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Research Article

Hepatoprotective Effect of the Leaf Extracts of *Trigonella foenum* Graecum and *Curcuma zeoderia* on Drug Induced Liver Injury in Albino Rats

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ABSTRACT

The hepatoprotective effect of ethanolic leaf extract of Trigonella foenum graecum and curcuma Zeoderia against paracetamol induced hepatic damage in albino rats was investigated. Ethanolic extracts from the leaves of Trigonella foenum graecum and curcuma Zeoderia at a dose level of 100mg/ml was administered orally daily once for 5 days as pretreatment and no side effects or injury to any organ was observed. Paracetamol at a single dose level of 500mg/kg body weight was given intraperitonially to induce hepatotoxicity. The substantially increased serum marker enzymes like Aspartate transaminase, Alanine Transaminase, Alkaline phophatase, Gamma glutamyl transferase, Lactate dehydrogenase, Creatine phosphokinase due to paracetamol treatment was restored towards normalization in rats treated with leaf extracts of Trigonella foenum graecum and curcuma zeoderia. Similarly the elevated levels of blood urea, serum creatinine, serum cholesterol, serum TGL due to paractamol intoxication was returned to normal when rats treated with the leaf extracts. Paracetamol induced hepatotoxicity causes the failure of the synthetic function of the liver which leads to Hypoproteinemia and hypolbuminemia. The protein levels are returned to normal when treated with the ethanolic leaf extracts. Due to paracetamol intoxication the reduced of non enzymic autioxidants such as Ascorbic (Vit.C), α – Tocopherol (Vit.E), GSH was restored to the normal level in rats treated with the leaf extracts. Paracetamol administration in rats also increased the lipid peroxidation process and results in imbalance in redox status due to oxidative stress which is evident from, the elevated values of TBARS. Enzymic antioxidant such as SOD, catalase, GPx levels reduced in rats treated with paracetamol was restored towards normal when animals treated along with the leaf extracts. The results of this study clearly showed that the ethanolic leaf extracts of Trigonella foenum graecum and curcuma zeoderia has got a potent hepato-protective effect against paracetamol induced liver injury in albino rats.

INTRODUCTION

'Food is medicine and Medicine is Food' perhaps the best proverb which forms the basis for the maintenance of good health and in the treatment of various diseases in the Indian medicine system. Although safe in most cases ancient treatments are not given due importance and ignored, may be due to the molecular composition of the medicines or their target actions are not well defined. The conventional or synthetic drugs used in the treatment of liver diseases sometimes can have serious side effects[1]. Phyto constituents of herbal medicines remains to be a major contributor in the treatment of liver diseases[2]. In the absence of a reliable liver protective drug in modern medicine, there are a number of medicinal preparations in the Indian medicine system recommended for the treatment of liver disorders. Liver in an important organ actively involved in many metabolic function and is the frequent target for a number of toxicants[3]. Let us try to build a healthy human society by implementing Indian medicine system in the health sector by way of using the extracts of various herbs, seeds, fruits and vegetables.

METHODOLOGY

The study comprises and to be conducted in six different groups as follows.

I. A group of six (6) albino rates weighing about 120-130 gms treated as normal control species.
II. A group of six albino rats comes under the pretreatment with leaf extracts of fenugreek.
III. The next group of six albino rats are treated with paracetamol which induces liver injury. The degree of liver and renal damage was evaluated in this group.
IV. In this group of six albino rats along with paracetamol drug, the leaf extract of Trigonella foenum graecum is also given and the protective effect of the herb was tested.
V. A group of six albino rats comes under the pretreatment with leaf extracts of curcuma zeoderia.

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Table 1: showing the values of Biochemical parameters Blood glucose, Urea, Creatinine, Cholesterol, TGL and HDL in blood

Group I: Normal control
Group II: Pretreatment with Trigonella foenum graecum leaf extract
Group III: Paracetamol induced hepatotoxicity
Group IV: Paracetamol with Trigonella foenum graecum leaf extract
Group V: Pretreatment with curcuma zeroderia leaf extract
Group VI: Paracetamol with curcuma zeroderia leaf extract

Parameter	Group I	Group II	Group III	Group IV	Group V	Group VI
Blood glucose Values are means ± S.D 'p' value	69.000 3.464 I & II N.S	66.500 1.378	56.833 1.472 I & III <0.05	70.166 1.169 III & IV <0.001	64.833 0.752 I & V N.S	68.666 0.516 III & VI N.S
Blood urea Values are means ± S.D 'p' value	18.166 1.472 I & II N.S	17.500 1.643	33.500 1.048 I & III <0.001	18.166 0.752 III & IV <0.001	16.166 1.169 I & V N.S	17.833 0.752 III & VI <0.001
Serum creatinine Values are means ± S.D 'p' value	0.750 0.054 I & II N.S	0.700 0.089	1.350 0.054 I & III <0.001	0.733 0.081 III & IV <0.001	0.650 0.654 I & V N.S	0.750 0.054 III & VI <0.001
Serum cholesterol Values are means ± S.D 'p' value	99.000 11.644 I & II N.S	96.666 2.943	136.833 1.602 I & III <0.05	110.833 2.014 III & IV <0.001	96.666 1.633 I & V N.S	101.666 2.065 III & VI <0.001
Serum triglyerides Values are means ± S.D 'p' value	48.333 2.160 I & II N.S	52.500 1.048	120.666 2.338 I & III <0.001	48.333 2.065 III & IV <0.001	53.666 0.816 I & V N.S	54.166 1.169 III & VI <0.001
HDL cholesterol Values are means ± S.D 'p' value	28.166 1.169 I & II N.S	30.666 1.211	35.500 1.048 I & III <0.001	28.833 0.983 III & IV <0.001	28.333 1.032 I & V N.S	28.666 0.816 III & VI <0.001

'p' value < 0.001, < 0.01, < 0.05 is considered as "significant"
'p' value N.S is considered as "non-significant"

VI. The last group of six albino rats, along with paracetamol drug the leaf extracts of curcuma zeoderia is also given and the hepatoprotective effect was studied.

Plant material

"Trigonella foenum graecum" is a plant in family **Fabaceae** (commonly known as fenugreek). It is used as a herb (the leaves) and as a spice (the seed). The leaves and sprouts are also eaten as vegetables. It is a common ingredient in many food items. They are the rich source of polysaccharide galactomannan. It also contains bioactive components such as volatile oils and alkaloids such as choline, trigonelline.

