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EFFECT OF "KARPURAVALLI" ON ANTIBIOTIC INDUCED HEPATOTOXICITY

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ABSTRACT

Liver is the vital organ in our body, which is involved in metabolism and independently involved in many biochemical functions. Liver disease has become one of the major cause of mortality and morbidity all over the world. It is a fifth most common cause of death. Drug induced hepatotoxicity manifests in many ways, from asymptomatic elevation of liver enzymes to complete hepatic failure. Pashanabhedi is an Ayurvedic drug botanically equated as **Coleus aromaticus Benth**. and traditionally used for treating liver disease. The present study was designed to evaluate the hepatoprotective effect of the aqueous extract of **Coleus aromaticus Benth.** on rifampicin (54mg/kg bw) induced hepatotoxicity. Wistar strain of rats were divided in to 6 groups with 6 rats each, group - 1 served as normal control, group - 2 served as disease control, group - 3, 4 & 5 were induced with rifampicin and treated with aqueous extract of **Coleus aromaticus Benth.** 100, 200, 300mg/kg bw orally for 21 days, group – 6 was induced with rifampicin and treated with std drug **silymarin** (20mg/kg BW for 21 days orally). After intoxicating with Rifampicin the following parameters were analysed - serum Aspartate transaminase (AST), Alanine transaminase (ALT), Alkaline phosphatase (ALP), Gamma glutamyl transferase (GGT), Bilirubin, liver glycogen, antioxidant status. Disease control rats showed increased levels of AST, ALT, ALP, Bilirubin, LPO and the levels of serum and tissue protein, GSH, SOD, GP_x, Glycogen were significantly decreased compared to normal control rats. The administration of different doses of aqueous extract of **Coleus aromaticus Benth** lead to the restoration of altered enzymatic and biochemical parameters.

The results of the present study clearly depicted the hepatoprotective potentials of aqueous extract of **Coleus aromaticus Benth.**

KEYWORDS: Hepatic failure, Coleus aromaticus Benth, Rifampicin, Silymarin, Hepatoprotective.

INTRODUCTION

The liver is a highly sensitive organ which plays a major role in maintenance and performance of the homeostasis in our body. It is the chief organ where important processes like metabolism and detoxification takes place.[1] The liver performs physiological functions in addition to which it protects the system from the hazards of harmful drugs and chemicals.[2] The major functions of the liver are carbohydrate, protein and fat metabolism, detoxification, secretion of bile and storage of vitamins.[3] Virus, alcohol, various drugs are some of the agents that cause liver disorders.[4] Liver diseases are considered to be serious health disorders and are the 5th most common cause of death[5] Drug induced hepatic injury is the most common reason cited for the withdrawal of an approved drug from the market. Despite the tremendous strides in modern `medicine, there are few drugs that stimulate liver function, offer protection to the liver from damage or help to regenerate hepatic cells.[2] Damage or injury to the liver is caused by exposure to an antituberculosis agent, rifampicin.[6] Rifampicin is an effective liver enzyme inducer. This is supported by release of aspartate and alanine aminotransferases and alkaline phosphatase in serum a decrease in the activity of Na^+ K^+ ATP ase, Ca^{2+} ATP ase and Mg $^{2+}$ ATP ase in liver promoting the up regulation of hepatic cytochrome p450 enzymes such as CYP2D6 and CYP3A4 which increases the rate of metabolism of many other drugs that are cleared by the liver.[7] Modern medicines have little to offer for alleviation of hepatic disorders. Even today folk remedies from plant source are being used for the protection of hepatic damages starting from ancient period.[8] Hence the present work was undertaken to scientifically prove the hepatoprotective nature of **Coleus aromaticus Benth** by an in – vivo study.

MATERIALS AND METHODS

Collection of plant material

The plants were collected from in and around Trichy and identified with the help of Flora of Presidency of Madras and authenticated with the voucher specimen deposited at the Rapinat Herbarium, Dept of Botany, St Joseph's College, Trichy.

Preparation of aqueous extract

The plant materials were shade dried and coarsely powdered. The powder was mixed with 6 times the volume of water, stirred and boiled continuously until the volume reduced to 1/3rd. The extract was filtered with muslin cloth. The residue was re extracted. The filterate was mixed and evaporated in a water bath till it reached a thick consistency. The extract was stored in refrigerator till further use.

