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ANTIOXIDANT AND LIPID LOWERING EFFECTS OF *ELAEOCARPUS GANITRUS* IN CHOLESTEROL FED RABBITS

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ABSTRACT: *Elaeocarpus ganitrus* Roxb. is reported to exhibit multifarious pharmacological activities. However no scientific study has been conducted to evaluate antiatherosclerotic /lipid lowering activity of *E. ganitrus* Roxb. The present study was designed to investigate the antihyperlipidaemic and antioxidant activity of 70% ethanolic extract of *E. ganitrus* seed (EGEE) in cholesterol fed hyperlipidaemic rabbits. The EGEE was administered at a dose level of 250 and 500 mg/kg/day (p.o.) for 60 days to hyperlipidaemic rabbits. Lipid profile in serum and antioxidant parameters in tissues (Liver, Heart and Aorta) were determined. The statistical analysis was carried out using one way ANOVA followed by Tukey's multiple comparison tests. EGEE showed a decrease in the levels of serum total cholesterol, triglycerides, phospholipids, LDL, VLDL ($P \leq 0.01$, ≤ 0.001) in a dose dependant manner in treated animals. HDL ratio improved profoundly as well as marked decline was noticed in atherogenic index after administration with EGEE. A considerable decrease in lipid per oxidation and a significant elevation in Glutathione, Catalase and SOD levels ($P \leq 0.01$, ≤ 0.001) were observed in EGEE treated rabbits. The overall experimental results suggests that the biologically active phytoconstituents such as phytosterols, fats, alkaloids, flavonoids, carbohydrates, proteins and tannins present in the EGEE may be responsible for the significant hypolipidaemic as well as antioxidant activity, signifying the potential protective role in coronary heart disease.

INTRODUCTION: In the face of unremitting advances in therapeutic interventional and surgical therapies for the treatment of atherosclerotic coronary disease the later remains the principal killer in the western and the developing world.¹ Dyslipidaemia and resultant atherosclerosis are believed to stem from the imbalance of the lipid metabolites in the affected organism.

Hyperlipidaemia (mainly increased level of total cholesterol (TC), triglycerides (TG) and low-density lipoprotein (LDL) cholesterol along with decrease in high-density lipoprotein (HDL) cholesterol contributes significantly to the manifestation and development of atherosclerosis and coronary heart diseases (CHDs).²

The World Health Organization report emphasizes that the cardio vascular diseases to be the leading cause of death and disability in India by 2020. It is usually established that oxidative stress is strongly related to atherogenesis.³ An antioxidant which inhibits oxidation of LDL should be effective for suppressing atherosclerosis.⁴

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Elaeocarpus ganitrus Roxb. belongs to family Elaeocarpaceae is a large evergreen broad-leaved tree. In Hindi it is recognized as Rudraksha⁵ is prevalent for its fascinating fruit stones and medicinal properties.

The widespread investigation of literature exposed that *E. ganitrus* Roxb. is an imperative basis of various pharmacologically and medicinally significant chemicals, such as indispensable triterpenes, tannins like geraniin and 3, 4, 5-trimethoxy geraniin, indolizidine alkaloids grandisines, rudrakine and flavnoids quercetin.

Furthermore it is noted to have myriad pharmacological activities that involve anti-inflammatory,⁷ analgesic,⁸ hypoglycemic,⁹ antidepressant,¹⁰ antiasthmatic,¹¹ sedative,⁸ antihypertensive,¹² antiulcerogenic,¹¹ anticonvulsant,¹³ and antimicrobial.¹⁴ As per our literature survey, no scientific study has been conducted to evaluate antiatherosclerotic/ cholesterol lowering activity of *E. ganitrus* Roxb. With this background information, the present study is undertaken to screen *E. ganitrus* Roxb. for its ability to decrease

lipid levels as well as antioxidant activity in hyperlipidaemic rabbits.

MATERIALS AND METHODS:

Collection of plant material: Authentic seeds of *E. ganitrus* were obtained from Jayoti Vidyapeeth Women's University, Jaipur and authenticated by authority of Department of Botany, University of Rajasthan, Jaipur. A voucher specimen number (RUBL21180) was submitted at University herbarium department for future reference.