"Curcuma zeoderia" is commonly known as Turmeric (or) curcumin. It is the principal curcuminoid of the popular Indian spice turmeric which is the member of the ginger family **"Zingiberaceae"**. The curcuminoids are natural phenols and are responsible for the yellow colour of the turmeric. It can exist in tautomeric forms such as 1,3 diketoform and two equivalent enol form. It is chemically known as diferuloylmethane. IUPAC (1E, 6E)-1,7bis(4 hydroxy-3 methoxy 1,6-heptadiene-3,5 dione 1. **"Enol"** form 2. **"Keto"** form

Extraction

The leaves of Trigonella foenum graecum were shade dried pulverized to a coarse powder and passed through a 40-mesh sieve and exhaustively extracted with 50% v/v ethanol is soxhlet apparatus at 60°C. The extract was evaporated under pressure until all the solvent had been removed and further removal of water was carried out by freeze drying to give an extract sample which is stored in the refrigerator. Known amount was weighed and dissolved in distilled water and used for the present investigation. The same procedure is repeated with the leaves of curcuma zeoderia and the extract was prepared.

Animals

Adult albino rats of wistar strain weighing 120-130 gm were used for the present investigation. The animals were maintained in well ventilated room temperature with natural 12 ± h day-night cycle in the propylene cages. A balanced rodent pellet diet along with tapwater ad libitum was provided, throughout the investigation period. The protocol was duly approved by the ethical committee.

Experimental design

The rats were divided into 6 groups with 6 animals in each group and were given dose schedule as follows.

Table 2: Showing the values of Biochemical parameters Bilirubin total, Direct, Indirect, Protein, Albumin and Globulin in blood

Group I: Normal control
Group II: Pretreatment with Trigonella foenum graecum leaf extract
Group III: Paracetamol induced hepatotoxicity
Group IV: Paracetamol with Trigonella foenum graecum leaf extract
Group V: Pretreatment with curcuma zeroderia leaf extract
Group VI: Paracetamol with curcuma zeroderia leaf extract

Parameter	Group I	Group II	Group III	Group IV	Group V	Group VI
Bilirubin-Total						
Values are means ± S.D	0.483 ± 0.075	0.0483 ± 0.075	0.666 ± 0.051	0.450 ± 0.054	0.433 ± 0.051	0.383 ± 0.075
'p' value	I & II N.S		I & III N.S	III & IV <0.01	I & V N.S	III & VI <0.01
Bilirubin-Direct						
Values are means ± S.D	0.200 ± 0.000	0.200 ± 0.000	0.233 ± 0.051	0.166 ± 0.051	0.133 ± 0.051	0.116 ± 0.040
'p' value	I & II N.S		I & III N.S	III & IV N.S	I & V N.S	III & VI N.S
Bilirubin-Indirect						
Values are means ± S.D	0.283 ± 0.075	0.283 ± 0.075	0.433 ± 0.051	0.283 ± 0.075	0.300 ± 0.063	0.266 ± 0.051
'p' value	I & II N.S		I & II N.S	III & IV N.S	I & V N.S	III & VI <0.05
Serum proteins						
Values are means ± S.D	7.210 ± 0.141	7.195 ± 0.089	6.009 ± 0.075	7.018 ± 0.089	7.185 ± 0.081	7.208 ± 0.075
'p' value	I & II N.S		I & III <0.001	III & IV <0.001	I & V N.S	III & VI <0.001
Serum albumin						
Values are means ± S.D	4.412 ± 0.040	4.390 ± 0.054	3.210 ± 0.051	4.198 ± 0.051	4.394 ± 0.054	4.407 ± 0.054
'p' value	I & II N.S		I & III <0.001	III & IV <0.001	I & V N.S	III & VI <0.001
Serum globulin						
Values are means ± S.D	2.800 ± 0.116	2.803 ± 0.054	2.820 ± 0.054	2.820 ± 0.081	2.771 ± 0.116	2.801 ± 0.121
'p' value	I & II N.S		I & III N.S	III & IV N.S	I & V N.S	III & VI N.S

'p' value < 0.001, < 0.01, < 0.05 is considered as "significant"
'p' value N.S is considered as "non-significant"

Group I: Normal control

After 7 days of normal diet and living conditions the animals were sacrificed by cervical decapitation under light ether anesthesia and blood was collected, plasma and serum was separated by centrifuging at 3000 rpm for 10 mins. The liver and kidneys were removed for the preparation of tissue homogenate and histopathological studies were also conducted.

Group II: Pretreatment with leaf extract

100 mg/ml of the Trigonella foenum graecum leaf extract was given orally for 5 days continuously as pretreatment and to study any side effects due to the leaf extract administration. After 5 days as in group I the animals were sacrificed. Blood samples and liver, kidney tissues are collected for further investigations.

Group III: Paracetamol induced hepatotoxicity

500 mg/kg body weight paracetamol was given as a single dose by intraperitonially, so as to induce liver injury[9,10]. After 24 hrs blood samples were collected as before, the animals were sacrificed so as to collect the liver and kidneys.

Group IV: Paracetamol + Trigonella foenum graecum leaf extract administration

In this group 500 mg/kg body wt of paracetamol was given intraperitonially, along with 500 mg/ml fenugreek leaf extract was given orally. After 24 hrs the animals were sacrificed as before and the blood and tissue samples are collected.

Group V: Pretreatment with curcumin zeoderia leaf extract

100 mg/ml of the curcumin leaf extract was given orally for 5 days continuously as pretreatment and to study any side effects due to the herbal intake. After 5 days animals were sacrificed as before so as to collect liver, kidney tissues and blood samples were also collected.

Group VI: Paracetamol with curcumin leaf extract

In this group 500 mg/kg body wt of paracetamol was given intraperitonially, along with 500 mg/ml or curcumin leaf extract was given orally for the study of hepatoprotective effect of the leaf extract on paracetamol induced hepatotoxicity. After 24 hrs blood samples were collected as before, the animals were sacrificed for further investigations.