Experimental models

Wistar strains of Albino rats of both sexes weighing 150 – 200g were used for the study. Animals were housed in well ventilated cages in the CPCSEA approved animal house. The protocol was approved by the Institutional Animal Ethics Committee. They were fed with pelleted rat chow and water ad libitum. They were acclimatised to the laboratory conditions for a week before starting the experiment.

Experimental design

The animals were divided in to six groups comprising of six rats each. Hepato toxicity was induced using Rifampicin at a dose of 54mg/kg bw orally for 3 days in 0.98% physiological saline. Group 1 served as normal control. Group 2 served as disease control (54mg 0f Rifampicin /kg BW in 0.98% Saline was administered orally for 3 days. Group III was induced with Rifampicin and treated with aqueous extract of Coleus aromaticus Benth. at a dose of 100mg/kg bw for 21 days orally. Group IV was induced with Rifampicin and treated with aqueous extract of Coleus aromaticus Benth. at a dose of 200mg/kg bw for 21 days orally. Group V was induced with Rifampicin and treated with aqueous extract of Coleus aromaticus Benth. at a dose of 300mg/kg bw for 21 days orally. Group VI was induced with Rifampicin and treated with Silymarin at a dose of 20mg/kg bw for 21 days orally. At the end of the experimental period the animals were sacrificed. The blood, serum and liver tissue were used for the studies.

All the biochemical parameters such as Aspartate transaminase (AST), Alanine transaminase (ALT), Alkaline phosphatase (ALP),[9] Gamma glutamyl transferase (GGT),[10] Bilirubin,[11] liver glycogen,[12] Protein,[13] GSH,[14] GP_X,[15] SOD.[16] LPO,[17] were measured.

STATISTICAL ANALYSIS

The data of results obtained were subjected to statistical analysis and expressed as mean ± SEM. The data were statistically analysed by one – way analysis of variance (ANOVA) and

p<0.05 was considered to be significant.

RESULTS

Group II animals showed an elevation in the levels of the marker enzyme which was restored to near normal in the plant drug treated groups. The results are depicted in table 1.

Table 1: Activities of liver marker enzymes in hepatotoxic and Coleus aromaticus Benth treated groups.

GROUPS	SGPT (IU/L)	SGOT (IU/L)	ALP (IU/L)	GGT (IU/L)
Group 1	41.7 ± 0.66	12.34 ± 0.7	597.2 ± 0.8	34.2 ± 0.301
Group 2	301.88± 0.043*	179.3 ± 0.043*	973.71 ± 0.08*	66.9 ± 0.4*
Group 3	253.1 ± 0.28	129.3 ± 0.44	881.4 ± 0.31	52.1 ± 0.36
Group 4	184.7 ± 0.27	55.9 ± 0.097	749.2 ± 0.345	44.2 ± 0.37
Group 5	42.1 ± 0.231**	14.56 ± 0.009**	535.52 ± 0.72	36.1 ± 0.42**
Group 6	53.32 ± 1.13	17.2 ± 0.6	532.21 ± 0.76**	27.38 ± 1.93

Values are ± SEM, n = 6

*p< 0.05 statistically significant when compared with Normal Control

**p< 0.05 statistically significant when compared with Disease Control

Group II animals showed an elevation in the level of bilirubin and reduction in the levels of liver glycogen and protein which was restored to near normal in the plant drug treated groups.

Table 2: Estimation of Protein, liver glycogen and Bilirubin.

Groups	Protein	Liver glycogen	Bilirubin
Group 1	7.2 ± 0.03	30.3 ± 0.64	0.98 ± 0.045
Group 2	4.33± 0.015*	14.13 ± 0.62*	3.3 ± 0.15*
Group 3	5.22± 0.37	18.3 ± 0.61	2.45 ± 0.45
Group 4	6.3 ± 0.027	22.6 ± 0.57	2.16 ± 0.33
Group 5	7.0 ± 0.25	29.2 ± 0.59**	1.2 ± 0.06
Group 6	7.9 ± 0.09**	34.12 ± 0.02	1.01 ± 0.04**

Values are ± SEM, n = 6

*p< 0.05 statistically significant when compared with Normal Control

**p< 0.05 statistically significant when compared with Disease Control

Group II animals showed an increased in the level of LPO and GSH, SOD, GP_X, were decreased. After the treatment with plant drug the levels were restored to near normal

Table 3: Assay of antioxidants and lipid peroxide.