Extraction of plant material: The seeds were coarsely powdered and extracted with 70% ethanol for 48 hrs, by soxhlet extraction method. Then ethanol was filtered and then separated under reduced pressure to obtain solid mass in a rotary evaporator and this was stored in a desiccator. Ethanolic extract of *E. ganitrus* seed contains indolizidine types of alkaloids, flavanoids, tannins, carbohydrate and proteins.¹⁵ Some dominant phytoconstituents in ethanolic extract of *E. ganitrus* which possess hypolipidaemic and antioxidant activity are depicted as:

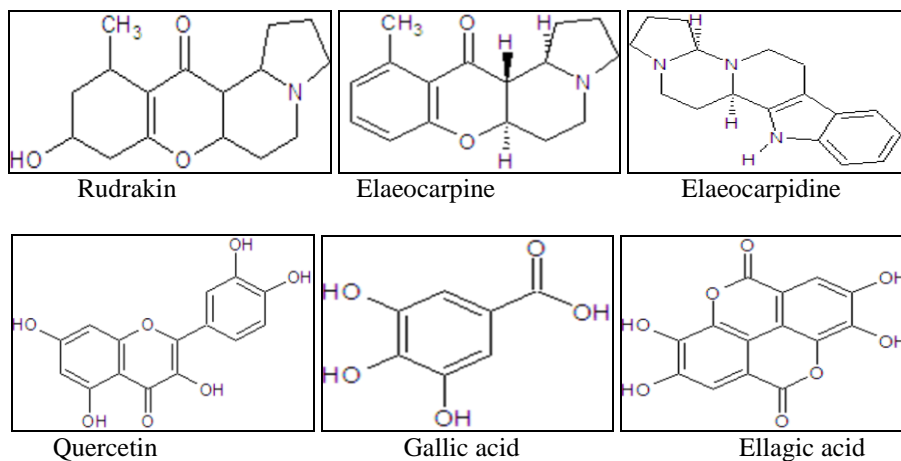


FIG. 1: CHEMICAL CONSTITUENTS OF *ELAEOCARPUS GANITRUS* ROXB.

Animal model: New Zealand white male rabbits weighing 1.50-2.0 kg were used in the study. The animals were acclimatized for 10 days before being used for the experiments. The animals were grouped (5 rabbits in each group) and housed in polypropylene cages at constant temperature and also maintained under a standard diet (Ashirwad Industrial Ltd., Punjab) and green leafy vegetables and water *ad libitum*. Experimental dose was administered to rabbits orally via gavage. The experimental protocol was approved by

Institutional Animal Ethical Committee (IAEC) and was executed according to the guidelines of Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA), India.

Acute Toxicity Study: The acute toxicity of the EGEE was determined using Albino mice weighing 20-25 gm. Animals were maintained on normal diet and water prior to and during the course of experiment. Fixed dose (OECD Guideline No. 423)

method of CPCSEA was adopted for the toxicity studies. EGEE was nontoxic and caused no mortality up to 5g/Kg orally in mice. Therefore, the LD₅₀ value of EGEE is >5g/Kg of body weight.

Experimental design:

The rabbits were divided into following groups:

Group I: Control –Placebo treated for 120 days.

Group II a: Cholesterol feeding for 60 days

Group II b: Cholesterol feeding for 120 days

Group III: Cholesterol feeding for 60 days then no treatment for next 60 days (*i.e.* from day 61-120)

Group IV a : Cholesterol feeding for 60 days then treated with 250 mg/Kg ethanolic extract of EGEE for next 60 days.

Group IV b: Cholesterol feeding for 60 days then treated with 500mg/Kg ethanolic extract of EGEE for next 60 days.

Cholesterol feeding: 500 mg cholesterol/kg. b. wt./rabbit/day in 5ml coconut oil Animal were sacrificed after completion of treatment, blood and tissue were taken out for biological examinations.

Induction of Hyperlipidaemia: Hyperlipidaemia was induced in New Zealand white male rabbits by daily oral administration of 500 mg cholesterol/kg. b. wt. /rabbit/day in 5ml coconut oil.