Biochemical parameters

EDTA anticoagulant was used to collect the whole blood and it is centrifuged to get plasma for the analysis of glucose and urea. Plain blood was also collected allowed

Table 3: showing the values of Biochemical parameters AST, ALT, ALP, GGT, LDH and CPK in blood
Group I: Normal control
Group II: Pretreatment with Trigonella foenum graecum leaf extract
Group III: Paracetamol induced hepatotoxicity
Group IV: Paracetamol with Trigonella foenum graecum leaf extract
Group V: Pretreatment with curcuma zeroderia leaf extract
Group VI: Paracetamol with curcuma zeroderia leaf extract

Parameter	Group I	Group II	Group III	Group IV	Group V	Group VI
AST Values are means ± S.D 'p' value	17.500 1.643 I & II N.S	16.500 1.048	116.500 10.802 I & III <0.001	17.333 0.816 III & IV <0.001	15.666 0.816 I & V N.S	18.166 0.752 III & VI <0.001
ALT Values are means ± S.D 'p' value	17.166 1.722 I & II N.S	14.333 0.816	79.166 6.177 I & III <0.001	15.833 2.137 III & IV <0.001	13.666 0.816 I & V N.S	14.333 0.816 III & VI <0.001
Alkaline phosphatase Values are means ± S.D 'p' value	63.166 1.940 I & II N.S	65.000 6.542	137.500 1.643 I & III <0.001	59.666 1.633 III & IV <0.001	61.833 1.169 I & V N.S	63.833 1.169 III & VI <0.001
GGT Values are means ± S.D 'p' value	12.000 1.095 I & II N.S	13.000 0.894	91.166 3.060 I & III <0.001	13.833 0.983 III & IV <0.001	12.500 1.048 I & V N.S	13.833 0.752 III & VI <0.001
LDH Values are means ± S.D 'p' value	93.500 3.834 I & II N.S	89.500 1.870	200.166 6.080 I & III <0.001	97.166 1.169 III & IV <0.001	86.000 0.894 I & V N.S	90.166 1.169 III & VI <0.001
CPK Values are means ± S.D 'p' value	27.166 1.940 I & II N.S	26.000 1.414	63.666 3.829 I & III <0.001	24.000 0.894 III & IV <0.001	26.166 0.752 I & V N.S	25.833 0.752 III & VI <0.001

'p' value < 0.001, < 0.01, < 0.05 is considered as "significant"
'p' value N.S is considered as "non-significant"

to clot, and the serum was separated. With the serum sample the following parameters are estimated; serum creatinine, cholesterol, triglycerides, HDL, serum bilirubin, serum proteins albumin, globulin, marker enzymes such as AST, ALT, ALP, GGTP, LDH, CPK, nonenzymic antioxidants Vit-C, Vit-E, GSH, TBARS for lipid peroxidation, enzymic antioxidant like SOD, catalase, and glutathione peroxidase.

Preparation of tissues

A 10% homogenate of the washed tissues (liver and kidneys) were prepared in 0.1 M Tris-HCl buffer pH 7.4. The above homogenates were used for the different biochemical parameters as above.

Histopathological studies

From the sacrificed rats the liver and kidneys was dissected out and cleaned well with cold physiological saline to remove blood and adhering tissues. The samples were then fixed in 10% formalin-saline and embedded in paraffin. Serial sections (5 μm thick) were stained with haematoxylin and eosin. The sections were examined under light microscope and photographs were taken. Histopathological examination of liver tissues shows the congestion and necrosis in hepatocytes due to paracetamol intoxication. However in animals when treated with leaf extracts and paracetamol the liver tissues show normal cellular architecture and no infiltration of inflammatory cells. The histopathological examination of liver and kidney tissues clearly demonstrates the hepatoprotective effect of the leaf extracts of Trigonella foenum graecum and curcuma zeoderia against paracetamol induced toxicity.

Statistical Analysis

Values were mean ± SEM from 6 animals in each group. The statistical analysis was carried out using analysis of variance (ANOVA) followed by Dunnet, 't' test. 'p' values < 0.001, < 0.01, < 0.05 were considered to be significant. 'p' values as 'N.S' is considered as non-significant.

RESULTS AND DISCUSSION

In the present study it was noted that in animals treated with paracetamol there is elevated levels of blood urea, serum creatinine, serum cholesterol, serum triglycerides as in group III indicates that paracetamol induces acute renal damage and fatty liver also. When animals treated along with the leaf extract of Trigonella foenum graecum and curcuma zeoderia the above levels are restored to normal

Table 4: Showing the values of Biochemical parameters Vit.C, Vit.E, GSH, TBARS, SOD, CATALASE, GPx in blood
Group I: Normal control
Group II: Pretreatment with Trigonella foenum graecum leaf extract
Group III: Paracetamol induced hepatotoxicity
Group IV: Paracetamol with Trigonella foenum graecum leaf extract
Group V: Pretreatment with curcuma zeroderia leaf extract
Group VI: Paracetamol with curcuma zeroderia leaf extract

Parameter	Group I	Group II	Group III	Group IV	Group V	Group VI
Vit.C Ascorbic acid						
Values are means ±	1.366	1.400	0.850	1.366	1.416	1.466
S.D	0.081	0.089	0.054	0.081	0.075	0.103
'p' value	I & II N.S		I & III <0.001	III & IV <0.001	I & V N.S	III & VI <0.001
Vit.E						
Values are means ±	1.166	1.216	0.833	1.166	1.266	1.250
S.D	0.054	0.075	0.051	0.051	0.081	0.054
'p' value	I & II N.S		I & III <0.001	III & IV <0.001	I & V N.S	III & VI <0.001
GSH						
Values are means ±	35.833	36.500	19.333	36.666	36.833	34.666
S.D	0.752	1.048	1.211	0.816	1.169	0.816
'p' value	I & II N.S		I & III <0.001	III & IV <0.001	I & V N.S	III & VI <0.001
TBARS						
Values are means ±	2.016	2.033	3.166	2.050	2.050	2.050
S.D	0.075	0.081	0.075	0.054	0.054	0.104
'p' value	I & II N.S		I & III <0.001	III & IV <0.001	I & V N.S	III & VI <0.001
SOD						
Values are means ±	3.000	3.066	1.766	2.983	3.116	3.116
S.D	0.089	0.121	0.081	0.075	0.075	0.075
'p' value	I & II N.S		I & III <0.001	III & IV <0.001	I & V N.S	III & VI <0.001
Catalase						
Values are means ±	49.833	50.000	25.833	49.833	49.833	47.166
S.D	1.472	0.894	0.752	1.169	0.752	0.752
'p' value	I & II N.S		I & III <0.001	III & IV <0.001	I & V N.S	III & VI <0.001
GPx						
Values are means ±	300.00	301.000	181.166	297.853	299.000	291.833
S.D	2.097	1.414	2.786	1.602	1.095	1.602
'p' value	I & II N.S		I & III <0.001	III & IV <0.001	I & V N.S	III & VI <0.001

