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Anti Tuberculosis Drug Induced Hepatotoxicity And The Hepatoprotective Effect Of The Ethanolic Leaf Extracts Of Trigonella Foenum Graecum And Curcuma Zeoderia In Albino Rats

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ABSTRACT

The hepatoprotective effect of ethanolic leaf extract of Trigonella foenum graecum and Curcuma zeoderia against anti tuberculosis drugs induced liver injury in albino rats was investigated. Ethanolic extracts from the leaves of Trigonella foenum graecum and Curcuma zeoderia at a dose level of 100 mg / ml was administered orally daily once for 5 days as pretreatment and no side effects or injury to any organ was observed. INH 15 mg/kg body wt, Rifampicin 20 mg / kg body weight, and pyrazinamide 35 mg / kg body wt for 45 days was given orally so as to induce hepatotoxicity. The substantially increased serum marker enzymes like AST, ALT, Alkaline phosphatase, GGTP, LDH, and CPK due to anti TB drugs treatment was restored towards normalization in rats treated with leaf extracts of Trigonella foenum graecum and Curcuma zeoderia. Similarly elevated values of blood urea and serum creatinine, serum cholesterol, serum triglycerides due to anti TB drug intoxication was returned to normal when rats treated with the leaf extracts. Anti TB drug induced hepatotoxicity causes the failure of the synthetic function of the liver which leads to hypoproteinemia and hypoalbuminemia as well. The protein levels are returned to normal when the animals are treated with the ethanolic leaf extracts during the drug therapy.

Due to the anti TB drugs intoxication the reduced values of non enzymic antioxidants such as ascorbic acid (vit.C), GSH, α-tocopherol (vit E) was restored to the normal level in rats treated with the leaf extracts. Anti TB drugs 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 levels of TBARS. Enzymicantioxidants such as catalase, superoxide dismutase (SOD) glutathione peroxidase (GPX) levels reduced in rats treated with anti TB drugs was restored towards normal when animals treated along with the leaf extracts. The results of this study clearly shows that the ethanolic leaf extracts of trigonella foenum graecum and curcuma zeoderia

has got potent hepatoprotective effect against anti TB drugs induced hepatotoxicity.

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 have serious side effects.[1]Phytoconstituents of herbal medicine 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 is the Indian medicine system recommended for the treatment of liver disorders. Liver is a versatile organ actively involved in many metabolic functions 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.

REVIEW OF LITERATURE

Many studies proved the Indian Spices used for cooking various food items protect our organs and safeguards our good health. Hepatoprotective effect was mediated through antioxidant mechanism, free radical scavenging, anti-inflammatory and anti fibrotic effect[4]. Previous studies show that curcuminand trigonellafoenumgraecum (turmeric and fenugreek) have got heptoprotective effects against various toxins.[5-8] The effect of leaf extracts of trigonella foenum graecum and curcuma zeoderia on drug induced liver disorders are not well established so far by biochemical mechanism. Oxidative stress is implicated as a common pathologic mechanism to the initiation and progression of hepatic damage in a variety of liver diseases. Now the recent studies emphasizes to explore the biochemical role in regulation of redox status, antioxidant defence mechanism, transcription factors protein kinases, cytokines, enzymes that have been linked to inflammation and the lipid peroxidation process, by the herbal, siddha, ayurvedha drugs which plays an important curative effects in our organ system.

SCOPE OF THE STUDY

The Indian spices used for cooking provides not only good taste but enhances protective effect to our organ system. In this study we want to explore the ameliorative effect of the leaf extracts of Trigonella foenum graecum and Curcuma zeoderia on hepatotoxicity induced by anti TB drugs.

a. To assess the extent of damage to the liver tissue by the toxins and the dearrangements in the normal metabolism.

b. To analyse the redox status and lipid peroxidation level.
c. To study the dynamic balance between prooxidant and antioxidant defense mechanism.
d. To find out the free radical scavenging status.
e. To evaluate the protective role of the leaft extracts on hepatocytes and on the whole the medicinal value of the leaf extracts which protects our organs.

METHODOLOGY

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

I. A group of six (6) albino rats weighing about 120-130 gms treated as normal control species.
II. A group of six (6) abino rats comes under the pretreatment with leaf extracts of trigonella foenum graecum (fenugreek).
III. The next group of six (6) albino rats are treated with anti TB drugs 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 anti TB drugs the leaf extracts of trigonella foenum graecum is also given and the protective role of the herb was tested.
V. A group of six albino rats comes under the pretreatment with leaf extracts of curcuma zeoderia.
VI. The last group of six albino rats along with anti TB drugs the leaf extracts of curcuma zeoderia is also given and the hepatoprotective effect was studied.

PLANT MATERIAL

1. `Trigonella foenum graecum' is a plant in a 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 compounds such as volatile oils and alkaloids such as choline, trigonelline.
2. `Curcuma zeoderia' is commonly known as turmeric (or) curcumin. It is the principal curcuminoid of the popular Indian spices turmeric which is the member of the ginger famiy "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 enolform. It is chemically known as diferuloylmethane.

IUPAC (1E, 6E), 1, 7 bis (4 hydroxy-3 methoxy 1, 6-heptadine-3, 4 dione).

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 in soxhelt 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 ± hour day-night cycle in the propylene cages. A balanced rodent pellet diet along with tapwater adlibitum 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:

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 the kidney were removed for the preparation of tissue homogenate and histopathological studies were also conducted.

GROUP II: PRETREATMENT WITH TRIGONELLA FOENUM GRAECUM LEAF EXTRACT

100 mg / ml of the Trigonella foenum graecm 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, liver and kidney tissues are collected for further investigations.

GROUP III: ANTI TB DRUGS INDUCED HEPATOTOXICITY

INH 15 mg/kg body weight, rifampicin 20 mg / kg body weight, and pyrazinamide 35 mg / kg body weight, for 45 days was given orally so as to induce hepatotoxicity[9,10]. After the treatment with the above drugs blood samples were collected as in the previous groups, the animals were sacrificed so as to collect the liver and kidneys.

GROUP IV: ANTI TB DRUGS + TRIGONELLA FOENUM GRAECUM LEAF EXTRACT ADMINISTRATION

The animals in this group are treated as in group III anti TB drugs administration is carried out along with the leaf extracts of trigonella foenum graecum at a dose level of 100 mg / ml for 45 days. Then the blood samples were collected, the animals were sacrificed to collect the liver and kidneys.

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 sacrified to collect liver and kidney tissues and blood samples were also collected.

GROUP VI: ANTI TB DRUGS + CURCUMIN LEAF EXTRACT

The animals in this group are treated with as in group III with anti TB drugs along with the leaf extracts of curcumin at a dose level of 100 mg /ml for 45 days. Then the blood samples were collected the animals were sacrificed to collect the liver and kidney tissues.

