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Original Article

Pharmacology Section

Effect of Hydroalcoholic Root Extract of *Aerva lanata* on Acetaminophen Induced Hepatotoxicity in Wistar Rats

PARTHIBAN GOVINDARAJU[1], SWITHRAA CHANDRASE KARAN[2], NILESHRAJ GOVINDARAJ[3]

ABSTRACT

Introduction: Acute acetaminophen poisoning leads to fulminant hepatic failure and renal tubular damage. N-Acetyl Cysteine (NAC), an antidote for acetaminophen poisoning, carries its own adverse effect profile such as anaphylactoid reactions, cerebral oedema and hyponatremia at high doses. *Aerva lanata*, an erect or prostate herbaceous weed has a wide range of medicinal uses like, hepatoprotection, nephroprotection, antiasthamatic and antiamoebic. Previous study on rats have shown that hydroalcoholic root extract of *Aerva lanata* has significant hepatoprotective property when administered before acetaminophen.

Aim: To evaluate the effect of hydroalcoholic root extract of *Aerva lanata* and NAC, as monotherapy and in combination, for acetaminophen induced hepatotoxicity in albino Wistar rats.

Materials and Methods: This was an experimental animal study. Thirty adult male albino Wistar rats were equally divided into five groups: group I-vehicle, group II-acetaminophen only, group III-acetaminophen+NAC, group IV-acetaminophen+*Aerva lanata* root extract, group V-Acetaminophen+NAC+*Aerva lanata* root extract. Hepatotoxicity was induced in rats belonging to groups II, III, IV and V using acetaminophen (2 g/kg p.o). All rats were sacrificed after 72 hours of drug administration, blood samples were sent for biochemical analysis. Liver and kidney samples were sent for histopathological studies. Results were analysed using one-way ANOVA followed by post hoc Dunnett t-test.

Results: Root extract of *Aerva lanata* significantly reduces the liver enzyme markers Aspartate Transaminase (AST), Alanine Transaminase (ALT), Gamma Glutamyl Transferase (GGT) and bilirubin) and blood urea concentration. The combination therapy (root extract with NAC) showed a highly significant decrease in AST, ALT, GGT ($p<0.001$), bilirubin ($p<0.01$) and blood urea ($p<0.001$) when compared with the paracetamol group. A significant reversal of liver injury was seen in histopathological studies.

Conclusion: The combination therapy showed better improvement of liver enzyme and renal parameters, along with significant improvement in histopathological changes. Hence, combination of hydroalcoholic root extract of *Aerva lanata* along with NAC can be effective in treating acetaminophen poisoning.

Keywords: Antidote, Herbal root extract, Liver damage, Paracetamol

INTRODUCTION

Drug induced hepatotoxicity leads to significant elevation of ALT more than three times the Upper Limit of Normal (ULN). The prevalence of drug induced liver injury is estimated to be 5% of all hospital admissions and 50% of all acute liver failures [1]. Elevated aminotransferases along with jaundice is associated with increased mortality and need for liver transplant [2].

Acetaminophen (Paracetamol), a Nonsteroidal Anti-Inflammatory Drug (NSAID), is often used in clinical practice as an antipyretic and an analgesic [3]. Easy availability of acetaminophen over the counter increases the risk of acute acetaminophen poisoning in both adults and children due to overdosage. The hepatic glucuronide conjugating ability is low in children. Even though the toxic dose of acetaminophen is > 10 g in adult, it is less in children [4]. N-Acetyl-P-Benzoquinone Imine (NAPQI), a toxic intermediate metabolite formed during the metabolism of acetaminophen is the substance responsible for hepatotoxicity [5].

N-acetyl Cysteine (NAC) is the traditional drug used for the treatment of acetaminophen poisoning. NAC helps in providing cysteine for glutathione synthesis and also forms an adduct with NAPQI directly. But it has adverse effects which include unpleasant taste, vomiting, anaphylactoid reactions and at high doses it might even cause cerebral oedema and hyponatremia [6].

Aerva lanata is an erect or prostate herbaceous weed belonging to the family Amaranthaceae. The leaves are obovate or sub-opticular with greenish white flowers. *Aerva lanata* has a wide variety of medicinal uses, namely antimicrobial, antiamoebic, nephroprotective, antiasthamatic, hypolipidemic, hepatoprotective [7].