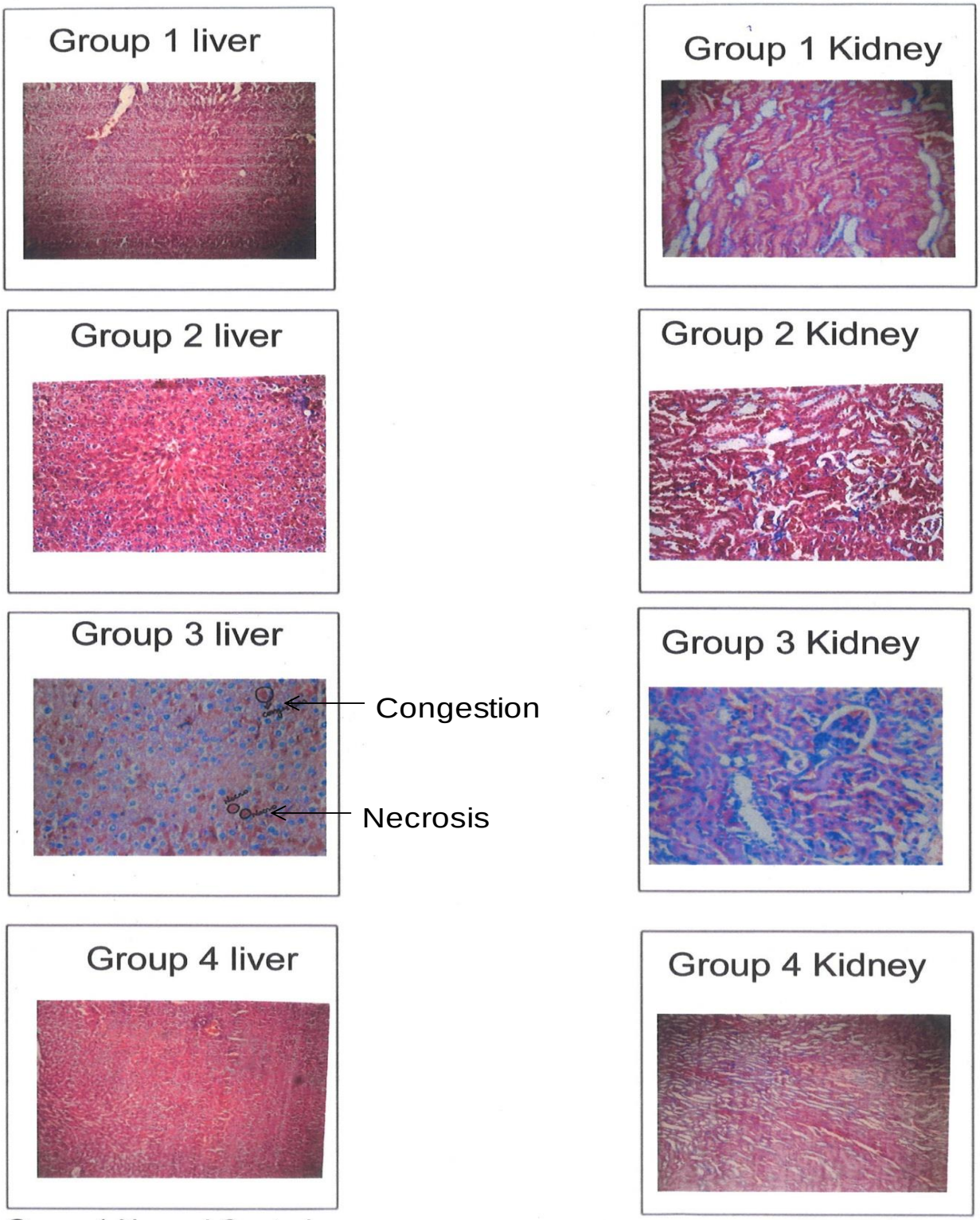
'p' value < 0.001, < 0.01, < 0.05 is considered as "significant"
'p' value N.S is considered as "non-significant"

as in Group IV and Group VI, clearly shows a protection against the injurious effects of paracetamol that may result from the interference with cytochrome P-450, resulting in the hindrance of the formation of hepato-toxic free radicals. The site specific oxidative damage in some susceptible amino acids of protein is now regarded as the major cause of metabolic dysfunction during pathogenesis[11].Bilirubin is the conventional indicator of liver diseases which measures the degree of jaundice. The elevated levels of serum bilirubin in Group III paracetamol intoxicated rats were significantly reduced in Group IV and Group VI animals treated with the leaf extracts. These biochemical restoration may be due to the inhibitory effects on cytochrome P-450 or/and promotion of its glucuronidation[12].

One of the major function of liver is to synthesis proteins such as albumin, α_1 globulin, α_2 globulin, β globulin, and fibrinogen. Due to the paracetamol in-toxication as in Group III serum proteins and albumin levels are significantly decreased when compared with normal controls as in Group I (p value < 0.001). Due to the liver cell injury the synthetic function of liver is affected results in hypoproteinemia. When the albino rats treated with paracetamol and the leaf extracts of fenugreek foenum graecum and curcuma zeoderia as in group IV and group VI, the levels of proteins albumin remains unaltered which shows the protective action of these leaf extracts, so that the synthetic function of liver is not affected.

Assessment of liver function can be made by estimating the activities of serum AST, ALT, ALP, LDH, GGT and CPK which are enzymes originally present in higher concentration in cytosol or mitochondria of the hepatic cells. When there is hepatopathy these enzymes leak into the blood stream in conformity with the extent of liver damage. The elevated levels of these entire marker enzymes observes in group III paracetamol treated rats in the present study corresponded to the extensive liver damage induced by the drug. The restoration of these enzyme levels to normal as in group IV and group VI animals treated with the leaf extract might probably due to presence of catechin, the phytochemicals present in the leaf extract. It is a clear manifestation of antihepatotoxic

Histopathological Examination



Group 1:Normal Control
Group 2: Pretreatment with Trigonella foenum Graecum leaf Extract
Group 3: Paracetamol induced toxicity
Group 4: Paracetamol + Trigonella foenum Graecum leaf Extract

action of the leaf extracts of Trigonella foenum graecum and curcuma zeoderia.

Nonenzymic antioxidants (Vit.C, Vit.E, GSH)

Vit.C is a water soluble, naturally occuring chain breaking antioxidant and cofactor in various enzymes[13]. Reacts with peroxyl radical thus breaking chain reaction of lipid peroxidation[14]. We have observed a decrease in Vit.C in paracetamol treated animals while the levels of Vit.C was not altered in animals treated with leaf extracts of Trigonella foenum graecum and curcuma zeoderia along with paracetamol drug. The decrease could be due to increased utilisation of vitamin C, as an antioxidant defense against increased Reactive Oxygen Species (ROS) or could be due to decrease in GSH concentration, because GSH involved in the recycling of vitamin C.