BIOCHEMICAL PARAMETERS

EDTA anticoagulant was used to collect the whole blood and it is centrifuged, to get plasma for the anlaysis of glucose and urea. Plain blood was also collected allowed 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, marker enzymes AST, ALT, ALP, GGTP, LDH, CPK, non enzymic 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 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 anti TB drugs intoxication. However in animals treated with leaf extracts and anti TB drugs 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 trigonellafoenumgraecum and curcuma zeoderiaagainst anti TB drug 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.

TABLE SHOWING THEVALUES OF BIOCHEMICAL PARAMETERS BLOOD GLUCOSE, UREA, CREATININE, CHOLESTEROL, TRIGLYCERIDES AND HDL IN BLOOD

Group-I: Normal control
Group-II: Pretreatment with trigonellafoenumgraecum leaf extract.
Group-III: Anti TB drugs induced hepatotoxicity
Group-IV: Anti TB drugs with Trigonellafoenumgraecum leaf extract
Group-V: Pretreatment with curcuma zeoderia leaf extract
Group-VI: Anti TB drugs with curcuma zeoderia 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	62.8333 0.9832 I&III N.S.	68.666 0.8165 III&IV<0.001	64.833 0.75 I&V N.S.	67.666 1.36626 III&VI<0.01
Blood urea Values are means ± S.D. `p' value	18.166 1.472 I&IIN.S.	17.500 1.643	27.3333 1.21106 I&III<0.001	18.1666 0.7527 III&IV<0.001	16.166 1.169 I&V N.S.	18.5 0.5477 III&VI<0.001
Serum Creatinine Values are means ± S.D. `p' value	0.750 0.054 I&IIN.S.	0.700 0.089	1.2 0.0632 I&III<0.001	0.7333 0.0516 III&IV<0.001	0.650 0.654 I&V.S	0.75 0.0548 III&VI<0.001
Serum Cholesterol Values are means ± S.D. `p' value	99.000 11.644 I&IIN.S.	96.666 2.943	123.5 2.1679 I&III<0.05	101.0 1.7888 III&IV<0.001	96.666 1.633 I&V N.S.	98.6666 1.2110 III&VI<0.001
Serum Triglycerides Values are means ± S.D. `p' value	48.333 2.160 I&IIN.S	52.500 1.048	100.1666 2.9269 I&III<0.001	52.0 1.4142 III&IV<0.001	53.6666 0.816 I&VN.S.	53.1666 1.1690 III&VI<0.001
HDL Cholesterol Values are means ± S.D. `p' value	28.166 1.69 I&IIN.S	30.666 1.211	34.4444 1.0327 I&III<0.001	26.5 1.3784 III&IV<0.001	28.333 1.032 I&VN.S.	26.0 0.8944 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 SHOWING THEVALUES OF BIOCHEMICAL PARAMETERS BILIRUBIN (TOTAL, DIRECT) PROTEIN, ALBUMIN, GLOBULIN AND GSH IN BLOOD

Group-I: Normal control
Group-II: Pretreatment with trigonellafoenumgraecum leaf extract.
Group-III: Anti TB drugs induced hepatotoxicity
Group-IV: Anti TB drugs with Trigonellafoenumgraecum leaf extract
Group-V: Pretreatment with curcuma zeoderia leaf extract
Group-VI: Anti TB drugs with curcuma zeoderia leaf extract

Parameter	**Group I**	**Group II**	**Group III**	**Group IV**	**Group V**	**Group VI**
Bilirubin Total	0.483	0.483	0.75	0.4333	0.433	0.4333
Values are means ± S.D.	0.075	0.075	0.0548	0.5164	0.051	0.0516
`p' value	I&IIN.S.		I&III<0.01	III&IV<0.001	I&VN.S.	III&VI<0.001
Bilirubin Direct	0.200	0.200	0.2666	0.20	0.133	0.2333
Values are means ± S.D.	0.000	0.000	0.05164	0.0	0.051	0.0516
`p' value	I&IIN.S.		I&IIIN.S.	III&IVN.S.	I&V N.S.	III&VI N.S.
Serum Proteins	4.9000	4.9100	4.4833	4.9666	4.8991	4.9166
Values are means ± S.D.	0.1414	0.1381	0.07527	0.05163	0.1414	0.0752
`p' value	I&IIN.S.		I&III<0.05	III&IV<0.001	I&V N.S.	III&VI<0.001
Serum Albumin	2.8167	2.8250	2.5333	2.8166	2.8167	2.8666
Values are means ± S.D.	0.0408	0.0516	0.0516	0.0752	0.048	0.0516
`p' value	I&IIN.S.		I&III<0.001	III&IV<0.01	I&V N.S.	III&VI<0.001
Serum Globulin	2.0833	2.0850	1.9500	2.1500	2.0824	2.0500
Values are means ± S.D.	0.0910	0.0812	0.0215	0.0124	0.0612	0.0215
`p' value	I&IIN.S.		I&IIIN.S.	III&IVN.S.	I&V N.S.	III&VIN.S.
Serum GSH	35.833	36.500	19.1666	35.8333	36.833	35.3333
Values are means ± S.D.	0.7528	1.048	0.7525	0.7528	1.169	1.6329
`p' value	I&IIN.S		I&III<0.001	III&IV<0.001	I&VN.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".

TABLE SHOWING THEVALUES OF BIOCHEMICAL PARAMETERS OF VIT C, VIT E, TBARS, SOD, CATALASE, GPX IN BLOOD

Group-I: Normal control
Group-II: Pretreatment with trigonellafoenumgraecum leaf extract.
Group-III: Anti TB drugs induced hepatotoxicity
Group-IV: Anti TB drugs with Trigonellafoenumgraecum leaf extract
Group-V: Pretreatment with curcuma zeoderia leaf extract
Group-VI: Anti TB drugs with curcuma zeoderia leaf extract

