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Hepatoprotective Activity of *Securinega leucopyrus* on CCl_4 Induced Liver Damage in Rats

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ABSTRACT
The plant Securinega leucopyrus is used for treating a number of diseases such as pneumonia, gonorrhea, malaria, chest pains, mental illness etc. In the present research we aimed to evaluate the protective effect of Securinega leucopyrus against CCl_4 induced hepatotoxicity in rats. Animals were divided into five groups (n=6), group-I served as control, group-II is disease control (CCl_4 only) III, IV, V, groups were treated silyamarin (Reference Standard), aqueous extract of Securinega leucopyrus (AESL - 100mg/kg and 300 mg/kg) respectively up to 14 days. On 14th day all group of animals were treated with CCl_4 to induce hepatotoxicity. After 24 hr of CCl_4 administration all the animals were scarified under ether anesthesia, blood was withdrawn from the animals by cardiac puncture and was subjected to biochemical, serum enzyme analysis. The liver was isolated from all the animals and was subjected to microscopic anatomy studies. AESL at the dose range of 300 mg/kg significantly decreases the levels of bilirubin, creatinine, SGOT, SGPT, ALP in serum of CCl_4 induced liver damaged rats. Histology suggests that the animals treated with AESL (300 mg/kg) was free of inflammation; oxidative stress induced by chemical as well as animal liver was protected from toxins obtained from CCl_4. From the results it can be concluded that traditional use of Securinega leucopyrus served as protective agent against the hepatotoxicity induced by chemicals.
Keywords: *Securinega leucopyrus, CCl_4, Liver Enzymes, Histopathology.*

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INTRODUCTION

The liver performs diverse functions that are essential for life. It directly receives; processes and stores materials absorbed from the digestive tract as well it reduces the toxicity by eliminate the xenobiotics which were reached to portal vein. It is the major site for metabolism of drugs and chemicals because of having enzyme family CYtp450 enzyme family [1]. The liver performs the normal metabolic homeostasis of the body as well as biotransformation, detoxification and excretion of many endogenous and exogenous compounds, including pharmaceutical and environmental chemicals. Drug-induced hepatotoxicity is a major cause of iatrogenic diseases, accounting for one in 600 to one in 3500 of all hospital admissions [2]. Oxidative stress is widely recognized as a detrimental pathological mechanism for the initiation and progression of various liver diseases. Reactive oxygen species (ROS) are mainly generated by cytochrome P450 enzymes in the mitochondria of hepatocytes. When excess ROS are generated, they interact with proteins, DNA, and lipids, resulting in cell injury. In the course of liver diseases, either from inflammatory or metabolic insults, disruption of the balance between oxidant and antioxidant mechanisms is commonly observed [3, 4].To prevent the damage caused by ROS, living organisms have developed an antioxidant defence system that includes the presence of non-enzymatic antioxidants and enzymes such as catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) [5]. It has been anticipated that in addition to these natural antioxidants, other synthetic or natural ROS scavengers may reduce the incidence of free radical-mediated diseases. The use of antioxidants in the prevention and cure of various diseases is intensifying, and there is considerable interest in the study of the antioxidant activities of molecules such as plant polyphenolic and carotenoid components [6, 7]. Antioxidants appear to act against disease processes by increasing the levels of endogenous antioxidant enzymes and decreasing lipid peroxidation. A number of studies showed that various herbal extracts could protect liver and kidney against CCl_4-induced oxidative stress by inhibiting lipid peroxidation and enhancing antioxidant enzyme activity [8].

Silymarin is a flavonolign and mixture of milk thistle (***Silybum marianum***), is one such important herbal hepatoprotective drug. Silymarin exhibits hepatoprotective effects by altering cytoplasmic membrane architecture and, in turn, preventing the penetration of hepatotoxic substances, such as carbon tetrachloride (CCl_4), thioacetamide and D-galactosamine [9].

MATERIAL AND METHODS

Plant collection and extraction: For the present investigation, stems of *Securinega leucopyrus* were collected from the medicinal garden of Chalapathi Institute of Pharmaceutical Sciences, Lam, Guntur. The plant was identified and authenticated by a botanist in Acharya Nagarjuna University. The stems of plant were dried under shade for twenty-one days and then size-reduced into powder with a mortar and pestle. About 30g of the stem powder was macerated with 150ml of water for 72 hours with occasional shaking totally 9.5% yield was obtained.