Vitamin E has a strong antioxidant capacity and has been used in several clinical disorders. It plays a major role in maintaining cell membrane integrity by limiting lipid peroxidation by Reactive Oxygen Species (ROS). The decrease in Vitamin E concentration in paracetamol induced liver injury as in group III could be due to increased utilisation in scavenging the oxy radicals generated or could be due to Vit.C low concentration because there is a well established interaction between Vitamin E and Vitamin C. In albino rats treated with leaf extracts of Trigonella foenum graecum and curcuma zeoderia along with paracetamol drug as in group IV and group VI animals, the levels of vitamin E and vitamin C remains unaltered as in normal control rats. It shows that leaf extracts of Trigonella foenum graecum and curcuma zeroderia have hepatoprotective action on liver cells due to its antioxidant properties, prevents lipid peroxidation and helps in scavenging free radicals formation.

GSH is one of the most important endogenous antioxidants. It plays the role of sulfhydryl (-SH) group provider for direct scavenging reactions. GSH acts both as a substrate in the scavenging reaction catalysed by Glutatione peroxidase (GPx) and as a scavenger of vitamin C and vitamin E radicals. In our study the serum GSH concentration significantly[15] decreased in paracetamol drug induced liver injury as in group III animals. It may be due to an increased utilisation of GSH. New GSH may be recovered from the oxidised form GSSG by glutathione reductase with the consumption of NADPH. The amount of NADPH may be reduced during drug induced liver injury, contributing a reduction in the effectiveness of mechanisms for recovering GSH. A more pronounced decrease in serum GSH is due to enhanced utilisation and decreased formation during paracetamol induced hepatotoxicity, because of increased lipid peroxidation.

Lipid peroxidation. (TBARS) There is marked increase in the concentration of TBARS in animals treated with paracetamol. Lipid peroxidation occurs from free radical attack on the electrophilic carbon atom adjacent to the double bond in polyunsaturated fatty acids. This biochemical reaction produces lipid radicals that can propagate the reactant by reacting with molecular oxygen to form lipid peroxy radicals, which may in turn react with other lipids to yield peroxides. This chain reaction can result in significant damage of membrane lipids and ultimately damage the integrity of plasma (or) organellar membrane[16].

Serum levels of TBARS found to be increased significantly in animals treated with paracetamol, where the hepatocellular damage occurs, due to lipid peroxidation by free radicals. Lipid peroxidation is a part of normal metabolism. Increased lipid peroxidation is due to the consequence of oxidative stress which occurs when the dynamic balance between prooxidant and antioxidant mechanism is impaired[17]. We observed increased concentration of TBARS indicating increased lipid peroxidation, which could be attributed to a deficiency of antioxidant defense mechanism when there is drug induced liver injury.

Enzymic antioxidants (SOD, catalase, GPx)

Superoxide dismutase catalysed dismutation of superoxide (O_2^-) into oxygen and Hydrogen peroxide (H_2O_2). They are the important antioxidant defense in nearly all cells exposed to oxygen. Superoxide is one of the main ROS in the cell; as a consequence SOD serves as a key antioxidant role. The physiological importance of SOD is illustrated by the severe pathologies evident in mice genetically engineered to lack these enzymes. Mice lacking SOD_2 die several days after birth due to massive oxidative stress; mice lacking SOD, develop a wide range of pathologies including hepatocellular carcinoma.

Catalase is powerful antioxidant enzyme catalyses the decomposition of H_2O_2 to water and oxygen. It is a very important enzyme in protecting the cell from oxidative damage by ROS (Reactive Oxygen Species). H_2O_2 is a harmful product of many metabolic processes, to prevent damage to cells and tissues it must be quickly converted into other less reactive substances such as gaseous oxygen and water molecule. $H_2O_2 \rightarrow H_2O + (O)$.

Glutathione peroxidase plays a vital role in the antioxidant defense mechanism. It is a selenium dependant enzyme (GPx) catalyses peroxide reduction utilising GSH as the substrate and converting it into GSSG[18]. In our study the levels of SOD, catalase and GPx in plasma, liver and kidney tissue found to be diminished to a very low level (p value < 0.001) in albino rats treated with paracetamol drug. The decrease may be due to oxidative stress and generation of ROS which causes liver injury. Increased utilisation of these enzymes SOD, catalase and GPx by the system leads to a decrease in their concentration. When the animals treated with the leaf extracts of Trigonella foenum graecum and Curcuma zeoderia along with paracetamol drugs as in Group IV and VI, due to hepatoprotective effect of these leaf extracts the values of SOD, catalase and GPx remains unaltered ('p' value Group III & IV is < 0.001 and 'p' value Group III & VI is < 0.001).

It clearly indicates the hepatoprotective action of these leaf extracts to the liver cells against paracetamol induced hepatotoxicity, due to their antioxidant role in scavenging the free radicals and Reactive Oxygen Species (ROS).

In albino rats treated with the leaf extracts of Trigonella foenum graecum and curcuma zeoderia along with paracetamol drug as in group IV and VI animals the increased levels of TBARS are restored to the normal level; and the altered values of GSH and GPx are also

returned to the normal control level. It clearly demonstrates that these leaf extracts have got potent hepatoprotective action due to its antioxidant properties as well as its ability to decrease the formation of proinflammatory cytokines.

Paracetamol drug

It is well established that paracetamol induces hepatotoxicity by metabolic activation; therefore it selectively causes injury to hepatocytes maintaining semi-normal metabolic function. Paracetamol an over the counter drug is used as antipyretic and analgesic which can lead to hepatic failure[19,20]. In therapeutic dose paracetamol is converted by drug metabolizing enzyme to water soluble metabolites and secreted in the urine[21,22]. Saturated and excess paracetamol is oxidatively metabolised by hepatic Cy P-450 system to a toxic metabolite namely N-acetyl-p-benzoquinoneimine NAPQI[23-25]. This is normally detoxified by GSH with both oxidative scavenger and redox regulation capacities[24]. Normally GSH is a major antioxidant system and a crucial component of host defense which is responsible for scavenging reactive free radicals to prevent liver injury[20]. The toxic dose of paracetamol caused the depletion of GSH which results in the accumulation of NAPQI which then covalently binds to the cystinyl sulfhydryl groups of cellular proteins results in the generation of Reactive Oxygen Species (ROS) (H_2O_2 O_2^- OH^-) hydrogen peroxide, superoxide anion and hydroxyl ion[26,27]. The cellular membrane is affected, induce lipid peroxidation and also cause hepatic necrosis.