Parameter	**Group I**	**Group II**	**Group III**	**Group IV**	**Group V**	**Group VI**
Vit C	1.3667	1.400	0.81666	1.3666	1.416	1.3833
Values are means ± S.D.	0.0816	0.089	0.0752	0.08164	0.075	0.0753
`p' value	I&IIN.S.		I&III<0.001	III&IV<0.001	I&VN.S.	III&VI<0.001
Vit E	1.1667	1.216	0.8166	1.15	1.266	1.1833
Values are means ± S.D.	0.0516	0.075	0.0752	0.0547	0.081	0.0753
`p' value	I&IIN.S.		I&III<0.001	III&IV<0.001	I&V N.S.	III&VI<0.001
T BARS	2.016	2.033	3.5666	2.05	2.050	2.0833
Values are means ± S.D.	0.075	0.081	0.0816	0.0547	0.054	0.14719
`p' value	I&IIN.S.		I&III<0.001	III&IV<0.001	I&V N.S.	III&VI<0.001
SOD	3.000	3.066	1.7833	3.05	3.116	2.9166
Values are means ± S.D.	0.0894	0.121	0.0753	0.1049	0.075	0.0753
`p' value	I&IIN.S.		I&III<0.001	III&IV<0.001	I&V N.S.	III&VI<0.001
Catalase	49.833	50.000	27.0	49.833	49.833	49.5
Values are means ± S.D.	1.4720	0.894	0.8944	0.9832	0.752	1.045
`p' value	I&IIN.S.		I&III<0.001	III&IV<0.001	I&V N.S.	III&VI<0.001
GPx	300.000	301.000	186.666	297.666	299.00	295.5
Values are means ± S.D.	2.0976	1.414	1.2110	1.0328	1.095	1.045
`p' value	I&IIN.S		I&III<0.001	III&IV<0.001	I&VN.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".

TABLE SHOWING THEVALUES OF BIOCHEMICAL PARAMETERS OF AST, ALT, ALKALINE PHOSPHATASE, LDH, GGT AND CPK IN BLOOD

Group-I: Normal control
Group-II: Pretreatment with trigonellafoenumgraecum leaf extract.
Group-III: Anti TB drugs induced hepatotoxicity
Group-IV: Anti TB drugs with Trigonellafoenumgraecum leaf extract
Group-V: Pretreatment with curcuma zeoderia leaf extract
Group-VI: Anti TB drugs with curcuma zeoderia leaf extract

Parameter	**Group I**	**Group II**	**Group III**	**Group IV**	**Group V**	**Group VI**
AST	17.500	16.500	112.666	19.5	15.666	19.833
Values are means ± S.D	1.643	1.048	1.7511	1.0488	0.816	1.4719
`p' value	I&II N.S.		I&III N.S.	III&IV<0.001	I&V N.S.	III&VI<0.0001
ALT	17.166	14.333	83.666	20.1666	13.666	21.333
Values are means ± S.D.	1.722	0.816	1.0327	1.1690	0.816	1.3662
`p' value	I&IIN.S.		I&III<0.001	III&IV<0.001	I&V N.S.	III&VI<0.001
ALK PO4 ase	63.1667	65.000	116.1666	61.5	61.833	62.8333
Values are means ± S.D.	1.9408	6.542	2.4832	1.5165	1.169	1.1690
`p' value	I&IIN.S.		I&III<0.001	III&IV<0.001	I&VN.S	III&VI<0.001
LDH	93.500	65.000	123.5	97.333	86.000	96.66
Values are means ± S.D.	3.834	1.870	2.1679	2.5033	0.894	3.9832
`p' value	I&IIN.S.		I&III<0.05	III&IV<0.001	I&VN.S	III&VI<0.001
GGT	12.000	13.000	90.00	13.333	12.500	13.666
Values are means ± S.D.	1.095	0.894	1.7888	1.0327	1.048	1.0327
`p' value	I&IIN.S		I&III<0.001	III&IV<0.001	I&V N.S.	III&VI<0.001
CPK	27.1667	26.000	60.8333	24.0	26.166	25.0
Values are means ± S.D.	1.9408	1.414	1.1690	0.8944	0.752	0.8944
`p' value	I&IIN.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".

TABLE SHOWING THEVALUES OF BIOCHEMICAL PARAMETERS OF GLUCOSE, UREA, CREATININE, CHOLESTEROL, TRIGLYCERIDES AND HDL IN LIVER HOMOGENATE

Group-I: Normal control
Group-II: Pretreatment with trigonellafoenumgraecum leaf extract.
Group-III: Anti TB drugs induced hepatotoxicity
Group-IV: Anti TB drugs with Trigonellafoenumgraecum leaf extract
Group-V: Pretreatment with curcuma zeoderia leaf extract
Group-VI: Anti TB drugs with curcuma zeoderia leaf extract

Parameter	**Group I**	**Group II**	**Group III**	**Group IV**	**Group V**	**Group VI**
Glucose	76.5	63.666	83.5	78.3333	62.666	78.3333
Values are means ± S.D	4.324	2.160	1.871	1.0328	1.633	0.0753
`p' value	I&II N.S.		I&III N.S.	III&IV<0.05	I&V N.S.	III&VI NS
Urea	20.166	17.833	29.3333	19.8333	15.000	21.0
Values are means ± S.D.	1.834	0.752	0.08165	0.07527	0.894	0.0894
`p' value	I&IIN.S.		I&III<0.001	III&IV<0.001	I&V<0.05	III&VI<0.001
Creatinine	0.866	0.5667	1.35	0.8666	0.550	0.85
Values are means ± S.D.		0.051				
`p' value	0.051		0.0547	0.0516	0.054	0.0547
	I&II<0.001		I&III<0.001	III&IV<0.001	I&V N.S	III&VI<0.001
Cholesterol	109.333	93.833	127.833	111.6666	95.833	110.1666
Values are means ± S.D.						
`p' value	8.733	1.169	1.4719	1.0327	1.169	1.1690
	I&IIN.S.		I&III<0.05	III&IV<0.001	I&V N.S.	III&VI<0.001
Triglycerides	59.000	53.500	102.0	66.5	56.666	66.8333
Values are means ± S.D.						
`p' value	5.403	1.048	2.097	1.0488	0.516	0.7527
	I&IIN.S		I&III<0.001	III&IV<0.001	I&VN.S.	III&VI<0.001
HDL	32.000	29.000	37.6666	33.8333	26.833	32.6666
Values are means ± S.D.	1.673	0.894	1.0327	1.1690	1.169	1.2110
`p' value						
	I&IIN.S		I&III<0.001	III&IV<0.05	I&VN.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".