Groups	GPx	LPO	SOD	GSH
Group 1	47 ± 0.23	2.53 ± 0.12	3.01 ± 0.02	44.4 ± 0.31
Group 2	27 ± 0.33*	7.1 ± 0.17*	0.74 ± 0.221	28.3 ± 0.083
Group 3	29.1 ± 0.32	4.31 ± 0.037	1.32 ± 0.43*	30.1 ± 0.55*
Group 4	39.8± 0.42	3.73 ± 0.982**	1.62 ± 0.53	41.73 ± 0.86
Group 5	47.1± 0.41**	2.14 ± 0.773	3.27 ± 0.098**	45.7 ± 0.67
Group 6	53.1 ± 0.12	1.25 ± 0.97	3.24 ± 0.15	46.23 ± 1.01**

Values are ± SEM, n = 6

*p< 0.05 statistically significant when compared with Normal Control

**p< 0.05 statistically significant when compared with Disease Control

DISCUSSION

Damage or injury is caused to the liver by exposure to an antituberculosis agent called rifampicin. Anti-tuberculosis agents are a relatively uncommon cause of liver damage.[18]

Rifampicin is an effective liver enzyme inducer. The release of aspartate, alanine aminotransferases and alkaline phosphatase in serum decrease in the activity of Na^+ K^+ ATP ase, Ca^{2+} ATP ase and Mg^{2+} ATP ase in liver indicates the damage caused by rifampicin in the liver. In addition to the elevated serum marker enzymes, the hepatic cytochrome p450 is upregulated. This in turn increases the detoxification process in the liver.[19]

Serum SGOT, SGPT, ALP and GGT are the most sensitive markers employed in the diagnosis of hepatic damge because these are cytoplasmic in location and are relased in to the circulation after cellular damage. Rifampicin induces cellular damage which enabled the release of these enzyme in to the circulation and hence elevated. The plant extract restored membrane integrity retaining the enzyme in the cytoplasm which is evident from the results.

The levels of tissue protein and hepatic glycogen marks the synthetic efficiency of the liver. The decrease is an indicator of liver necrosis. The plant drug efficiently repairs the necrosed tissue and improves the synthetic functions of the liver. It also augments the activity of glycogen synthesis.

Bilirubin assay is a sensitive tool to substantiate the functional integrity of the liver and severity of necrosis. Bilirubin also measures the binding, conjugation and excretory capacity of hepatocytes and is proportional to the erythrocyte degradation rate. Increase in serum bilirubin levels may be found in hepatocellular damge, haemolytic jaundice or hepatitis.

Rifampicin injury causes significant degeneration of hepatocytes and blockade of the bile ducts which results in to significant increase in the bilirubin level.[19]

Oxidative stress in rifampicin induced hepatotoxicity was also noted to play a significant role in the regression phase of hepatic hyperplasia with the generation of lipid peroxide. The generated lipid peroxide accumulates in the hepatic tissue reducing the activity of the free radicalscavenging system. GSH is a tripeptide non enzymatic biological antioxidant present in the liver. It is a critical determinant of tissue susceptibility to oxidative damage and depletion of hepatic GSH has been shown to be associated with enhanced lipid peroxidation.[20]

Biological systems protect themselves against the damaging effects of activated species by several means. These include free radical scavengers and chain reaction terminators enzyme such as SOD, GSH and GP_X system. The SOD dismutase superoxide radicals O_2^- in to H_2O_2 and O_2 participating with other antioxidant enzymes in the enzymatic defence against oxygen toxicity. SOD plays an important role in the elimination of ROS derived from the peroxidative process of xenobiotics in liver tissues.[21]

CONCLUSION

The present study concludes that the aqueous extract of Coleus aromaticus Benth possesses antioxidant activity and shows a protective effect against Rifampicin induced hepa totoxicity in experimental rats.

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