CONCLUSION

In conclusion the ethanolic leaf extracts of Trigonella foenum graecum and curcuma zeoderia afforded hepatoprotective action against paracetamol induced liver injury. Possible mechanism that may be responsible for the protective effect is due to the free radical scavenging function, by intercepting those radicals involved in the paracetamol metabolism by microsomal enzymes. By trapping oxygen related free radicals, the leaf extracts could hinder their interaction with polyunsaturated fatty acids and prevent lipid peroxidation processes. The present study clearly demonstrates that the leaf extracts which contains phytochemicals such as flavanoids and glycosides are strong antioxidants which protects the liver cells against the drug induced intoxication.

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Table 5: showing the values of Biochemical parameters Glucose, Urea, Creatinine, Cholesterol, Triglycerides and HDL cholesterol in Liver Homogenate

Group I: Normal control
Group II: Pretreatment with Trigonella foenum graecum leaf extract
Group III: Paracetamol induced hepatotoxicity
Group IV: Paracetamol with Trigonella foenum graecum leaf extract
Group V: Pretreatment with curcuma zeroderia leaf extract
Group VI: Paracetamol with curcuma zeroderia leaf extract

Parameter	Group I	Group II	Group III	Group IV	Group V	Group VI
Glucose Values are means ± S.D 'p' value	76.500 4.324 I & II < 0.05	63.666 2.160	59.166 0.752 I & III <0.05	70.500 1.048 III & IV <0.001	62.666 1.633 I & V <0.05	62.666 1.966 III & VI N.S
Urea Values are means ± S.D 'p' value	20.166 1.834 I & II N.S	17.833 0.752	34.833 1.169 I & III <0.001	18.833 0.752 III & IV <0.001	15.000 0.894 I & V < 0.05	15.000 0.632 III & VI <0.001
Creatinine Values are means ± S.D 'p' value	0.866 0.051 I & II <0.001	0.5667 0.051	1.466 0.081 I & III <0.001	0.666 0.081 III & IV <0.001	0.550 0.054 I & V <0.001	0.600 0.063 III & VI <0.001
Cholesterol Values are means ± S.D 'p' value	109.333 8.733 I & II N.S	93.833 1.169	137.333 2.065 I & III <0.05	111.833 3.311 III & IV <0.001	95.833 1.169 I & V N.S	94.333 1.032 III & VI <0.001
Triglyerides Values are means ± S.D 'p' value	59.000 5.403 I & II N.S	53.500 1.048	124.333 3.326 I & III <0.001	49.000 1.549 III & IV <0.001	56.666 0.516 I & V N.S	55.000 0.894 III & VI <0.001
HDL cholesterol Values are means ± S.D	32.000 1.673 I & II N.S	29.000 0.894	36.833 1.940 I & III N.S	28.333 1.032 III & IV <0.01	26.833 1.169 I & V <0.05	28.000 0.632 III & VI <0.01

'p' value						

'p' value < 0.001, < 0.01, < 0.05 is considered as "significant"
'p' value N.S is considered as "non-significant"

Table 6: Showing the values of Biochemical parameters Bilirubin total, Direct, Indirect, Protein, Albumin and Globulin in Liver Homogenate

Group I: Normal control
Group II: Pretreatment with Trigonella foenum graecum leaf extract
Group III: Paracetamol induced hepatotoxicity
Group IV: Paracetamol with Trigonella foenum graecum leaf extract
Group V: Pretreatment with curcuma zeroderia leaf extract
Group VI: Paracetamol with curcuma zeroderia leaf extract

Parameter	Group I	Group II	Group III	Group IV	Group V	Group VI
Bilirubin Total						
Values are means	0.550	0.433	0.683	0.466	0.400	0.383
± S.D	0.054	0.051	0.075	0.051	0.000	0.040
'p' value	I & II N.S		I & III N.S	III & IV <0.05	I & V N.S	III & VI <0.01
Bilirubin Direct						
Values are means	0.200	0.150	0.200	0.150	0.116	0.100
± S.D	0.000	0.054	0.000	0.054	0.040	0.000
'p' value	I & II N.S		I & III N.S	III & IV N.S	I & V N.S	III & VI <0.001
Bilirubin Indirect						
Values are means	0.0350	0.283	0.483	0.316	0.283	0.283
± S.D	0.054	0.040	0.075	0.075	0.040	0.040
'p' value	I & II N.S		I & III N.S	III & IV <0.05	I & V N.S	III & VI <0.01
Proteins						
Values are means	7.381	7.368	6.083	7.341	7.290	7.350
± S.D	0.116	0.116	0.075	0.051	0.054	0.075
'p' value	I & II N.S		I & III <0.001	III & IV <0.001	I & V N.S	III & VI <0.001
Albumin						
Values are means	4.375	4.350	3.102	4.292	4.413	4.326
± S.D	0.081	0.054	0.054	0.054	0.054	0.040
'p' value	I & II N.S		I & III <0.001	III & IV <0.001	I & V N.S	III & VI <0.001
Globulin						
Values are means	3.012	3.020	3.002	3.051	2.912	3.035
± S.D	0.054	0.103	0.051	0.075	0.089	0.063
'p' value	I & II N.S		I & III N.S	III & IV N.S	I & V N.S	III & VI N.S

'p' value < 0.001, < 0.01, < 0.05 is considered as "significant"
'p' value N.S is considered as "non-significant"

Table 7: Showing the values of Biochemical parameters AST, ALT, Alkaline phosphatase, GGT, LDH, CPK in Liver Homogenate

Group I: Normal control
Group II: Pretreatment with Trigonella foenum graecum leaf extract
Group III: Paracetamol induced hepatotoxicity
Group IV: Paracetamol with Trigonella foenum graecum leaf extract
Group V: Pretreatment with curcuma zeroderia leaf extract
Group VI: Paracetamol with curcuma zeroderia leaf extract

Parameter	Group I	Group II	Group III	Group IV	Group V	Group VI
AST						
Values are means	23.333	17.833	108.166	20.333	13.166	14.333
± S.D	3.614	0.752	4.490	0.816	0.983	0.516
'p' value	I & II N.S		I & III <0.001	III & IV <0.001	I & V N.S	III & VI <0.001
ALT						
Values are means	21.000	13.000	82.833	17.500	11.333	11.666
± S.D	1.264	0.894	6.080	2.429	0.516	0.816
'p' value	I & II <0.001		I & III <0.001	III & IV <0.001	I & V <0.001	III & VI <0.001
ALP	73.166	59.166	140.833	64.166	58.666	60.000