TABLE SHOWING THEVALUES OF BIOCHEMICAL PARAMETERS BILIRUBIN TOTAL, BILIRUBIN DIRECT, PROTEIN, ALBUMIN, GLOBULIN AND TBARS IN LIVER HOMOGENATE

Group-I: Normal control
Group-II: Pretreatment with trigonellafoenumgraecum leaf extract.
Group-III: Anti TB drugs induced hepatotoxicity
Group-IV: Anti TB drugs with Trigonellafoenumgraecum leaf extract
Group-V: Pretreatment with curcuma zeoderia leaf extract
Group-VI: Anti TB drugs with curcuma zeoderia leaf extract

Parameter	**Group I**	**Group II**	**Group III**	**Group IV**	**Group V**	**Group VI**
Bilirubin Total	0.550	0.433	0.7666	0.51666	0.400	0.55
Values are means ± S.D	0.054	0.051	0.0516	0.0408	0.000	0.0547
`p' value	I&II N.S.		I&III N.S.	III&IV<0.001	I&V N.S.	III&VI <0.01
Bilirubin Direct	0.200	0.150	0.333	0.2166	0.116	0.25
Values are means ± S.D	0.000	0.054	0.0516	0.0408	0.040	0.0548
`p' value	I&IIN.S.		I&III N.S.	III&IV N.S.	I&V N.S	III&VI N.S
Protein	7.381	7.368	6.115	7.312	7.290	7.298
Values are means ± 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	4.375	4.350	3.205	4.202	4.413	4.300
Values are means ± S.D.	0.081	0.054	0.054	0.040	0.054	0.040
`p' value	I&IIN.S.		I&III<0.001	III&IV<0.001	I&V N.S.	III&VI<0.001
Globulin	3.012	3.020	2.910	3.110	2.912	3.029
Values are means ± S.D.	0.054	0.103	0.051	0.075	0.075	0.063
`p' value	I&IIN.S		I&III N.S	III&IV N.S	I&VN.S.	III&VI N.S.
TBARS	2.133	1.966	3.7166	2.3333	1.966	2.3833
Values are means ± S.D.	0.0816	0.081	0.0752	0.0516	0.051	0.0753
`p' value	I&II N.S		I&III<0.001	III&IV<0.001	I&VN.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".

TABLE SHOWING THEVALUES OF BIOCHEMICAL PARAMETERS OF AST, ALT, ALKALINE PHOSPHATASE, GGT, LDH AND CPK IN LIVER HOMOGENATE

Group-I: Normal control
Group-II: Pretreatment with trigonellafoenumgraecum leaf extract.
Group-III: Anti TB drugs induced hepatotoxicity
Group-IV: Anti TB drugs with Trigonellafoenumgraecum leaf extract
Group-V: Pretreatment with curcuma zeoderia leaf extract
Group-VI: Anti TB drugs with curcuma zeoderia leaf extract

Parameter	**Group I**	**Group II**	**Group III**	**Group IV**	**Group V**	**Group VI**
AST Values are means ± S.D `p' value	23.333 3.614 I&II N.S.	17.833 0.752	100.1666 2.1369 I&III<0.001	25.1666 1.4719 III&IV<0.001	13.166 0.983 I&V N.S.	27.6666 1.0327 III&VI<0.001
ALT Values are means ± S.D `p' value	21.000 1.264 I&II <0.001	13.000 0.894	72.000 1.6733 I&III<0.001	26.5 1.3784 III&IV N.S.	11.333 0.516 I&V<0.001	26.8333 1.4719 III&VI<0.001
Alkaline phosphatase Values are means ± S.D. `p' value	73.166 3.970 I&II N.S.	59.166 1.722	137.5 1.0488 I&III<0.001	79.8333 1.1690 III&IV<0.001	58.666 1.366 I&V N.S	80.666 1.2110 III&VI<0.001
GGT Values are means ± S.D. `p' value	20.333 0.081 I&II N.S.	12.000 1.414	88.833 1.1690 I&III<0.001	24.1666 0.7527 III&IV<0.001	10.833 0.752 I&V N.S.	24.666 2.0656 III&VI<0.001
LDH Values are means ± S.D. `p' value	101.333 2.732 I&II N.S	85.000 4.000	200.5 1.378 I&III<0.001	105.6666 0.8165 III&IV N.S	83.000 0.894 I&VN.S.	106.0 1.5491 III&VI<0.001
CPK Values are means ± S.D. `p' value	32.000 1.414 I&II N.S	26.833 1.472	59.333 1.5055 I&III<0.001	35.0 1.0954 III&IV<0.001	24.666 1.366 I&V N.S.	35.333 1.2110 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 SHOWING THEVALUES OF BIOCHEMICAL PARAMETERS OF VIT C, VIT E, GSH, SOD, CATALASE, GPX IN LIVER HOMOGENATE

Group-I: Normal control
Group-II: Pretreatment with trigonellafoenumgraecum leaf extract.
Group-III: Anti TB drugs induced hepatotoxicity
Group-IV: Anti TB drugs with Trigonellafoenumgraecum leaf extract
Group-V: Pretreatment with curcuma zeoderia leaf extract
Group-VI: Anti TB drugs with curcuma zeoderia leaf extract

Parameter	**Group I**	**Group II**	**Group III**	**Group IV**	**Group V**	**Group VI**
VIT C	1.450	1.383	0.8666	1.3666	1.350	1.400
Values are means ± S.D	0.104	0.075	0.0516	0.0516	0.054	0.0632
`p' value	I&II N.S.		I&III<0.001	III&IV<0.001	I&V N.S.	III&VI<0.001
VIT E	1.166	1.216	0.7333	1.1333	1.216	1.1
Values are means ± S.D	0.051	0.075	0.0516	0.0516	0.075	0.0632
`p' value	I&II N.S		I&III<0.001	III&IV<0.001	I&V N.S	III&VI<0.001
GSH	37.666	36.666	20.3333	35.1666	37.166	35.1666
Values are means ± S.D.	1.032	1.032	0.8165	0.7527	1.472	0.7527
`p' value	I&II N.S.		I&III<0.001	III&IV<0.001	I&V N.S	III&VI<0.001
SOD	3.116	3.116	1.8333	2.9166	3.200	2.8333
Values are means ± S.D.	0.075	0.075	0.0516	0.7527	0.063	0.1032
`p' value	I&II N.S.		I&III<0.001	III&IV<0.001	I&V N.S.	III&VI<0.001
Catalase	51.833	50.500	27.1666	49.3333	51.500	47.3333
Values are means ± S.D.	1.169	1.048	0.9831	1.0327	1.048	0.8164
`p' value	I&II N.S		I&III<0.001	III&IV<0.001	I&VN.S.	III&VI<0.001
GPx	303.166	295.000	196.833	290.666	299.000	287.00
Values are means ± S.D.	2.137	4.472	1.4719	1.211	1.095	1.4142
`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".