Previous studies on rats show that root extract of the plant *Aerva lanata* have hepatoprotective activity when administered before acetaminophen as a prophylaxis [8]. But the implication of the plant as treatment for paracetamol poisoning and its possible synergism with NAC remains unexplored.

This study aimed to find out the effect of hydroalcoholic root extract of *Aerva lanata* when given orally, alone and in combination with NAC in treatment (instead of prophylaxis) of hepatotoxicity induced by acetaminophen in male albino Wistar rats and to assess its renoprotective effect.

MATERIALS AND METHODS

This was an experimental animal study and 30 adult male albino Wistar rats were selected for the experiment. Rats were divided randomly into five groups. Each group contained six rats. This study was conducted for a period of four weeks (August 2014) in Sri Manakula Vinayagar Medical College and Hospital, Puducherry. Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines were adhered and Institutional Animal Ethics Committee clearance (SMVMCH- IAEC 1524/10/2013) was obtained before the research.

Inclusion criteria: Albino Wistar rats, male or female, age more than 12 weeks were included in this study.

Exclusion criteria: Animals with co-morbidities and knock-out animals were excluded in this study.

Study Procedure

Root of *Aerva lanata* plant was collected from Tiruchirappalli district, Tamil Nadu, India. Freshly collected plant materials were washed under running tap water and distilled water to remove adhering dust, then dried under shade and mechanically reduced to moderate coarse powder. The coarse powder was defatted with petroleum ether and then extracted with 80% ethanol using soxhlet apparatus. The extract was then concentrated using a rotary evaporator at 40ºC under reduced pressure. The concentrated extract was then transferred to a china dish and heated in a thermostat-controlled water bath until it was completely dry. Rats were grouped as follows and given their respective treatments [Table/Fig-1].

Group I	Vehicle (distilled water)
Group II	Acetaminophen only 2 g/kg p.o
Group III	Acetaminophen 2 g/kg p.o After 2 hr; NAC 140 mg/kg p.o (0 hr) NAC 70 mg/kg p.o (24 hr) NAC 70 mg/kg p.o (48 hr)
Group IV	Acetaminophen 2 g/kg p.o After 2 hr; *Aerva lanata* 200 mg/kg p.o (0 hr) *Aerva lanata* 200 mg/kg p.o (24 hr) *Aerva lanata* 200 mg/kg p.o (48 hr)
Group V	Acetaminophen 2 g/kg p.o After 2 hr; NAC and *Aerva lanata* root extract in combination

[Table/Fig-1]: Grouping of animals.
NAC: N-acetyl cysteine

Doses were selected on the basis of previous studies [8-11]. Distilled water was used as a vehicle. After 24 hours of the last dose of drug (i.e., 72 hours from the first dose) all the animals were anaesthetised using ether and 2 mL of blood samples from each animal from all groups were taken from retro orbital venous plexus of eye using capillary tubes. All animals were sacrificed using high dose of pentobarbitone. For histopathological study, a portion of liver and kidney tissue was separated and placed in a neutral buffered formalin for fixation. After regular processing, tissues were embedded in paraffin wax, and then sectioned (4-5 µm) using a microtome. Sections were stained using Haematoxylin and Eosin (H&E). Histopathological changes in tissue morphology were noted.

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences (SPSS) software version 16.0 was used. Data were analysed by one-way analysis of variance (ANOVA) and results were expressed as mean±Standard Deviation (SD). Significance of difference between groups was further analysed with Dunnett's (2-sided) test for post hoc comparisons. The p-value of <0.05 was considered statistically significant.

RESULTS

1. Effect on AST, ALT and GGT levels

Vehicle treated animals (group I) showed that the AST and ALT levels were maintained at a mean value of 164.16±11.39 and 78±9.25, respectively. Acetaminophen administration (group II) resulted in a significant increase (p<0.001) in both AST and ALT levels when compared with vehicle treated group (group I). Group III animals administered with NAC monotherapy showed a significant decrease (p<0.01) in AST and ALT levels compared with acetaminophen group (group II). *Aerva lanata* root extract monotherapy (group IV) also showed a significant decrease in AST and ALT levels (p<0.05) on comparison with acetaminophen group (group II), whereas combination therapy (group V) of *Aerva lanata* root extract and NAC showed a highly significant decrease of AST level when compared with acetaminophen (p<0.001), NAC (p<0.01) and *Aerva lanata* root extract (p<0.001) treated animals. ALT level of animals belonged to combination therapy group also showed a significant reduction (p<0.001) on comparison with acetaminophen group animals (group II) as illustrated in [Table/Fig-2].