Experimental design:

Selection of animal: In this study sprague- dawley rats of either sex (weighing 250-300g) were obtained from the animal house of Chalapathi Institute of Pharmaceutical Sciences and Guntur. The animals were kept under standard temperature of about 22 °C, 12-h light/dark cycle. The protocol was approved (Approval no.05/IAEC/CLPT/2018-2019; DT: 05/01/2019) by Institutional Animal Ethical Committee (IAEC) and conducted according to Committee for the Purpose of Control and Supervision of Experimental Animals (Reg. No. 1048/PO/Re/S/07/CPCSEA).

Induction of hepatotoxicity: CCl4 was administered through intraperitonial to animals for inducing hepatotoxicity**,** by mixing with olive oil with at a ratio of 1:1 and from that solution; 1.5mg/kg is administered to all animals except normal control [10].

Grouping of animals:

The animals were weighed and divided into 5 groups with 5 rats in each group as follows**.**

(i) Group-I: Animal received normal saline.
(ii) Group-II: Administered with CCl4 (3ml/kg, i.p) on the day of 14 alone, served as which is a disease Control.
(iii) Group-III: Administered with Silymarin (50mg/kg, p.o) for 14 days, which is used as a Standard Group.
(iv) Group-IV: Administered with AESL (100 mg/kg, p.o) for 14 days,
(v) Group-V: Administered with AESL (300 mg/kg, p.o) for 14 days

On day 14, one hour prior to the administration of standard and test drugs, CCl4 is administered. At the end of the experiment blood from the all-group animals was collected via heart puncture under ether anesthesia.

Measurement of blood parameters: The Blood levels of SGOT, SGPT, ALP, creatinine, bilirubin was estimated by standard analytical techniques.

Histopatholigical studies: All animals were sacrificed and isolated the liver from abdomen cavities, to find out morphological and histological changes [11].

Statistical analysis: All results were reported in the form of mean± SEM, and the analysis was done by one way –ANOVA, the significance level was taken as ($p<0.05$).

RESULTS

Phytochemical analysis. *Securinega leucopyrus* extract demonstrates the presence of flavonoids, tannins, saponins, alkaloids, terpenoids and phenols [4].

Table-1: Phytoconstituents of *Securinega leucopyrus*

S.No.	Phytoconstituents	AESL
1	Alkaloid	+
2	Unsaturated Sterols	-
3	Phenolics	+
4	Flavonoids	+
5	Saponins	-
6	Tannins	+
7	Glycosides	+
8	Terpenoids	+
9	Carbohydrates	+
10	Proteins	+

Table-2: Effect of AESL on biochemical factors in CCl_4 induced liver damaged rats

Groups	ALP	SGOT	SGPT	Total Bilirubin (µg/lt)	Creatinine	Urea
Normal control	48 ± 0.24	24 ± 0.12	15 ± 0.075	0.5 ± 0.003	0.7 ± 0.004	17 ± 0.085
Disease control	54 ± 0.27	49 ± 0.245	46 ± 0.23	0.9 ± 0.005	1.0 ± 0.005	36 ± 0.18
Standard	50 ± 0.25	26 ± 0.13	28 ± 0.14	0.7 ± 0.004	0.7 ±0.004**	22 ± 0.11
AESL (100mg/kg)	63 ± 0.315	45 ± 0.225	41 ± 0.205	0.9 ±0.005**	0.85 ± 0.004	32 ± 0.16
AESL (300mg/kg)	59 ± 0.295	40 ± 0.2	32 ± 0.16	0.8 ±0.004**	0.8 ± 0.004	28 ± 0.28

Note: The valves are expressed in mean± SEM, n=6,*(p<0.05), *** (p<0.001), ** (p<0.005), **** (p<0.0001) indicate the significance vs disease control