Collection of blood: On the 61st day or 121st day of respective treatment blood was collected by cardiac puncture, under mild ether anaesthesia and the serum was separated by centrifugation after 30 minutes and stored at -20°C for biochemical analysis.

Biochemical analysis: The serum total cholesterol, triglycerides, phospholipids, high - density lipoprotein (HDL), low density lipoprotein (LDL) were measured in an autoanalyzer using special kits (Accurex, Biomedical Pvt. Ltd.) and very low density cholesterol was calculated by using formula VLDL: TG/5. Tissues (Liver, Heart and Aorta) were homogenized by homogenizer and analysed for antioxidant parameters *i.e.* Lipid Peroxidation, ¹⁶ Catalase, ¹⁷ Glutathione, ¹⁸ and Super Oxide Dismutase (SOD). ¹⁹ HDL Ratio, ²⁰ Atherogenic Index and Deviation Percentage were calculated as:

$$\text{HDL Ratio} = \frac{\text{HDL Cholesterol}}{\text{Total Cholesterol} - \text{HDL Cholesterol}} \times 100$$

$$\text{Atherogenic Index} = \frac{\text{LDL-Cholesterol} + \text{VLDL- Cholesterol}}{\text{HDL Cholesterol}}$$

$$\text{Deviation Percent} = \frac{\text{Final Value} - \text{Initial value}}{\text{Initial Value}} \times 100$$

Statistical analysis

The results were expressed as mean±S.E.M. Statistical analysis was carried out by using One way ANOVA followed by Tukey's multiple comparison tests using Graphpad PRISM software (version 5). P values <0.05 were considered as statistically significant.

RESULTS AND DISCUSSION: Findings of the current study suggested that administration with EGEE significantly attenuated the elevated total cholesterol, triglyceride, phospholipid, lipoprotein cholesterol (HDL, LDL and VLDL) concentrations in cholesterol induced hyperlipidaemic rabbits. A marked reduction was also observed in atherogenic index and the HDL ratio improved significantly after supplementation with seed extract at a dose level of 250 and 500 mg/kg b.wt/day.

As **Table 1** illustrated that rabbits fed on cholesterol (Group–IIa and IIb) showed a highly significant rise ($P \leq 0.001$) in the concentration of serum total cholesterol level as compared to control. Whereas, the total cholesterol levels of groups treated with 250 and 500 mg/kg/day EGEE were significantly reduced -63.19% and -70.02% respectively when compared to group-IIb animals and a decline of only -22.65% was noticed in no treatment group. Further, IVa and IVb group animals showed significant fall ($P \leq 0.001$) in the level of total cholesterol in comparison to no treatment group rabbits.

A significant elevation in serum cholesterol level after cholesterol feeding in rabbits were probably due to the overproduction of VLDL in the liver or by delayed catabolism of VLDL or both. ^{21, 22} The reduction in serum cholesterol level after treatment with EGEE may be due to improved elimination of LDL from plasma by mounting LDL-receptor activity.²³

The strong presence of flavonoids in extract may contribute to antihypercholesterolemic effect as they decrease the levels of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) and decrease in apo- B secretion in hepatocytes.^{24, 25}

Further as shown in **Table 1**, serum triglyceride level was trending upward in hyperlipidaemic groups IIa, IIb ($P \leq 0.001$) when compared to control but the downward trend was observed in the treatment group ($P \leq 0.001$) at various doses *i.e.* 250 mg and 500 mg/kg.b.wt/day in comparison to hyperlipidaemic group IIb. Treatment groups showed -49.08% and -66.41% reductions in serum triglyceride level whereas no treatment group showed only -26.65% reduction when compared to hyperlipidaemic rabbits. Extract treated group further demonstrated a significant decrease ($P \leq 0.01$, $P \leq 0.001$) in triglyceride level when compared to group III animals.