Values are means ± S.D 'p' value	3.970 I & II <0.05	1.722	1.602 I & III <0.001	1.472 III & IV <0.001	1.366 I & V <0.05	0.894 III & VI <0.001
GGT Values are means ± S.D 'p' value	20.333 0.816 I & II <0.001	12.000 1.414	93.833 2.926 I & III <0.001	17.166 1.169 III & IV <0.001	10.833 0.752 I & V <0.001	11.000 0.632 III & VI <0.001
LDH Values are means ± S.D 'p' value	101.333 2.732 I & II <0.01	85.000 4.000	204.333 5.715 I & III <0.001	99.833 1.472 III & IV <0.001	83.000 0.894 I & V <0.001	82.500 1.048 III & VI <0.001
CPK Values are means ± S.D 'p' value	32.000 1.414 I & II <0.05	26.833 1.472	65.833 3.430 I & III <0.001	25.000 0.894 III & IV <0.001	24.666 1.366 I & V <0.001	25.166 0.983 III & VI <0.001

'p' value < 0.001, < 0.01, < 0.05 is considered as "significant"
'p' value N.S is considered as "non-significant"

Table 7: showing the values of Biochemical parameters Vit.C, Vit.e, GSH, TBARS, SOD, Catalase, GPx in Liver Homogenate

Group I: Normal control
Group II: Pretreatment with Trigonella foenum graecum leaf extract
Group III: Paracetamol induced hepatotoxicity
Group IV: Paracetamol with Trigonella foenum graecum leaf extract
Group V: Pretreatment with curcuma zeroderia leaf extract
Group VI: Paracetamol with curcuma zeroderia leaf extract

Parameter	Group I	Group II	Group III	Group IV	Group V	Group VI
Vit.C Ascorbic acid Values are means ± S.D 'p' value	1.450 0.104 I & II N.S	1.383 0.075	0.850 0.054 I & III <0.001	1.366 0.051 III & IV <0.001	1.350 0.054 I & V N.S	1.333 0.051 III & VI <0.001
Vit.E Values are means ± S.D 'p' value	1.166 0.051 I & II N.S	1.216 0.075	0.750 0.054 I & III <0.001	1.200 0.063 III & IV <0.001	1.216 0.075 I & V N.S	1.183 0.075 III & VI <0.001
GSH Values are means ± S.D 'p' value	37.666 1.032 I & II N.S	36.666 1.032	20.666 1.211 I & III <0.001	36.500 1.048 III & IV <0.001	37.166 1.472 I & V N.S	37.166 0.983 III & VI <0.001
TBARS Values are means ± S.D 'p' value	2.133 0.081 I & II N.S	1.966 0.081	3.733 0.051 I & III <0.001	2.066 0.051 III & IV <0.001	1.966 0.051 I & V N.S	1.983 0.075 III & VI <0.001
SOD Values are means ± S.D 'p' value	3.116 0.075 I & II N.S	3.116 0.075	1.866 0.051 I & III <0.001	3.050 0.104 III & IV <0.001	3.200 0.063 I & V N.S	3.233 0.081 III & VI <0.001
Catalase Values are means ± S.D 'p' value	51.833 1.169 I & II N.S	50.500 1.048	27.166 0.752 I & III <0.001	50.500 1.048 III & IV <0.001	51.500 1.048 I & V N.S	51.833 0.983 III & VI <0.001
GPx Values are means ± S.D 'p' value	303.166 2.137 I & II N.S	295.000 4.472	182.166 2.228 I & III <0.001	300.166 1.169 III & IV <0.001	299.000 1.095 I & V N.S	291.833 1.602 III & VI <0.001

'p' value < 0.001, < 0.01, < 0.05 is considered as "significant"
'p' value N.S is considered as "non-significant"

Table 8: Showing the values of Biochemical parameters Glucose, Urea, Creatinine, Cholesterol, Triglycerides, HDL cholesterol in Kidney Homogenate

Group I: Normal control
Group II: Pretreatment with Trigonella foenum graecum leaf extract
Group III: Paracetamol induced hepatotoxicity
Group IV: Paracetamol with Trigonella foenum graecum leaf extract
Group V: Pretreatment with curcuma zeroderia leaf extract
Group VI: Paracetamol with curcuma zeroderia leaf extract

Parameter	Group I	Group II	Group III	Group IV	Group V	Group VI
Glucose Values are means ± S.D 'p' value	78.500 1.378 I & II N.S	66.000 1.549	59.000 0.894 I & III <0.001	70.500 1.048 III & IV <0.001	61.333 1.366 I & V <0.001	67.167 0.752 III & VI <0.001
Urea Values are means ± S.D 'p' value	20.000 0.894 I & II N.S	17.833 0.752	36.500 1.516 I & III <0.001	18.833 0.752 III & IV <0.001	16.500 1.048 I & V <0.05	18.000 0.632 III & VI <0.001
Creatinine Values are means ± S.D 'p' value	0.933 0.051 I & II <0.001	0.733 0.051	1.616 0.075 I & III <0.001	0.716 0.075 III & IV <0.001	0.733 0.051 I & V <0.001	0.833 0.051 III & VI <0.001
Cholesterol Values are means ± S.D 'p' value	108.333 9.048 I & II N.S	96.166 0.752	139.000 1.095 I & III <0.05	111.833 3.311 III & IV <0.001	97.833 1.472 I & V N.S	105.666 1.211 III & VI <0.001
Triglycerides Values are means ± S.D 'p' value	65.500 1.378 I & II <0.001	55.500 1.378	129.500 13.322 I & III <0.001	49.000 1.549 III & IV <0.001	54.833 2.137 I & V <0.001	55.666 2.582 III & VI <0.001
HDL cholesterol Values are means ± S.D 'p' value	35.666 1.378 I & II <0.001	29.500 0.836	38.166 0.752 I & III <0.05	28.333 1.032 III & IV <0.001	27.666 0.516 I & V <0.001	27.833 0.752 III & VI <0.001

'p' value < 0.001, < 0.01, < 0.05 is considered as "significant"
'p' value N.S is considered as "non-significant"

Table 9: Showing the values of Biochemical parameters Bilirubin total, Direct, Indirect, Protein, Albumin, Globulin in Kidney Homogenate

Group I: Normal control
Group II: Pretreatment with Trigonella foenum graecum leaf extract
Group III: Paracetamol induced hepatotoxicity
Group IV: Paracetamol with Trigonella foenum graecum leaf extract
Group V: Pretreatment with curcuma zeroderia leaf extract
Group VI: Paracetamol with curcuma zeroderia leaf extract