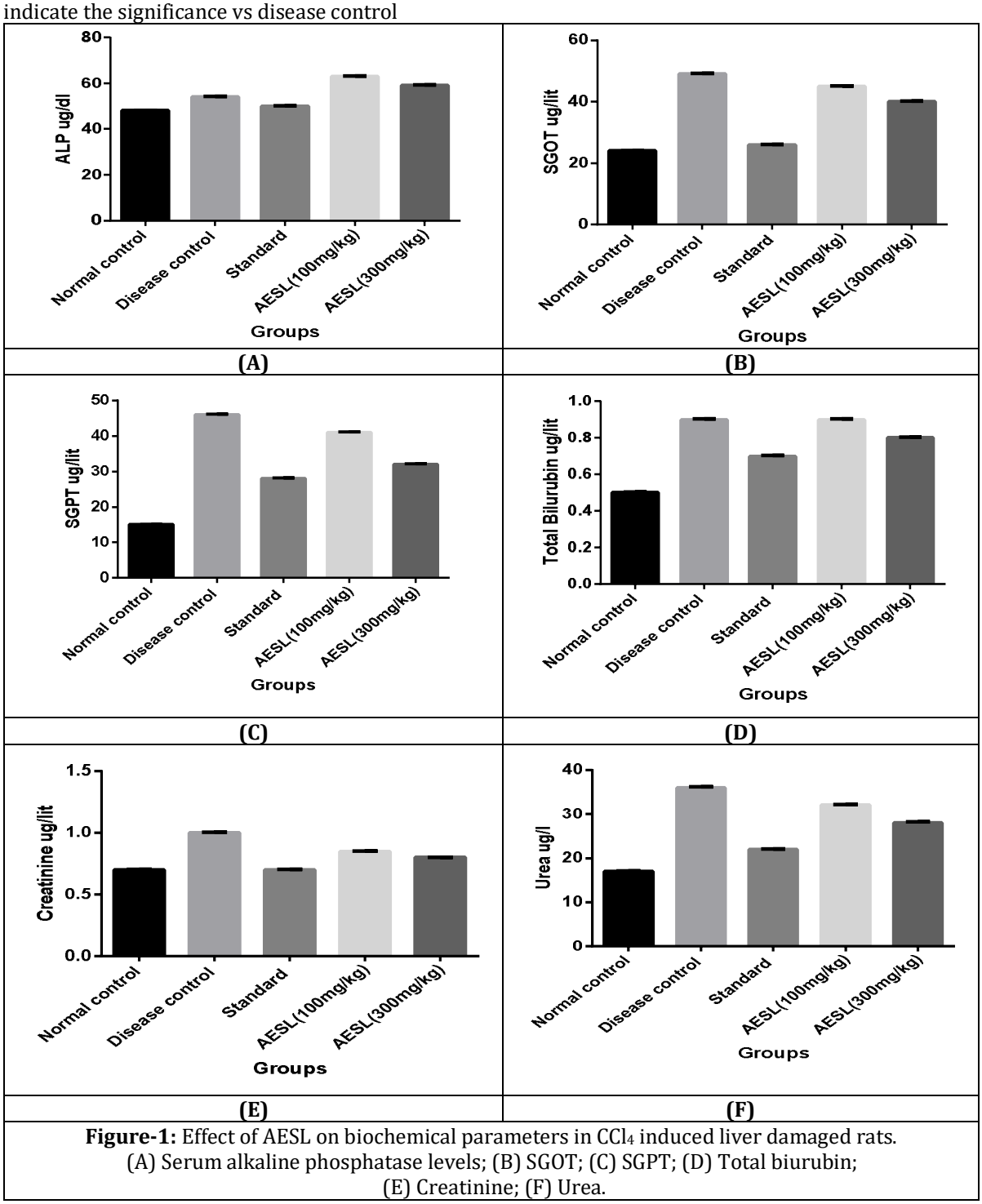

Figure-1: Effect of AESL on biochemical parameters in CCl_4 induced liver damaged rats. (A) Serum alkaline phosphatase levels; (B) SGOT; (C) SGPT; (D) Total biurubin; (E) Creatinine; (F) Urea.