Cholesterol feeding elevates serum triglyceride levels essentially by preventing its uptake and clearance by inhibiting catabolising enzymes like lipoprotein lipase (LPL) and lecithin cholesterol acetyl transferase (LCAT).²⁶ EGEE significantly suppresses the elevated blood concentration of TGs through increased expression and activity of lipoprotein lipase (LPL) and to decrease hepatic synthesis and secretion of triglycerides.²⁷ It could be due to inhibition of lipolysis so that fatty acid do not get converted into triglyceride.²⁸

Serum phospholipid concentration demonstrated an increment after 60 days and 120 days of cholesterol feeding when compared to control rabbits as depicted in **Table 1**. A significant decline ($P \leq 0.001$) was noticed in post-treatment with EGEE (*i.e.* dose 250 mg/kg.b.wt./day reduction was -32.81% and 500mg/kg.b.wt/day reduction was -67.34%) whereas in no treatment group reduction was -13.39% when compared to group IIb animals.

It could be clearly observed from **Table 1**, that treatment with EGEE extract resulting in a marked decrease in phospholipid level as compared to the level of the no treatment hypolipidaemic animals ($P \leq 0.01$ and $P \leq 0.001$). The reduction in phospholipid levels in EGEE treated animals possibly due to a higher level of phospholipase that metabolized the blood phospholipids in cholesterol fed animals.²⁹

In the present study, there was elevation in serum LDL level in response to cholesterol feeding as compare to normal control group. (**Table 1**) In contrast, as depicted in **Table 1** the EGEE extract produced a significant decrease ($P \leq 0.001$) in the levels of LDL-cholesterol (*i.e.* reduction was -71.24 % in 250 mg./kg.b.wt./day and -80.73% in 500 mg./kg.b.wt./day) when compared with hyperlipid- aemic rabbits (Group IIb). LDL level was brought down to only -23.94% in no treatment group (Group III). A significant fall ($P \leq 0.001$) was noticed after oral administration of EGEE at various doses (250mg and 500mg/kg.b.wt/day) when compared to no treatment hyperlipidaemic rabbits. One of the key steps in the development of atherosclerosis is oxidative modification of LDL. The LDL- cholesterol lowering could result from a reduced LDL- synthesis and/ or an increased LDL metabolism.³⁰

Cholesterol feeding resulted in a rise in serum VLDL-Cholesterol levels in group IIa and IIb when compared to control group. (**Table 1**) On the other hand, as shown in Table 1 the induction of hyperlipidaemia in rabbits followed by treatment with plant extract at both the dose level *i.e.* 250 and 500 mg./kg.b.wt./day caused a significant reduction ($P \leq 0.001$) in the serum levels of VLDL-cholesterol -51.75% and -54.64% respectively whereas no treatment group brought down it only -22.72% in comparison to hyperlipidaemic rabbits (120 days). Further, a significant ($P \leq 0.001$) decline in VLDL level was observed when group IVa and IVb was compared to group III animals. Oral administration of EGEE brought down the VLDL cholesterol levels markedly. The reduction might be due to an increased uptake by extrahepatic tissues as well as by increasing the fractional catabolic rate of LDL cholesterol and by increasing the liver LDL receptors activity.³¹

In hyperlipidaemic rabbits, HDL cholesterol in comparison to total cholesterol was showing downward trend, whereas after treatment with EGEE it showed upward trend in dose dependent manner (**Table 1**). **Table 1** illustrated that Cholesterol/phospholipid ratio (C/P ratio) was elevated after cholesterol feeding for 60 and 120 days respectively which was reduced after treatment with EGEE extract.

Further HDL ratio significantly improved in a dose dependent manner after administration with EGEE as indicated in **Table 1**. The atherogenic index (AI) which is the measure of the extent of atherosclerotic lesions based on serum lipids is

determined in all five groups. An ameliorative action of plant extract on atherogenic index was observed in both EGEE extract treated groups in a dose dependant manner.

