenase levels were significantly higher in paracetamol control groups throughout the duration of the study compared to all other treatment groups whereas it was significantly higher in all groups at the same period compared to the normal group. *Z. officinale* reduced lactate dehydrogenase level in a dose dependent manner with *Z. officinale* at 200mg/kg reducing lactate dehydrogenase level by 34.02%, at 300mg/kg it was reduced by 37.47% whereas at 450mg/kg it was lowered by 40.25% after the duration of the study when compared to paracetamol control at week 4. Silymarin at 100mg/kg reduced lactate dehydrogenase level by 63.08% after the duration of the study compared with paracetamol control at week 4 (Table 4). Normal control had no significant effect on lactate dehydrogenase level whereas paracetamol treated control raised lactate dehydrogenase level by 6.79%.

Table 4: Ameliorative Effects of *Z. officinale* extracts on lactate dehydrogenase level of paracetamol induced hepatotoxic rats.

Lactate Dehydrogenase Level (IU/L)						
TREATMENTS	DOSAGE	WEEK0	WEEK4	WEEK8	WEEK12	% change after 12weeks
ME	1.0ml/kg	$103.78\pm 5.54^{1,a}$	$105.00\pm 5.15^{1,a}$	$104.56 \pm 5.20^{1,a}$	$103.44 \pm 5.13^{1,a}$	-
PARA	750mg/kg	$104.67\pm 5.57^{1,a}$	$390.89 \pm 18.21^{2,b}$	$409.67\pm 10.71^{3,b}$	$417.44 \pm 9.22^{4,b}$	6.79
ZO	200mg/kg	$103.00 \pm 5.96^{1,a}$	$260.78\pm 6.99^{2,g,f,d}$	$260.78 \pm 6.99^{3,2,j,h,e}$	$257.89 \pm 11.77^{4,2,i}$	-34.02
ZO	300mg/kg	$103.67\pm 6.02^{1,a}$	$244.22 \pm 13.50^{2,h,e,c}$	$244.22 \pm 13.50^{3,2,j,g,d}$	$244.44 \pm 15.02^{4,3,j}$	-37.47
ZO	450mg/kg	$104.22 \pm 5.89^{1,a}$	$238.67 \pm 16.61^{2,l,h,e}$	$238.67 \pm 16.61^{3,2,k,j,g,f,d,c}$	$233.56 \pm 16.58^{4,3,k,c}$	-40.25
SL	100mg/kg	$103.22 \pm 5.26^{1,a}$	$165.11 \pm 18.15^{2,j}$	$165.11 \pm 18.15^{3,2,l}$	$144.33 \pm 13.10^{4,l}$	-63.08

Values given represents the Mean ± SD of 9 observations, mean values labeled with the same number superscripts (1 – 4) along the same row are not significantly different at 5% significance level ($p < 0.05$). Mean values labeled with the same alphabets superscripts (a – l) on the same column are not significantly different at 5% significance level ($p < 0.05$). ME = 5% Methanol solution represents the Non- hepatotoxic control, PARA = Paracetamol negative control, ZO = Z. officinale and SL= Silymarin representing hepatotoxic control. % change = % change from para treated at weeks 4 compared to all treatments groups at week 12. Negative % change denotes decrease; Positive % change denotes an increase.

Total Serum Bilirubin Level

Z. officinale extracts produced a duration dependent significant ($p < 0.05$) reductions in the total serum bilirubin level of paracetamol hepatotoxic rats after the duration of treatment when compared with those of paracetamol and silymarin control rats. Total serum bilirubin levels were significantly higher in paracetamol control groups throughout the duration of the study compared to all other treatment groups whereas it was significantly higher in all groups at the same period compared to the normal group. *Z. officinale* reduced total serum bilirubin level in a dose dependent manner across the duration of the study with *Z. officinale* at 200mg/kg reducing total serum bilirubin level by 56.86%, at 300mg/kg it was reduced by 68.35% whereas at 450mg/kg it was lowered by 73.95% after the duration of treatments when compared to paracetamol control at week 4. Silymarin at 100mg/kg reduced total serum bilirubin level by 82.35% after the duration of the study compared with paracetamol control at week 4 (Table 5). Normal control had no significant effect on total serum bilirubin level whereas paracetamol treated control raised total serum bilirubin level by 33.89%.