Groups	Treatment (Oral)	AST (ULN)	ALT (ULN)	GGT (ULN)
Group I	Vehicle	164.16±11.39	78±9.25	5.21±0.53
Group II	Acetaminophen (2 g/kg)	235.16±22.13$^{\Delta\Delta\Delta}$	101.5±9.81$^{\Delta\Delta\Delta}$	9.3±0.23$^{\Delta\Delta\Delta}$
Group III	Acetaminophen (2 g/kg) After 2 hours N-acetylcysteine	211.17±6.76**	84.66±8.16**	8.2±0.23**
Group IV	Acetaminophen (2 g/kg) After 2 hours *A. lanata* root extract	215±7.79*	89.83±6.14*	8.4±0.92*
Group V	Acetaminophen (2 g/kg) After 2 hours N-acetylcysteine+ *A. lanata* root extract	187.83±7.02***$^{\$\$\#\#\#}$	81.66±5.04***	7.11± 0.46***$^{\$\#\#}$

[Table/Fig-2]: Effect of *Aerva lanata* root extract, alone and in combination with N-Acetylcysteine (NAC) on AST, ALT and GGT levels of experimental Wistar rats.
AST (Aspartate transaminase), ALT (Alanine transaminase), GGT (Gama glutamyl transferase)
NAC (140, 70, 70 mg/kg) and *Aerva lanata* (200, 200, 200 mg/kg);
Values are expressed as Mean±SD for all five groups (n=6 in each group);
*p<0.05; **p<0.01; ***p<<0.001 as compared with acetaminophen (group II) group;
$^{\$}$p<0.05; $^{\$\$}$p<0.01; $^{\$\$\$}$p<<0.001 as compared with NAC treated (group III) group;
$^{\#}$p<0.05; $^{\#\#}$p<0.01; $^{\#\#\#}$p<<0.001 as compared with *Aerva lanata* root extract (group IV) group;
$^{\Delta}$p<0.05; $^{\Delta\Delta}$p<0.01; $^{\Delta\Delta\Delta}$p<<0.001 as compared with vehicle treated (group I) group;
Comparison was done by one-way ANOVA followed by Post-Hoc Dunnett's (2-sided) test

The GGT values of vehicle treated animals (group I) showed a mean value of 5.21±0.53. This value was raised significantly (p<0.001) on administration of acetaminophen (group II). *Aerva lanata* root extract and NAC combination therapy showed a highly significant reduction of GGT values (p<0.001) on comparison with acetaminophen group. Combination therapy also showed a significant reduction of GGT values when compared with NAC monotherapy (p<0.01) and *Aerva lanata* root extract monotherapy (p<0.05) treated groups as depicted in [Table/Fig-2].

2. Effect on bilirubin levels

Bilirubin (mean) levels of vehicle treated rats (group I) were 0.66±0.08 (Total bilirubin) and 0.21±0.04 (direct bilirubin). When acetaminophen was administered (group II), significant increase in both total bilirubin (p<0.01) and direct bilirubin (p<0.001) were seen on comparison with vehicle treated animals (group I). Treatment with NAC per se (group III) showed a significant decrease (p<0.05) of both total and direct bilirubin levels when compared with acetaminophen group animals. Similar reduction of bilirubin levels (p<0.05) was seen in the group which received *Aerva lanata* root extract monotherapy (group IV). However, group V animals who received combination therapy of *Aerva lanata* root extract and NAC showed a highly significant reduction of both total and direct bilirubin levels (p<0.01) when compared with acetaminophen group animals as depicted in [Table/Fig-3].