TABLE 1: EFFECT OF ETHANOLIC EXTRACT OF *E. GANITRUS* ON SERUM BIOCHEMISTRY IN RABBIT

Identification	Group	Total Cholesterol	Triglyceride	Phospholipid	mg/dl			Chol/Phospho Ratio	HDL Ratio	Atherogenic Index
					VLDL Chol.	LDL Chol.	HDL Chol.			
Control (Placebo treated) from day 1-120	I	123.33 ± 7.75	77.05 ± 4.12	119.72 ± 5.25	15.41 ± 0.825	60.92 ± 1.30	43.07 ± 1.24	1.03	53.66	1.98
Atherodiet + Chol.feeding* from day 1-60	II a	615.00 ^a	346.33 ^a	374.41 ^a	69.26 ^a	372.19 ^a	138.14 ^a	1.64	28.96	3.19
% Deviation (I)		±21.79	±20.25	±7.02	±4.05	±11.40	±2.34	+59.22	-46.03	+61.11
Atherodiet + Chol.feeding* from day 1-120	II b	1041.66a	475.66a	611.00a	95.13a	644.67a	148.89 a	1.70	16.67	4.96
% Deviation (I)		±27.82	±9.02	±8.50	±1.80	±10.33	±3.58	+65.04	-68.93	+150.50
Atherodiet + Chol.feeding* from day 1-60. No treatment from day 61-120	III	475.66 ^b	254.00 ^b	324.26 ^b	50.80 ^b	283.07 ^b	115.36	1.46	32.01	2.89
% ^d Deviation (IIa)		±17.85	±8.32	±11.72	±1.66	±6.42	^b ±5.38	-10.97	+10.53	-9.40
Atherodiet + Chol.feeding* from day 1-60+ <i>Elaeocarpus ganitrus</i> ethanolic extract** from day 61-120	IV a	226.33 ^{b,d}	176.33 ^{b,d}	253.89 ^{b,e}	35.26 ^{b,d}	107.03 ^{b,d}	73.40 ^{b,d}	0.89	47.99	1.93
% Deviation (IIa)		±15.10	±6.74	±15.31	±1.34	±4.75	±2.37	-45.73	+65.71	-39.49
Atherodiet + Chol.feeding* from day 1-60+ <i>Elaeocarpus ganitrus</i> ethanolic extract*** from day 61-120	IV b	184.33 ^{b,d}	116.33 ^{b,d}	122.26 ^{b,d}	23.26 ^{b,d}	71.70 ^{b,d}	66.27 ^{b,d}	1.50	56.13	1.43
% Deviation (IIa)		±4.48	±4.09	±4.39	±0.81	±5.73	±3.30	-8.53	+93.81	-55.17

*Cholesterol feeding -500mg/ kg.b.wt in 5 ml coconut oil / day

** *E. ganitrus*- 250 mg/ kg.b.wt. / day

*** *E. ganitrus* 500mg/ kg.b.wt. / day

Values± 5 determination

a- P≤0.001 Highly Significant

b- P≤0.001 Highly Significant

c- P≤0.01 Significant

d- P≤0.001 Highly Significant

e- P≤0.01 Significant

ns- non significant

Group IIa, IIb compared with Group I
Group III, IV a and IVb compared with Group IIb
Group IV a and IV b compared with Group III

The ratio of LDL-C to HDL-C is also a protective indicator of cardio vascular disease incidence. The cholesterol induction produced a significant increase of this marker. The administration of EGEE provides a beneficial action on rabbit lipid metabolism with regard to the reduction of AI. Again, the administration of EGEE significantly improved the HDL ratio showing the beneficial effect of this plant in preventing atherosclerosis incidence. For analyzing lipid peroxidation, MDA levels were measured in liver, heart and aorta homogenates. A significant rise ($P \leq 0.001$) in MDA was observed in the hyperlipidaemic rabbits in comparison with the control. Moreover, lipid peroxidation was significantly reduced ($P \leq 0.01$

and $P \leq 0.001$) as depicted by the lower levels of MDA in liver, heart and aorta after oral administration of EGEE in a dose-dependent manner when compared with hyperlipidaemic rabbits (**Fig. 1**). This indicates that EGEE extract react with peroxy radicals including the inhibition of lipid peroxidation chain propagation.³²

The level of GSH was lower in the animals fed with cholesterol when compared to control ones in all the three tissues. A significant elevation ($P \leq 0.001$ and $P \leq 0.01$) was observed in GSH content of all the three organs when treated with EGEE at the dose level of 250 and 500 mg/kg. b. wt./day (**Fig. 2**).