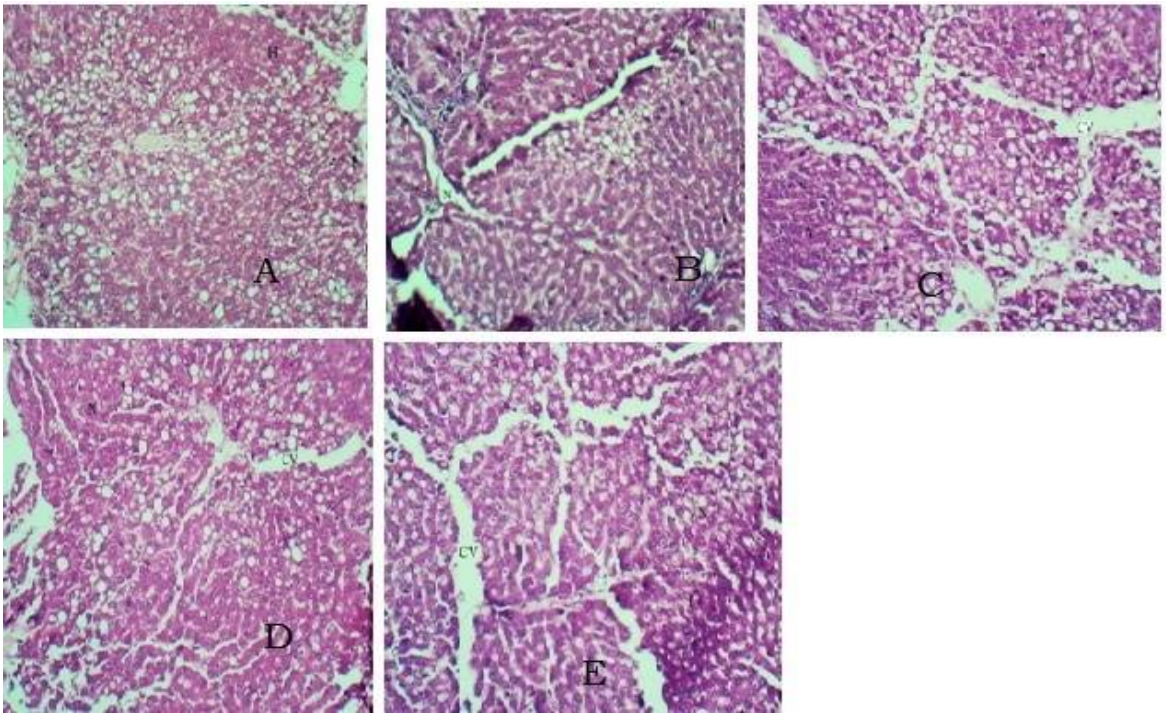

Figure.2. Histology of liver tissue of animals (a) Normal control; (b) Disease control; (c) Silymarin (Reference standard); (d)AESL(100mg/kg); (e) AESL (300mg/kg)

Microscopic observations of liver tissue pre-treated with AESL(100 mg/kg and 300 mg/kg) followed by treatment with CCl_4 to induced liver toxicity: (a) Normal control characterized by normal hepatic cell with nucleus and central vein; (b) Liver tissue of CCl_4 treated animals showing massive necrosis, haemorrhage, and inflammation; (c) Liver tissue of silymarin followed by CCl_4 treatment showing preservation of normal hepatocytes; (d) Animals pre-treated with AESL (100mg/kg) followed by CCl_4 shows tissue necrosis and inflammation; (e) Animals treated with AESL (300mg/kg) followed by CCl_4 shown mild inflammation.

DISCUSSION

Animals treated with CCl_4 causes increased formation of pro-oxidants (trichloromethyl radical) and a concomitant decrease in the antioxidant status of the cell. Over production of these oxygen radicals causes an imbalance in oxidant-antioxidant capacity and increased attacks on unsaturated fatty acids of lipid structures leading to lipid peroxidation and damage the proteins. The antioxidant capacity of cell is less while compare to oxidant concentration in hepatocytes, due these serum levels of SGPT/SGOT, ALP will be elevated in the blood. Similarly, animals received CCl_4 alone without any standard or AESL, markedly elevated serum levels of ALP, SGOT, SGPT, urea, bilirubine and creatinine, which indicates the severity of liver injury due to change in the function of liver cells by those chemicals. However, the rats pre-treated with AESL showed significant improvements in the cyto-architecture of rat liver and reduced the inflammation. The results suggested that animals pre-treated with AESL could palliate the liver injuries perhaps by its anti-oxidative effect, normalizing the levels of enzymes along with decreased production of free radicals by eliminating the deleterious effect of toxic metabolites of CCl_4. Changes in biochemical indices and histopathological appearance in the silymarin, AESL (300mg/kg) treated animals shown a significant hepatoprotective effect compare to CCl_4 alone treated animals .

CONCLUSION

The Liver damage and Hepatotoxicity induced by CCl_4 - was significantly inhibited by oral treatment of *Securinega leucopyrus* extract at 300mg/kg. In addition the liver inhibitor defense systems was promoted as well AESL dose-dependently suppress the CCl_4 induced oxidative damage and related organ damages. Decreasing of ALP, SGOT, SGPT levels, changes in the total bilirubin, urea contents and enzyme activities evidenced that *Securinega leucopyrus* extracts have favorable ameliorating protective effect on CCl_4-induced hepatotoxicity.

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