TABLE SHOWING THEVALUES OF BIOCHEMICAL PARAMETERS OF GLUCOSE, UREA, CREATININE, CHOLESTEROL, TRIGLYCERIDES AND HDL IN KIDNEY HOMOGENATE

Group-I: Normal control
Group-II: Pretreatment with trigonellafoenumgraecum leaf extract.
Group-III: Anti TB drugs induced hepatotoxicity
Group-IV: Anti TB drugs with Trigonellafoenumgraecum leaf extract
Group-V: Pretreatment with curcuma zeoderia leaf extract
Group-VI: Anti TB drugs with curcuma zeoderia leaf extract

Parameter	**Group I**	**Group II**	**Group III**	**Group IV**	**Group V**	**Group VI**
Glucose	78.500	66.000	68.666	75.000	61.333	74.166
Values are means ± S.D	1.378	1.549	1.032	1.414	1.366	1.602
`p' value	I&II N.S.		I&III<0.001	III&IV<0.001	I&V<0.001	III&VI <0.01
Urea	20.000	17.833	29.00	20.500	16.500	19.833
Values are means ± S.D.	0.894	0.752	0.894	1.048	1.048	1.169
`p' value	I&II N.S.		I&III<0.001	III&IV<0.001	I&V 0.05	III&VI<0.001
Creatinine	0.933	0.733	1.416	0.9166	0.733	0.883
Values are means ± S.D.	0.051	0.051	0.075	0.075	0.051	0.075
`p' value	I&II<0.001		I&III<0.001	III&IV<0.001	I&V<0.001	III&VI<0.001
Cholesterol	108.333	96.166	126.00	107.00	97.833	108.500
Values are means ± S.D.	9.048	0.752	1.414	1.788	1.472	2.428
`p' value	I&II N.S.		I&III<0.05	III&IV<0.001	I&V N.S.	III&VI<0.001
Triglycerides	65.500	55.500	119.833	68.833	54.833	69.833
Values are means ± S.D.	1.378	1.378	4.262	1.169	2.137	1.471
`p' value	I&II<0.001		I&III<0.001	III&IV<0.001	I&V<0.001	III&VI<0.001
HDL	35.666	29.500	37.500	33.333	27.666	32.5
Values are means ± S.D.	1.378	0.836	1.048	0.816	0.516	1.049 III&VI<0.001
`p' value	I&II N.S		I&III N.S	III&IV<0.01	I&V<0.001	

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

TABLE SHOWING THEVALUES OF BIOCHEMICAL PARAMETERS OF BILIRUBIN TOTAL, BILIRUBIN DIRECT, PROTEIN, ALBUMIN, GLOBULIN AND TBARS IN KIDNEY HOMOGENATE

Group-I: Normal control
Group-II: Pretreatment with trigonellafoenumgraecum leaf extract.
Group-III: Anti TB drugs induced hepatotoxicity
Group-IV: Anti TB drugs with Trigonellafoenumgraecum leaf extract
Group-V: Pretreatment with curcuma zeoderia leaf extract
Group-VI: Anti TB drugs with curcuma zeoderia leaf extract

Parameter	**Group I**	**Group II**	**Group III**	**Group IV**	**Group V**	**Group VI**
Bilirubin Total	0.533	0.433	0.633	0.433	0.366	0.433
Values are means ± S.D	0.051	0.051	0.051	0.056	0.051	0.056
`p' value	I&II N.S.		I&III N.S.	III&IV<0.001	I&V <0.05	III&VI <0.01
Bilirubin Direct	1.183	0.133	0.25	0.150	0.116	0.133
Values are means ± S.D	0.048	0.051	0.054	0.054	0.040	0.052
`p' value	I&II N.S.		I&III N.S.	III&IV N.S.	I&V N.S	III&VI N.S
Protein	5.200	5.195	4.766	5.033	5.190	5.066
Values are means ± S.D.	0.051	0.054	0.081	0.081	0.054	0.051
`p' value	I&II N.S.		I&III<0.001	III&IV<0.05	I&V N.S	III&VI<0.01
Albumin	2.916	2.911	2.450	2.833	2.882	2.856
Values are means ± S.D.	0.075	0.051	0.054	0.051	0.075	0.054
`p' value	I&II N.S.		I&III<0.001	III&IV<0.001	I&V N.S.	III&VI<0.001
Globulin	2.283	2.284	2.316	2.200	2.308	2.210
Values are means ± S.D.	0.075	0.048	0.075	0.089	0.051	0.075
`p' value	I&II N.S		I&III N.S	III&IV N.S	I&V N.S.	III&VI N.S.
TBARS	2.083	0.050	3.566	2.166	2.033	2.200
Values are means ± S.D.	0.075	0.054	0.081	0.081	0.051	0.089
`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".

TABLE SHOWING THEVALUES OF BIOCHEMICAL PARAMETERS OF AST, ALT, ALKALINE PHOSPHATASE, GGT, LDH AND CPK IN KIDNEY HOMOGENATE

Group-I: Normal control
Group-II: Pretreatment with trigonellafoenumgraecum leaf extract.
Group-III: Anti TB drugs induced hepatotoxicity
Group-IV: Anti TB drugs with Trigonellafoenumgraecum leaf extract
Group-V: Pretreatment with curcuma zeoderia leaf extract
Group-VI: Anti TB drugs with curcuma zeoderia leaf extract

Parameter	**Group I**	**Group II**	**Group III**	**Group IV**	**Group V**	**Group VI**
AST	22.00	17.666	93.00	23.833	13.500	25.5
Values are means ± S.D	1.414	0.816	1.788	0.752	1.048	1.048
`p' value	I&II <0.05		I&III<0.001	III&IV<0.001	I&V<0.001	III&VI<0.001
ALT	21.000	14.333	88.00	22.166	11.500	24.333
Values are means ± S.D	1.095	1.211	2.366	1.169	0.547	1.032
`p' value	I&II <0.001		I&III<0.001	III&IV<0.001	I&V<0.001	III&VI<0.001
Alkaline phosphatase	77.000	60.666	134.333	80.000	60.166	78.666
Values are means ± S.D.	1.264	1.751	1.751	1.414	1.169	0.816
`p' value	I&II <0.001		I&III<0.001	III&IV<0.001	I&V<0.001	III&VI<0.001
GGT	20.166	12.500	89.666	25.166	11.833	27.166
Values are means ± S.D.	1.169	0.547	1.751	1.472	0.752	0.753
`p' value	I&II <0.001		I&III<0.001	III&IV<0.001	I&V<0.001	III&VI<0.001
LDH	87.333	86.833	194.666	94.500	83.333	94.666
Values are means ± S.D.	1.472	2.137	1.966	1.378	1.169	1.751
`p' value	I&II N.S		I&III<0.001	III&IV<0.001	I&V<0.05	III&VI<0.001
CPK	28.000	28.500	58.166	31.333	26.166	32.166
Values are means ± S.D.	1.095	1.224	1.169	0.817	0.752	1.169
`p' value	I&II N.S		I&III<0.001	III&IV<0.001	I&V N.S.	III&VI<0.001