It is possible that extract might have reduced the extent of oxidative stress, leading to lesser GSH degradation or increase in the biosynthesis of GSH.^{33, 34} The CAT and SOD activity appeared to be lower in the hypercholesterolaemic groups in

comparison to control group in all the three organs. In contrast statistically significant elevation ($P \leq 0.01$ and $P \leq 0.001$) was observed in catalase (**Fig. 3**) as well as SOD activity (**Fig.4**) of liver, heart and aorta in EGEE administered rabbits.

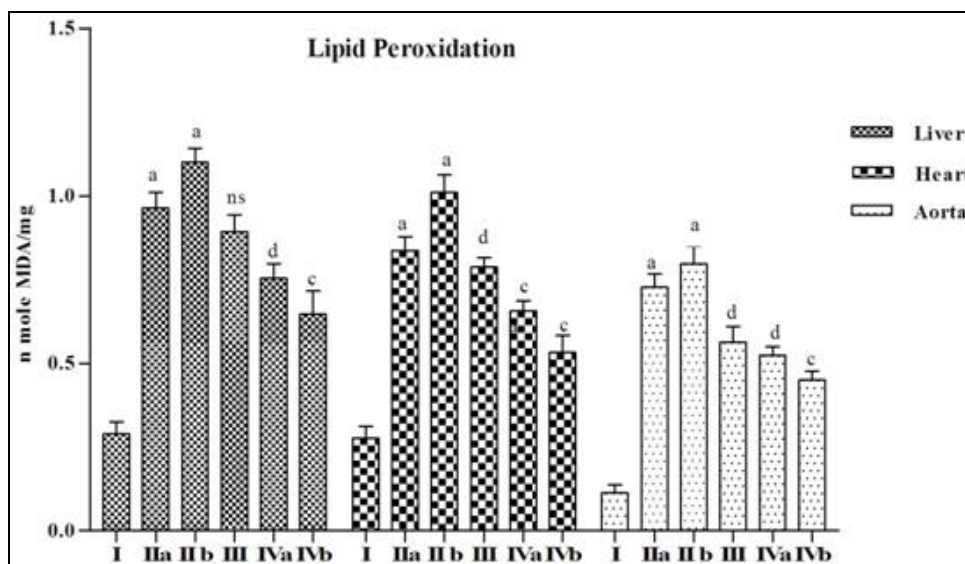


FIG. 1: EFFECT OF ETHANOLIC EXTRACT OF *E.GANITRUS* ON LIPID PEROXIDATION IN RABBITS

Values \pm 5 determinations

- a- $P \leq 0.001$ Highly Significant Group IIa, IIb compared with Group I
- b- $P \leq 0.01$ Significant
- c- $P \leq 0.001$ Highly Significant Group III, IVa, IVb compared with Group IIb
- d- $P \leq 0.01$ Significant
- ns- Non Significant