Groups	Treatment (Oral)	Total bilirubin (mg/dL)	Direct bilirubin (mg/dL)
Group I	Vehicle	0.66±0.08	0.21±0.04
Group II	Acetaminophen (2 g/kg)	0.81±.0.07$^{\Delta\Delta}$	0.35±0.05$^{\Delta\Delta\Delta}$
Group III	Acetaminophen (2 g/kg) After 2 hours N-Acetylcysteine	0.68±0.09*	0.25±0.05*
Group IV	Acetaminophen (2 g/kg) After 2 hours *A. lanata* root extract	0.7±0.06*	0.26±0.05*
Group V	Acetaminophen (2 g/kg) After 2 hours N-Acetylcysteine + *A. lanata* root extract	0.66±0.05**	0.23±0.05**

[Table/Fig-3]: Effect of *Aerva lanata* root extract, alone and in combination with N-Acetylcysteine (NAC) on bilirubin levels of experimental Wistar rats.
NAC (140, 70, 70 mg/kg) and *Aerva lanata* (200, 200, 200 mg/kg);
Values are expressed as Mean±SD for all five groups (n=6 in each group);
*p<0.05; **p<0.01; ***p<<0.001 as compared with acetaminophen (group II) group;
$^{\Delta}$p<0.05; $^{\Delta\Delta}$p<0.01; $^{\Delta\Delta\Delta}$p<<0.001 as compared with vehicle treated (group I) group;
Comparison was done by one way ANOVA followed by Post-Hoc Dunnett's (2-sided) test

3. Effect on renal parameters

Blood urea concentration and serum creatinine values of vehicle treated animals (group I) were maintained at mean values of 19.88±0.91 and 0.33±0.08, respectively. A marked increase (p<0.001) in blood urea concentration was seen after administration of acetaminophen (group II) when compared with vehicle treated animals (group I). In the group treated with NAC alone (group III), no significant alterations in blood urea and serum creatinine levels were seen when compared with the untreated acetaminophen group animals. (group II) *Aerva lanata* root extract monotherapy group animals (group IV) showed a highly significant decrease in blood urea concentration compared with acetaminophen (p<0.001) and NAC (p<0.01) treated groups. Combination therapy of *Aerva lanata* root extract and NAC also showed a highly significant reduction of blood urea levels on comparison with acetaminophen (p<0.001), NAC monotherapy (p<0.001) and *Aerva lanata* root extract monotherapy (p<0.05) treated groups as shown in [Table/Fig-4].

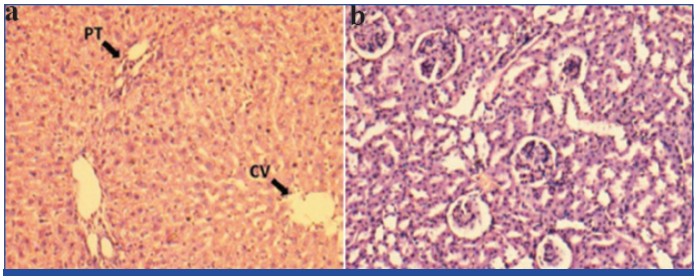
Groups	Treatment (Oral)	Blood urea (mg/dL)	Serum creatinine (mg/dL)
Group I	Vehicle	19.88±0.91	0.33±0.08
Group II	Acetaminophen (2 g/kg)	27.38±0.7$^{\Delta\Delta\Delta}$	0.38±0.07
Group III	Acetaminophen (2 g/kg) After 2 hours N-Acetylcysteine	26.71±0.17	0.35±0.10
Group IV	Acetaminophen (2 g/kg) After 2 hours *A. lanata root*	24.63±0.71$^{***\$\$}$	0.36±0.08
Group V	Acetaminophen (2 g/kg) After 2 hours N-Acetylcysteine + *A. lanata root*	23.13±0.89$^{***\$\$\$\#}$	0.35±0.05

[Table/Fig-4]: Effect of *Aerva lanata* root extract, alone and in combination with N-Acetylcysteine (NAC) on renal parameters of experimental Wistar rats.
NAC (140, 70, 70 mg/kg) and *Aerva lanata* (200, 200, 200 mg/kg);
Values are expressed as Mean±SD for all five groups (n=6 in each group);
*p<0.05; **p<0.01; ***p<<0.001 as compared with acetaminophen (group II) group;
$^{\$}$p<0.05; $^{\$\$}$p<0.01; $^{\$\$\$}$p<<0.001 as compared with NAC (group III) group;
# p<0.05; $^{\#\#}$p<0.01; $^{\#\#\#}$p<<0.001 as compared with *Aerva lanata* root extract (group IV) group;
$^{\Delta}$p<0.05; $^{\Delta\Delta}$p<0.01; $^{\Delta\Delta\Delta}$p<<0.001 as compared with vehicle treated (group I) group;
Comparison was done by one way ANOVA followed by Post-Hoc Dunnet's (2-sided) test