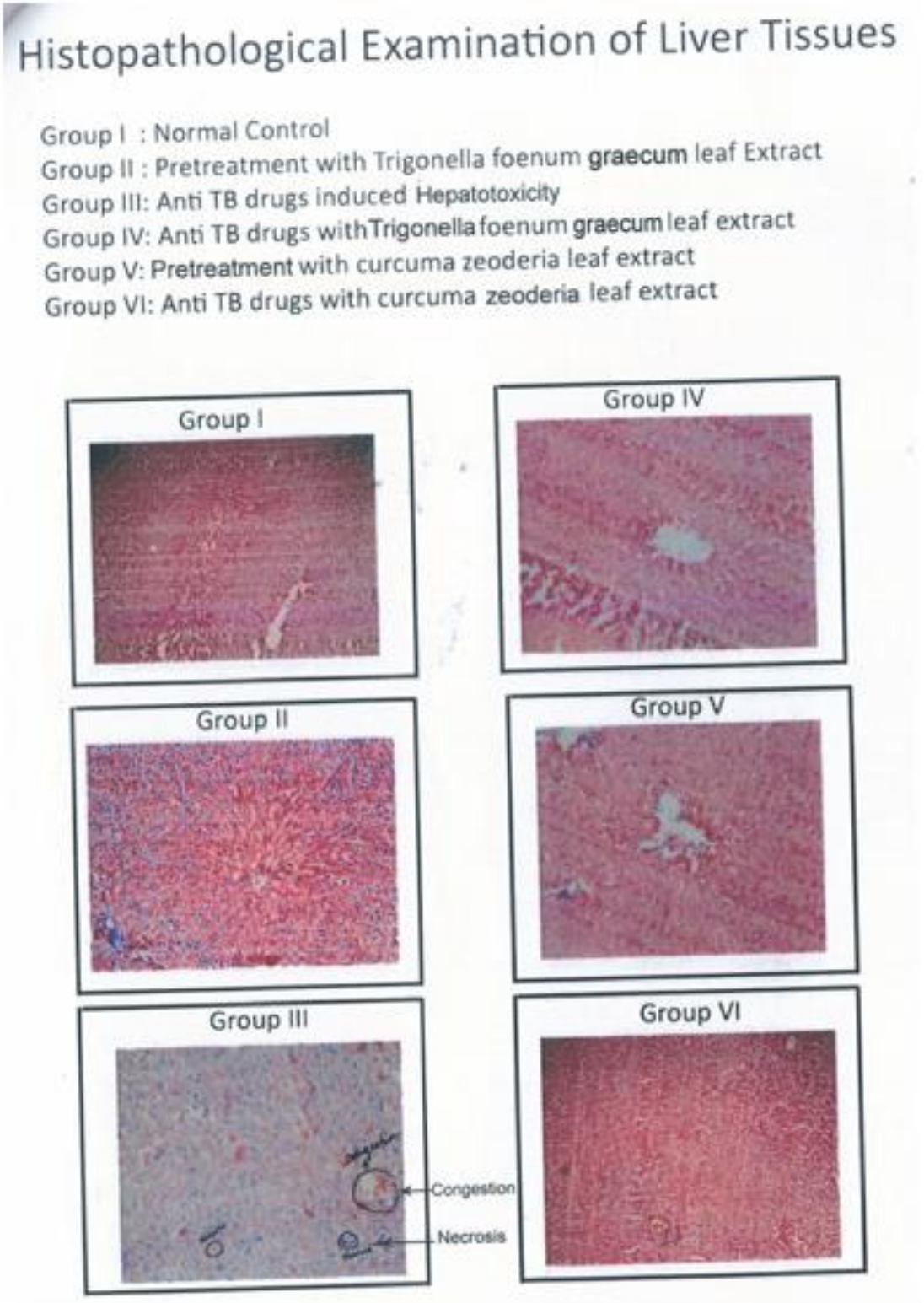
`p' value < 0.001, <0.01, <0.05 is considered as significant.
`p' value N.S. is considered as "non-significant".

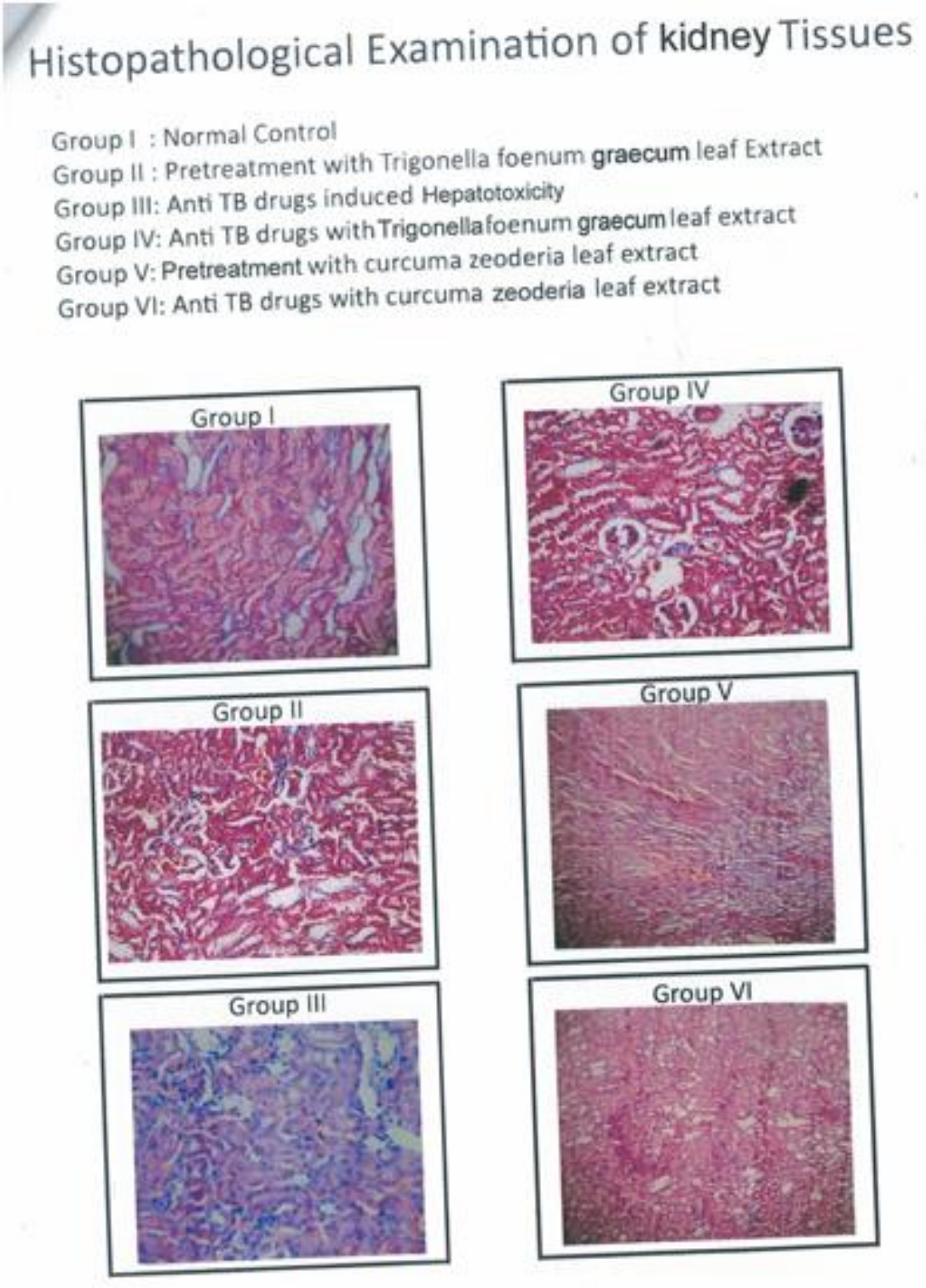
TABLE SHOWING THEVALUES OF BIOCHEMICAL PARAMETERS OF VIT C, VIT E, GSH, SOD, CATALASE, GPX IN KIDNEY HOMOGENATE