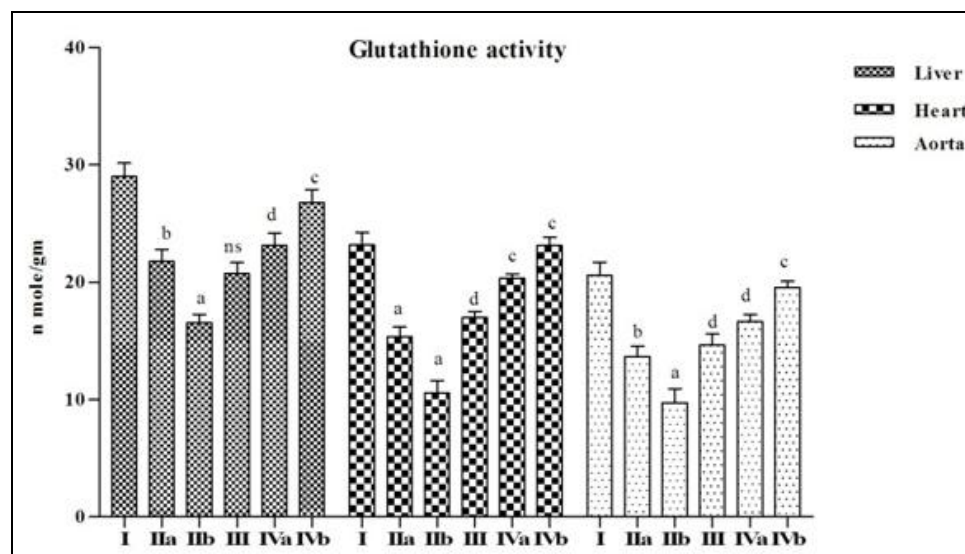


FIG. 2: EFFECT OF ETHANOLIC EXTRACT OF *E. GANITRUS* ON GLUTATHIONE ACTIVITY IN RABBITS

Values \pm 5 determinations

- a- $P \leq 0.001$ Highly Significant Group IIa, IIb compared with Group I
- b- $P \leq 0.01$ Significant
- c- $P \leq 0.001$ Highly Significant Group III, Iva, IVb compared with Group IIb
- d- $P \leq 0.01$ Significant
- ns- Non Significant

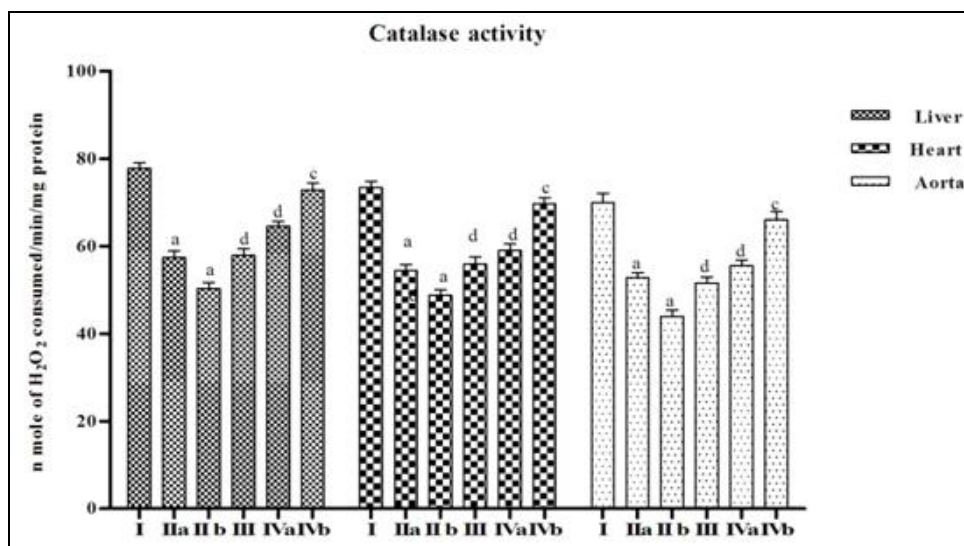


FIG. 3: EFFECT OF ETHANOLIC EXTRACT OF *E.GANITRUS* ON CATALASE ACTIVITY IN RABBITS

Values ± 5determinations

- a- P ≤ 0.001 Highly Significant Group IIa, IIb compared with Group I
- b- P ≤ 0.01 Significant
- c- P ≤ 0.001 Highly Significant Group III, IVa, IVb compared with Group IIb
- d- P ≤ 0.01 Significant
- ns- Non Significant