Parameter	Group I	Group II	Group III	Group IV	Group V	Group VI
Bilirubin Total Values are means ± S.D 'p' value	0.533 0.051 I & II N.S	0.433 0.051	0.483 0.040 I & III N.S	0.466 0.051 III & IV N.S	0.366 0.051 I & V <0.05	0.350 0.054 III & VI N.S
Bilirubin Direct Values are means ± S.D 'p' value	0.183 0.048 I & II N.S	0.133 0.051	0.166 0.051 I & III N.S	0.150 0.054 III & IV N.S	0.116 0.040 I & V N.S	0.100 0.000 III & VI N.S
Bilirubin Indirect Values are means ± S.D 'p' value	0.350 0.054 I & II N.S	0.300 0.000	0.316 0.040 I & III N.S	0.316 0.040 III & IV N.S	0.250 0.054 I & V N.S	0.250 0.054 III & VI N.S
Protein	7.015	7.019	6.082	7.002	7.018	7.005

Values are means ± S.D 'p' value	0.089 I & II N.S	0.081	0.075 I & III <0.001	0.051 III & IV <0.001	0.054 I & V N.S	0.793 III & VI <0.001
Albumin Values are means ± S.D 'p' value	4.230 0.075 I & II N.S	4.201 0.063	3.252 0.075 I & III <0.001	4.198 0.089 III & IV <0.001	4.205 0.054 I & V N.S	4.210 0.075 III & VI <0.001
Globulin Values are means ± S.D 'p' value	2.785 0.040 I & II N.S	2.818 0.121	2.830 0.063 I & III N.S	2.804 0.081 III & IV N.S	2.813 0.089 I & V N.S	2.795 0.175 III & VI N.S

'p' value < 0.001, < 0.01, < 0.05 is considered as "significant"
'p' value N.S is considered as "non-significant"

Table 10: Showing the values of Biochemical parameters AST, ALT, Alkaline Phosphatase, GGT, LDH, CPK in Kidney Homogenate

Group I: Normal control
Group II: Pretreatment with Trigonella foenum graecum leaf extract
Group III: Paracetamol induced hepatotoxicity
Group IV: Paracetamol with Trigonella foenum graecum leaf extract
Group V: Pretreatment with curcuma zeroderia leaf extract
Group VI: Paracetamol with curcuma zeroderia leaf extract

Parameter	Group I	Group II	Group III	Group IV	Group V	Group VI
AST Values are means ± S.D 'p' value	22.000 1.414 I & II <0.05	17.666 0.816	106.000 2.756 I & III <0.001	20.333 0.816 III & IV <0.001	13.500 1.048 I & V <0.001	14.833 0.752 III & VI <0.001
ALT Values are means ± S.D 'p' value	21.000 1.095 I & II <0.001	14.333 1.211	81.833 4.622 I & III <0.001	17.500 2.429 III & IV <0.001	11.500 0.547 I & V <0.001	12.000 0.894 III & VI <0.001
Alk. phosphatase Values are means ± S.D 'p' value	77.000 1.264 I & II <0.001	60.666 1.751	140.333 1.032 I & III <0.001	64.166 1.472 III & IV <0.001	60.166 1.169 I & V <0.001	61.833 1.169 III & VI <0.001
GGT Values are means ± S.D 'p' value	20.166 1.169 I & II <0.001	12.500 0.547	90.500 3.563 I & III <0.001	17.196 1.134 III & IV <0.001	11.833 0.752 I & V <0.001	11.666 0.516 III & VI <0.001
LDH Values are means ± S.D 'p' value	87.333 1.472 I & II N.S	86.833 2.137	197.666 7.501 I & III <0.001	99.833 1.472 III & IV <0.001	83.833 1.169 I & V <0.05	85.000 0.894 III & VI <0.001
CPK Values are means ± S.D 'p' value	28.000 1.095 I & II N.S	28.500 1.224	63.500 3.016 I & III <0.001	25.000 0.894 III & IV <0.001	26.166 0.752 I & V N.S	25.833 0.983 III & VI <0.001

'p' value < 0.001, < 0.01, < 0.05 is considered as "significant"
'p' value N.S is considered as "non-significant"

Table 11: Showing the values of Biochemical parameters Vit.C, Vit.e, GSH, TBARS, SOD, Catalase, GPx in Kidney Homogenate

Group I: Normal control
Group II: Pretreatment with Trigonella foenum graecum leaf extract
Group III: Paracetamol induced hepatotoxicity
Group IV: Paracetamol with Trigonella foenum graecum leaf extract
Group V: Pretreatment with curcuma zeroderia leaf extract
Group VI: Paracetamol with curcuma zeroderia leaf extract

Parameter	Group I	Group II	Group III	Group IV	Group V	Group VI

Vit.C Ascorbic acid Values are means ± S.D 'p' value	1.250 0.104 I & II N.S	1.483 0.075	0.850 0.054 I & III <0.01	1.366 0.051 III & IV <0.001	1.350 0.054 I & V N.S	1.300 0.063 IV & VI <0.001
Vit.E Values are means ± S.D 'p' value	1.150 0.054 I & II N.S	1.283 0.075	0.750 0.054 I & III <0.001	1.200 0.063 III & IV <0.001	1.250 0.054 I & V N.S	1.233 0.081 III & VI <0.001
GSH Values are means ± S.D 'p' value	37.833 1.169 I & II N.S	38.000 0.632	19.833 1.169 I & III <0.001	36.666 0.816 III & IV <0.001	37.500 0.547 I & V N.S	37.333 0.516 III & VI <0.001
TBARS Values are means ± S.D 'p' value	2.083 0.075 I & II N.S	2.050 0.054	3.816 0.075 I & III <0.001	2.066 0.051 III & IV <0.001	2.033 0.051 I & V N.S	2.000 0.063 III & VI <0.001
SOD Values are means ± S.D 'p' value	3.183 0.075 I & II N.S	3.266 0.051	1.933 0.051 I & III <0.001	3.033 0.081 III & IV <0.001	3.266 0.051 I & V N.S	3.266 0.051 III & VI <0.001
Catalase Values are means ± S.D 'p' value	51.833 0.752 I & II N.S	51.666 1.505	28.166 0.752 I & III <0.001	50.833 1.169 III & IV <0.001	51.833 1.169 I & V N.S	51.333 1.366 III & VI <0.001
GPx Values are means ± S.D 'p' value	300.666 1.211 1.095 I & II N.S	295.666 4.033	183.833 3.606 I & III <0.001	300.666 1.211 III & IV <0.001	299.833 0.752 I & V N.S	290.333 1.366 III & VI <0.001

'p' value < 0.001, < 0.01, < 0.05 is considered as "significant"
'p' value N.S is considered as "non-significant"

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