Group-I: Normal control
Group-II: Pretreatment with trigonellafoenumgraecum leaf extract.
Group-III: Anti TB drugs induced hepatotoxicity
Group-IV: Anti TB drugs with Trigonellafoenumgraecum leaf extract
Group-V: Pretreatment with curcuma zeoderia leaf extract
Group-VI: Anti TB drugs with curcuma zeoderia leaf extract

Parameter	**Group I**	**Group II**	**Group III**	**Group IV**	**Group V**	**Group VI**
VIT C	1.250	1.483	0.850	1.266	1.350	1.216
Values are means ± S.D	0.104	0.075	0.054	0.051	0.054	0.048
`p' value	I&II N.S.		I&III<0.001	III&IV<0.001	I&V N.S.	III&VI<0.001
VIT E	1.150	1.283	0.750	1.166	1.250	1.150
Values are means ± S.D	0.054	0.075	0.054	0.082	0.054	0.055
`p' value	I&II N.S		I&III<0.001	III&IV<0.001	I&V N.S	III&VI<0.001
GSH	37.833	38.000	19.166	35.833	37.500	35.666
Values are means ± S.D.	1.169	0.632	1.169	0.752	0.547	1.366
`p' value	I&II N.S.		I&III<0.001	III&IV<0.001	I&V N.S	III&VI<0.001
SOD	3.183	3.266	1.983	2.933	3.266	2.816
Values are means ± S.D.	0.075	0.051	0.075	0.121	0.051	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	51.833	51.666	28.500	49.500	51.833	48.5
Values are means ± S.D.	0.752	1.505	0.548	0.548	1.169	0.548
`p' value	I&II N.S		I&III<0.001	III&IV<0.001	I&VN.S.	III&VI<0.001
GPx	300.666	295.666	194.500	296.00	299.833	293.00
Values are means ± S.D.	1.211	4.033	1.378	1.414	0.752	1.265
`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".


Histopathological Examination of Liver Tissues
Group I : Normal Control
Group II : Pretreatment with Trigonella foenum graecum leaf Extract
Group III: Anti TB drugs induced Hepatotoxicity
Group IV: Anti TB drugs with Trigonella foenum graecum leaf extract
Group V: Pretreatment with curcuma zeoderia leaf extract
Group VI: Anti TB drugs with curcuma zeoderia leaf extract
Group I
Group IV
Group II
Group V
Group III
Group VI
Congestion
Necrosis


Histopathological Examination of kidney Tissues
Group I : Normal Control
Group II : Pretreatment with Trigonella foenum graecum leaf Extract
Group III: Anti TB drugs induced Hepatotoxicity
Group IV: Anti TB drugs with Trigonella foenum graecum leaf extract
Group V: Pretreatment with curcuma zeoderia leaf extract
Group VI: Anti TB drugs with curcuma zeoderia leaf extract
Group I
Group II
Group III
Group IV
Group V
Group VI

DISCUSSION

In the present study it was noted that in animals treated with anti tuberculosis drug there is elevated levels of blood urea, serum creatinine, serum cholesterol, serum triglycerides as in group III indicated that anti TB drugs induces acute renal failure and causes fatty liver as well. When animals treated along with the left extract of Trigonellafernumgraecum and Curcuma zeoderia the above levels are restored to normal as in group IV and group VI, clearly shows a protection against the injurious effects of anti TB drugs that may result from the interference with cytochrome P.450, resulting in the hindrance of the formation of hepatotoxic 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 anti TB drug intoxicated rats were significantly reduced in group IV and group VI animals treated with the leaf extracts. The 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, $\alpha_1$globulin α_2 globulin, β globulin, and fibrinogen. Due to the anti TB drug intoxication 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 anti TB drugs and the leaf extracts of Trigonellafoenumgraecum 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 the enzymes originally present in higher concentration in cytosol or mitochondria of the hepatic cells. When there is hepatopathy these enzymes leak into blood stream in conformity with the extent of liver damage. The elevated levels of these entire marker enzymes observed in group III anti TB drug 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 action of the leaf extracts of trigonellafoenumgraecum and curcuma zeoderia.

NONENZYMIC ANTIOXIDANTS (Vit C, Vit E, GSH)

Vit C is a water soluble naturally occurring 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 anti TB drug treated animals while the levels of vit C was not altered in rats treated with leaf extracts of Trigonella foenum graecum and curcuma zeoderia along with anti TB drugs. The decrease could be due to the increased utilization of vitamin C, as an antioxidant

defense against increased (ROS) Reactive Oxygen Species or could be due to the 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 anti TB drug induced liver injury as in group III could be due to increased utilization in scavenging the oxy radicals generated or could be due to vitamin C low concentration because there is a well established interaction between vitamin E and vitamin C.
In albino rats treated with leaf extracts of Trigonellafoenumgraecum and curcuma zeoderia along with anti TB 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 Trigonellafoenumgraecum and curcuma zeoderia have hepatoprotective action on liver cells due to its antioxidant properties, prevents lipid peroxidation and helps in scavenging free radical 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 the enzyme glutathione peroxidase (GPx) and as a scavenger of vitamin C and vitamin E radicals[(15)]. In our study the serum GSH concentration significantly decreased in anti TB drug induced liver injury as in group III animals. It may be due to an increased utilization of GSH. New GSH may be recovered from the oxidized 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 utilization and decreased formation during anti TB drug induced hepatotoxicity because of increased lipid peroxidation.