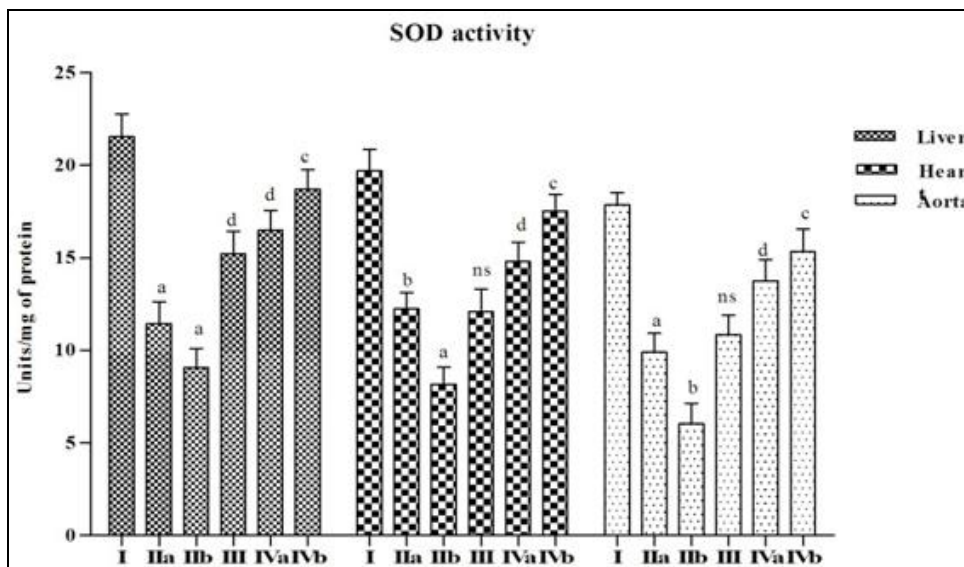


FIG. 4: EFFECT OF ETHANOLIC EXTRACT OF *E. GANITRUS* ON SOD ACTIVITY IN RABBITS

Values ±5 determinations

- a- P ≤ 0.001 Highly Significant Group IIa, IIb compared with Group I
- b- P ≤ 0.01 Significant
- c- P ≤ 0.001 Highly Significant Group III, IVa, IVb compared with Group IIb
- d- P ≤ 0.01 Significant
- ns- Non Significant

EGEE treated hyperlipidaemic rabbits had considerably elevated levels of SOD and CAT, reversing the ill effects of hyperlipidaemia. It is well known that flavonoids and polyphenols are natural antioxidants but have also been reported to significantly increase SOD and CAT activities.^{35,36} Total phenolic content in *E.ganitrus* was detected

to be 56.79±1.6 mg gallic acid equivalents/g of dry material. Total flavonoids in *E. ganitrus* were detected to be 18.58± 0.3 mg rutin equivalents/g of dry material.³⁷ These findings recommend that the antioxidant capacity of EGEE is by virtue of phenolics and flavonoid components.

Flavonoids defend alpha tocopherol and conceivably other antioxidants against oxidation.³⁸ Furthermore, Lee *et al.*, 2011³⁹ suggested that quercetin as a preventive measure against cardiovascular risk.

Berberine (BBR), an alkaloid isolated from the Chinese herb Huanglian, upregulates hepatic LDLR expression by extending the half-life of LDLR mRNA without affecting gene transcription.⁴⁰ It is possible that the presence of alkaloids like:

(+)- elaeocarpiline, isoelaecarpiline,
 (-)-epielaecarpiline,
 (+)-epiisoeleocarpiline,
 (+)-epialloelaecarpiline,
 (-)-alloelaecarpiline, elaeocarpidine, pseudoepi-
 isoelaecarpiline and rudrakin in EGEE⁴¹ may possess LDLR mRNA stabilization property and stimulating effect on hepatic LDLR expression. Bharti 2013⁴² revealed that kaempferol and Quercetin were found to dominate in seeds of EGEE. Quercetin supplementation altered expression profiles of several lipid metabolism-related genes in HFD control mice.⁴³ Further the kaempferol reduced the accumulation of visceral fat and improved hyperlipidaemia in HFD-fed obese rats by increasing lipid metabolism.⁴⁴

In accordance with these results, it may be confirmed that due to the presence of biologically active phytoconstituents such as alkaloids, flavanoids and tannins in the ethanolic extract, may demonstrates the multitarget, multicomponent features for regulating lipid metabolism.⁴⁵

In conclusion, it can be said that the ethanolic extract of *Elaeocarpus ganitrus* seed exhibited a significant cardioprotective as well as antioxidant activity in rabbits. To elucidate the precise mechanism of action and expression studies related to lipid metabolism of specific biological moiety, further processing of ethanolic fraction of *E. ganitrus* is required to establish the efficacy of the EGEE as a hypolipidaemic drug.

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CONFLICTS OF INTEREST: Nil

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