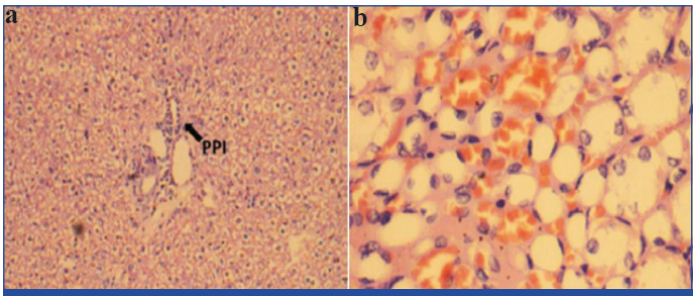
No significant changes in creatinine values were observed in any of the treatment groups.

4. Histopathological examination of liver and kidney

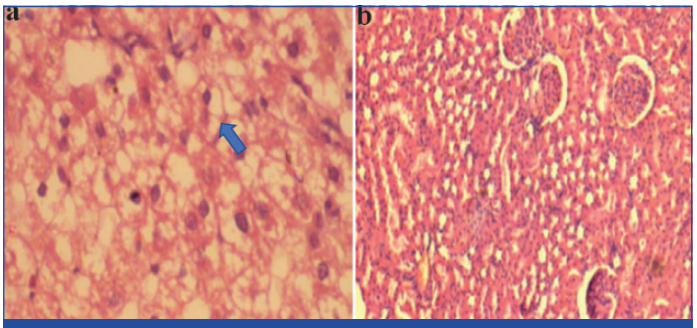
Histological profile of group I animals treated with distilled water (vehicle treated) shows normal hepatic architecture with radially placed hepatic cells, large spherical nucleus and granular cytoplasm. Areas around portal triad and Central Vein (CV) showed no apparent injury. The [Table/Fig-5a] Liver sections of group II animals who received acetaminophen alone showed extensive fatty changes, cloudy swelling, parenchymal haemorrhage, Periportal Inflammation (PPI), vascular dilatation and congestion [Table/Fig-6a]. Group III animals treated with NAC showed mild cloudy swelling and focal mild fatty changes [Table/Fig-7a]. *Aerva lanata* root extract monotherapy (group IV) showed normal hepatocytes with vascular congestion and dilatation. Occasional mild cloudy swelling is seen [Table/Fig-8a]. Combination therapy of *Aerva lanata* root extract and NAC in group V showed normal hepatic architecture with mild vessel dilatation and focal mild cloudy swelling [Table/Fig-9a]. Histopathological examinations of sections of kidney tissue from group I (Vehicle) which received distilled water showed normal architecture with glomeruli and tubules [Table/Fig-5b]. Kidney sections of group II animals showed congested blood vessels as shown in [Table/Fig-6b]. Group III, IV, V showed normal architecture of kidney [Table/Fig-7b-9b].



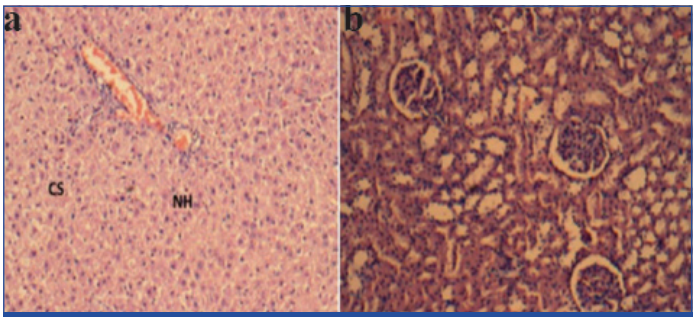
[Table/Fig-5a-b]: Normal architecture of liver with central vein (CV) and portal traid (H&E 4X): (a) and Kidney showing glomeruli and tubules (H&E 10X): (b) (group I).