Lipid peroxidation (TBARS)

There is marked increase in the concentration of Thiobarbituric acid reactive substances in animals treated with Anti TB drugs. 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 anti TB drugs, 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 catalyseddismutation 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 SOD2 die several days after birth due to massive oxidative stress, mice lacking SOD develop a wide range of pathologies including hepatocellular carcinoma.

Catalase is a powerful antoxidant 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. $H_2O_2 \rightarrow$ H2O + (O).

Glutathione peroxidase plays a vital role in the antioxidant defense mechanism. It is a selenium dependent enzyme (GPX) catalyses peroxide reduction utilizing GSH as the substrate and converting it into GSSG(18). In our study the levels of SOD, catalase, and glutathione peroxidase in plasma, liver and kidney tissue found to be diminished to a very low level (p value <0.001) in albino rats treated with anti TB drugs. The decrease may be due to oxidative stress and generation of ROS which causes liver injury. Increased utilization of these enzymes SOD, catalse and GPX by the system leads to a decrease in their concentration. When the animals treated with the leaf extracts of trigonellafoenumgraecum and curcuma zeoderia along with anti TB drugs as in group IV and VI due to the hepatoprotective effect of these leaf extracts the values of SOD, catalase, GPX remains unaltered (`p' value group III & IV is < 0.001 and `p' value for group III & VI is < 0.001).It clearly indicates the hepotoprotective action of these leaf extracts to the liver cells against anti TB drug induced heptotoxicity, due to their antioxidant role in scavenging the free radicals and reactive oxygen species (ROS).

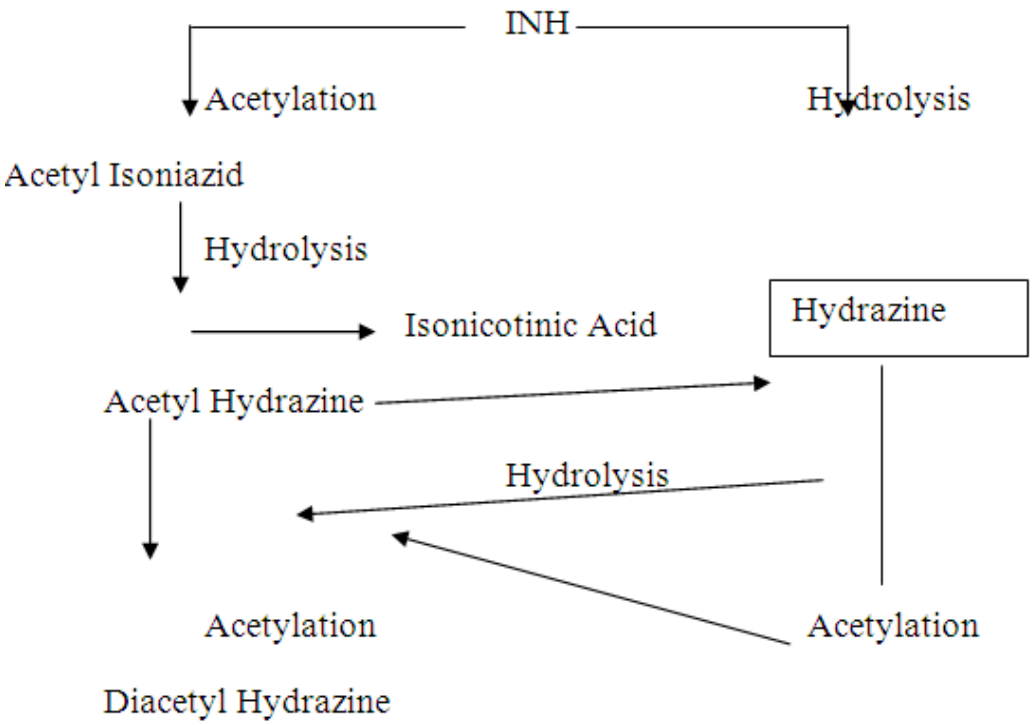
In albino rats treated with the leaf extracts of Trigonellafoenumgraecum and curcuma zeoderia alongwith anti TB drug as in group IV and VI animals the increased levels of TBARS are restored to the normal level, and the altered values of GSH SOD, catalase and GPX are also returned to the normal control level. It clearly demonstrates that these leaf extracts have got potent hepatoprotectiveaction due to its antioxidant properties as well as its ability to decrease the formation of Proinflammatory cytokines.

Anti Tuberculosis drug

The treatment and management of Tuberculosis is a 6 months course of Isoniazid, rifampicin, pyrazinamide and ethambutol. Compliance is important for curing tuberculosis. Most of the case studies show that INH induced hepatotoxicity manifests mainly as hepatocellular steatosis and necrosis and it has been suggested that toxic metabolites bind covalently to cell macromolecules (19-21). Rifampicin causes hepatic lesions characterized by hepatocellular changes with centrilobular necrosis.

INH induced hepatotoxicity is mainly caused by toxic metabolites. Most anti TB drugs are liposouble and their elimination requires biotransformation into more water soluble compounds. It is done by cytochrome P-450 (CYP-450) enzymes followed by glucuronidation or sulfation resulting in toxic metabolites which can easily be eliminated. Also the metabolic step by which detoxification involved glutathione which can covalently bind to toxic compounds by the enzyme glutathione-Stransferase (22). The predominant metabolic pathway of INH metabolism is acetylation by hepatic enzyme N-acetyl transferase-2 (NAT-2). Isoniazid (Isonicotinic acid hydrazide, INH) is acetylated into acetyl isoniazid and then hydrolysed into acetyl hydrazine and isonicotinic acid. Acetyl hydrazine is either hydrolysed to hydrazine (or) again acetylated into diacetylhydrazine (23).

INH METABOLISM



Most previous workers prove that acetyl hydrazine is the toxic metabolite of INH (24). But most recent studies shows that hydrazine and not INH (or) acetyl hydrazine is most likely to be the cause of INH induced hepatotoxicity(25). Rifampicin is the potent inducer of the hepatic CYP-450 system in the liver and in the intestine, thereby increasing metabolism of many other compounds. Rifampicin induces INH hydrolase increasing hydrazine production which explains the higher toxicity when combined with INH (i.e. INH + R).

CONCLUSION

In conclusion the ethanolic leaf extracts of trigonellafoneumgraecum and curcuma zeoderia afforded hepatoprotectiveaction against anti TB drug 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 anti TB drug 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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