Table 5: Ameliorative Effects of *Z. officinale* extracts on total serum bilirubin of paracetamol induced hepatotoxic rats

Total Serum Bilirubin Level (mg/dl)						
TREATMENTS	DOSAGE	WEEK0	WEEK4	WEEK8	WEEK12	% change after 12weeks
ME	1.0ml/kg	$0.52\pm 0.16^{1,a}$	$0.53\pm 0.15^{1,a}$	$0.54\pm 0.16^{1,a}$	$0.51\pm 0.13^{1,a}$	-
PARA	750mg/kg	$0.55\pm 0.15^{1,a}$	$3.57\pm 0.37^{2,b}$	$4.19\pm 0.36^{3,b}$	$4.78\pm 0.49^{4,b}$	33.89
ZO	200mg/kg	$0.55\pm 0.13^{1,a}$	$2.94\pm 0.45^{2,i}$	$2.44\pm 0.23^{3,i}$	$1.54\pm 0.26^{4,I,g,c}$	-56.86
ZO	300mg/kg	$0.51\pm 0.40^{1,a}$	$2.58\pm 0.33^{2,j,f,c}$	$1.86\pm 0.42^{3,j,g,f}$	$1.13\pm 0.37^{4,j,h,e,d}$	-68.35
ZO	450mg/kg	$0.57\pm 0.12^{1,a}$	$2.21\pm 0.39^{2,k,f}$	$1.35\pm 0.46^{3,k,h,e}$	$0.93\pm 0.26^{4,k,e,h}$	-73.95
SL	100mg/kg	$0.52\pm 0.13^{1,a}$	$0.93\pm 0.28^{2,l}$	$0.75\pm 0.25^{1,2,a}$	$0.63\pm 0.2^{4,1,a}$	-82.35

Values given represents the Mean ± SD of 9 observations, mean values labeled with the same number superscripts (1 – 4) along the same row are not significantly different at 5% significance level ($p < 0.05$). Mean values labeled with the same alphabets superscripts (a – l) on the same column are not significantly different at 5% significance level ($p < 0.05$). ME = 5% Methanol solution represents the Non- hepatotoxic control, PARA = Paracetamol negative control, AC = Allium cepa, AS = Allium sativum, ZO = Z. officinale and SL= Silymarin representing hepatotoxic control. % change = % change from para treated at weeks 4 compared to all treatments groups at week 12. Negative % change denotes decrease, Positive % change denotes an increase.

The aminotransferases (ALT and AST) are the most frequently utilized and specific indicators of hepatocellular necrosis [28]. The significant increase observed in the level of serum aminotransferase (AST and ALT) in paracetamol treated rats compared to the normal rats in this study could be due to hepatocellular damage because these enzymes are normally located in the cytoplasm and released into the circulation after cellular damage [29]. Silymarin and *Z. officinale* treatment reduced the level of aminotransferase enzymes in the serum. *Z. officinale* mechanism of action could be by the prevention of the intracellular enzyme release and its membrane stabilizing and antioxidant effects [30]. This is more so as *Z. officinale* is rich in strong antioxidant and are well documented against reactive oxygen species-mediated damage [31, 32]. The reduction in ALP levels by extracts may suggest repairing of rats liver by *Z. officinale* extracts. Possible mechanisms that may be responsible for the protection of paracetamol induced liver damage by *Z. officinale* may be by its ability to act as a free radical scavenger thereby intercepting those radicals involved in paracetamol metabolism. Because they trap oxygen related free radicals, *Z. officinale* could prevent their interaction with polyester fatty acids and would stop the enhancement of lipids peroxidative processes [33, 34, 35]. The active ingredients in *Z. officinale* 6- gingerol could also possibly have increased the levels of glutathione which binds to the toxic metabolites of paracetamol such as N- acetyl- p- benzoquinone imine (NAPQI) and increased its rate of excretion from the body.

Lactate dehydrogenase level was decreased in a dose independent fashion by *Z. officinale*, after the duration of the study. Previous researchers reported decrease in hepatic LDH after carbon tetrachloride intoxication which is supportive of this study [36, 37]. Elevated total serum bilirubin observed in paracetamol hepatotoxic rats suggested abnormal conjugation of bilirubin by the liver due to generalized hepatocellular damage [38]. Decrease in total serum bilirubin observed in this study was reported by previous works, [39]. The possible mechanism of action of *Z. officinale* on decreasing total serum bilirubin may be through their antioxidative effects, because *Z. officinale* has active ingredients that are capable of free radical scavenging in living system [40].

It was evident that *Z. officinale* showed potent hepatorestorative properties, it was able to reduce significantly all the elevated biochemical parameters due to paracetamol hepatotoxicity. This result could be pursued for the clinical importance of *Z. officinale* in hepatoprotection and its nutraceutical role in human diet, because of the increased use of natural herbs worldwide and Nigeria in particular.

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