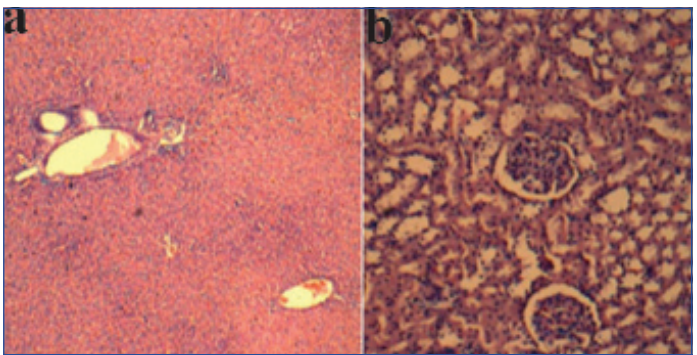
[Table/Fig-6a-b]: Liver showing extensive Periportal Inflammation (PPI) (H&E 10X): (a) and Kidney showing congested blood vessels. (H&E 40X); (b) (group II).



[Table/Fig-7a-b]: Liver showing mild cloudy swelling and mild fatty changes. (H&E 10X) (a). Normal architecture of kidney showing glomeruli and tubules. (H&E 10X) (b). (group III).



[Table/Fig-8a-b]: Liver showing normal hepatocytes (NH) with mild cloudy swelling (CS). (H&E 10X) (a). Normal architecture of kidney showing glomeruli and tubules. (H&E 10X) (b) (group IV).



[Table/Fig-9a-b]: Liver showing normal hepatocytes with mild vascular dilatation. (H&E 4X) (a). Normal architecture of kidney showing glomeruli and tubules. (H&E 10X) (b). (group V).

DISCUSSION

The traditional drug NAC used as an antidote for acetaminophen poisoning is associated with increased risk of adverse drug reactions like anaphylactoid reaction, etc. There is an a need of a drug with lesser adverse reactions. This study evaluated the effect of

hydroalcoholic root extract of *Aerva lanata* in treating acetaminophen induced hepatotoxicity in experimental albino Wistar rats.

1. Liver parameters

(i) AST and ALT: In this study, acetaminophen group showed a significant increase in AST and ALT levels when compared with vehicle treated group ($p<0.001$). Treatment with NAC alone reduces the AST and ALT levels ($p<0.01$) on comparison with acetaminophen group, which was similar to the study conducted by Kamalakannan N et al., demonstrating NAC significantly reduced the AST levels of Wistar rats [12]. The present study suggested that *Aerva lanata* root extract monotherapy significantly decreased the AST and ALT levels ($p<0.05$) compared to acetaminophen treated group. Reduction in aminotransferase levels was similar to another study [13] which showed that *Aerva lanata* root extract monotherapy significantly decreased AST and ALT levels when compared with acetaminophen treated animals.

Moreover, the combination of *Aerva lanata* root extract and NAC showed a significant reduction of the AST and ALT levels compared to acetaminophen group ($p<0.001$) and also showed a highly significant decrease in AST level ($p<0.01$) compared to *Aerva lanata* monotherapy and NAC monotherapy groups. This profound decrease in aminotransferase levels could be due to the additive effect of these two drugs (*Aerva lanata* root extract and NAC) when given together.

(ii) GGT: Increase in GGT value was seen in acetaminophen treated group in comparison with vehicle treated group ($p<0.001$). NAC reduced the GGT values when given alone ($p<0.01$) on comparison with acetaminophen group which is on par with the study conducted by Kamalakannan N et al., [12]. Present study showed that monotherapy with *Aerva lanata* root extract significantly reduced the GGT levels when compared with animals which received acetaminophen alone ($p<0.05$). Our study results were also identical to Rajkapoor B et al., which includes a significant decrease in GGT level by Phyllanthus polyphyllus leaf extract monotherapy when compared with acetaminophen treated group [14]. Furthermore present study also showed that *Aerva lanata* root extract when given in combination with NAC reduced the GGT levels in a highly significant manner on comparison with both acetaminophen group ($p<0.001$) and NAC monotherapy group animals ($p<0.05$)

(iii) Bilirubin: Administration of acetaminophen showed a significant increase of total ($p<0.01$) and direct bilirubin ($p<0.001$) levels when compared with animals in the vehicle treated group which is similar to the study conducted by Ramana Rao R et al., Iyanda AA and Adeniyi FAA and Soni RK et al., [15-17]. NAC and *Aerva lanata* root extract monotherapy showed a reduction of both total and direct bilirubin ($p<0.05$) in a similar fashion, whereas highly significant decrease in bilirubin levels were observed in the group which received combination of *Aerva lanata* root extract and NAC when compared with acetaminophen treated group ($p<0.01$). This is also identical to the results of Manokaran S et al., which produced a significant reduction of bilirubin levels [8]. No significant difference in bilirubin levels was observed on comparison with NAC or root extract monotherapy. This combination therapy showed a favourable decrease in liver parameters namely AST, ALT, GGT, bilirubin levels which could be due to possible synergistic action among the two drugs.

2. Renal Parameters

Significant elevation of blood urea in acetaminophen group animals ($p<0.001$) on comparison with vehicle treated group is identical to the study conducted by Pathan MM et al., [18]. In present study, administration of NAC alone showed no decrease in blood urea when compared with acetaminophen group. The present study showed that *Aerva lanata* root extract when given alone or in combination with NAC produced a highly significant reduction ($p<0.001$) in blood urea level on comparison with acetaminophen group. This result is in conjunction with the study conducted by Barkavi R and Venkatalakshmi P who demonstrated decrease in both urea and creatinine levels [19]. Similar reduction in blood urea concentration was also seen when compared with NAC monotherapy ($p<0.001$) group animals. However, no significant changes in creatinine levels were observed in any treatment groups of the current study.

3. Histopathological studies

In the current study, animals in the vehicle treated group showed a normal histological liver profile. The sections of livers of animals belonged to acetaminophen group (group II) showed cloudy swelling, fatty changes, parenchymal haemorrhage, PPI, vascular dilatation and congestion which is at par with the study conducted by Kanchana N and Sadiq M [20]. Histopathological liver profiles of animals belonged to both *Aerva lanata* root extract monotherapy and in combination with NAC showed a significant improvement over the animals of acetaminophen group. It is also evident from the results that the combination therapy produced significant reversal of the hepatotoxicity induced by acetaminophen, with normal hepatic architecture and occasional focal mild cloudy swelling.

Even though, many studies have been done on NAC in treating hepatotoxicity induced by acetaminophen, only a few have been conducted on hepatoprotective effect of *Aerva lanata* root extract. No study has been conducted by combining NAC and *Aerva lanata* root extract in exploring their synergistic effect in animal models. Standard animal model for hepatotoxicity was used in this study. Liver and renal parameters along with histopathological examination were also monitored in this study and showed that the combination therapy has significant effect in treating hepatotoxicity induced by acetaminophen along with renoprotective property.

Limitation(s)

This study carries its own limitations like the phytochemical analysis for hydroalcoholic root extract of *Aerva lanata* was not done and the total protein and serum albumin values were not included. The effects of this extract on gluconeogenesis of liver was not studied, and toxicity studies for this extract needs to be explored.

CONCLUSION(S)

It is to conclude that the hydroalcoholic root extract of *Aerva lanata* has a significant effect in treatment of hepatotoxicity induced by acetaminophen. However, combination therapy is a better treatment regimen compared with the monotherapy of NAC or *Aerva lanata* root extract. It has additional hepatoprotective and renoprotective effects. Hence, combination of hydroalcoholic root extract of *Aerva lanata* along with NAC can be effective in treating acetaminophen poisoning. It is worthwhile to consider this aspect for further clinical trials and application in patients with acetaminophen over dosage.

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PARTICULARS OF CONTRIBUTORS:
1. Team Leader, Department of Medical Review Safety Physician, Accenture Operations Pvt. Ltd., Chennai, Tamil Nadu, India.
2. Assistant Professor, Department of Biochemistry, Government Thiruvannamalai Medical College and Hospital, Thiruvannamalai, Tamil Nadu, India.
3. Assistant Professor, Department of Pharmacology, Government Thiruvannamalai Medical College and Hospital, Thiruvannamalai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Nileshraj Govindaraj,
Flat F1, Sai Nivas, Sai Balaji Foundation, Nanmangalam, Chennai, Tamil Nadu, India.
E-mail: nileshgovindaraj@gmail.com

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