

Hepatoprotective Effects of *Ageratum conyzoides* L. on Biochemical Indices Induced by Acetaminophen Toxicity in Wistar rats

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ABSTRACT

Ageratum conyzoides L. (Compositae) has been used in various parts of the world for the treatment of various diseases based on their age-old use in folklore system. Present study was aimed to investigate the hepatoprotective activity of acetone and n-hexane extracts of *Ageratum conyzoides* in wistar rats following acetaminophen (APAP) induced hepatotoxicity. Single high dose exposure of APAP significantly ($p < 0.05$) increased in ALT, AST, and GGT activity and levels of BUN, CR, unconjugated bilirubin and A/G ratio, whereas activity of LDH-P, total protein, albumin, globulin and conjugated bilirubin were significantly ($p < 0.05$) reduced as compared to control. Pre-exposure with acetone and n-hexane extracts of *A. conyzoides* restore the values of ALT, GGT, LDH-P, albumin, unconjugated and conjugated bilirubin as compared to control whereas the AST, globulin, A/G ratio, BUN and CR levels are not restored by administration of plant extracts. It is evident from observations that acetone and n-hexane extracts of *A. conyzoides* was able to restore the levels of SGPT, SGOT, LDH and bilirubin as an indication of the stabilization of plasma membrane as well as repair of hepatic tissue damages caused by APAP.

INTRODUCTION

Liver, the most versatile complex internal organ of mammalian body, plays a vital role in synthesis of macromolecules, homeostasis of internal environment and conversion of endogenous and exogenous chemical to harmless and excretable compounds. Since chronic hepatic diseases stand as one of the foremost health troubles worldwide, with liver cirrhosis and drug induced liver injury leading to death in western and developing countries. Among drug induced liver injury, acetaminophen (APAP) is one of the most widely used hepatotoxic drugs, is safe at therapeutic doses, but causes liver failure in overdoses (Lewerenz *et al.*, 2003). When a normal dose is used, APAP is metabolized via glucuronidation and sulfuration reactions occurring primarily in the liver, and results in water-soluble metabolites that are excreted via kidney. A small fraction of the drug is subjected to oxidation reactions catalyzed by CYP450 enzymes in the liver, resulting in generation of N-acetyl-p-benzoquinoneimine (NAPQI), a highly reactive intermediate that

triggers ensuing liver damage (Mitchell *et al.*, 1973; Nelson, 1990). Alterations in the liver functions due to damage further aggravated the conditions due to improper metabolism of exogenous and endogenous molecules. APAP induced hepatotoxicity is a major health issue that challenges not only health care professionals but also the pharmaceutical industry and drug regulatory agencies (Gillette, 2000). Traditional medicines are effective in certain disease of liver and are based on their age-old use in folklore system of medicine. Because of diverse protective nature of herbal preparations, which are accessible and do not require laborious pharmaceutical synthesis have been tried to minimize the hepatic damage induced by different chemical agents. (Subramonium and Puspagadan, 1999; Hatem *et al.*, 2010).

Ageratum conyzoides L. (Compositae) has been used in various parts of the world like Africa, Asia and South America as folk medicine (Gonzalez *et al.*, 1991). Phytochemical investigations on *A. conyzoides* have identified a number of secondary metabolites such as flavonoids, monoterpenes, sesquiterpenes, coumarins etc (Sultana *et al.*, 2012). Various investigations have verified its analgesic effect in rats (Menut *et al.*, 1993), antioxidative effect (Jagetia *et al.*, 2003), hepatoprotective effects (Ita *et al.*, 2009) and as a blood booster (Ita *et al.*, 2007).

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The plant has appreciable antioxidant property and protective action against carbon tetrachloride induced hepatotoxicity (Atoui *et al.*, 2003; Hatem *et al.*, 2010) thus, present study was aimed to exploration of protection on biochemical parameters by acetone and n-hexane extracts of *Ageratum conyzoides* against acetaminophen induced hepatotoxicity in wistar rats.

MATERIALS AND METHODS

Collection and Preparation of plant extracts

Whole plant of *Ageratum conyzoides* L (AC) were collected after proper identification by the curator of the Herbarium, Botany Department, University of Jammu from the R S Pura, Jammu. The fresh plant materials collected were air-dried for a period of two weeks and were pre-crushed in a mortar and later pulverized into fine powder using electric blender. The powder will be sieved through a mesh (2mm mesh size). Sieved powder of plant was used for preparation of acetone and n-hexane extracts. Extract were prepared by adding 10 gm of the plant powder in 200 ml of solvent in extract container of soxhlet extractor equipment. Extraction process was done for 24 hrs at 45-65°C & semisolid viscous masses were dried at 40°C in rotary evaporator and thereafter stored in airtight containers at refrigerated conditions -20°C till until further uses. The extract and the reference drug were suspended in carboxy methyl cellulose (CMC) (0.5 %) in distilled water separately and used for *in vivo* investigations.

Drugs & Chemicals

Acetaminophen and silymarin were obtained from Sigma Chemical Company (St. Louis MO, USA). All other chemicals utilized were analytical grade obtained either from Hi Media (Mumbai) or SD-Fine Chemicals (Mumbai).

Experimental protocol

The study was conducted on apparently healthy 42 wistar rats of either sex weighing 150 to 250g procured from Indian Institute of Integrative Medicine (CSIR Lab), Jammu. Animals were randomly divided into seven groups with six rats in each group. The animals were maintained under standard managemental conditions, provided standard pelleted ration and drinking water *ad libitum*. A daily cycle of 12 h of light and 12 h of darkness was provided to animals. Prior to start of experiment, the rats were acclimatized in the laboratory conditions for a period of more than 3 weeks. The normal control (Group I) will be receiving only distilled water for seven days, Group II receive carboxy methylcellulose (0.5% CMC) 1ml/rats/day and a single oral dose of acetaminophen (3g/kg, bw) on the fifth day of the administration. Group-III was fed with standard drug silymarin 100mg/kg, bw orally daily for seven days and received acetaminophen at 3g/kg bw orally on the fifth day. Group IV and V received acetone and n-hexane extracts of *A. conyzoides* (200mg/kg, bw, orally) for seven days respectively. Group VI and VII received pretreatment of the acetone and n-hexane extracts for

seven days respectively and acetaminophen was administered on the fifth day of the seven days administration. At the end of the experiment (48 hours after acetaminophen administration i.e. day 7) blood from all the animals were collected from infra orbital fossa in a clean, sterilized test tubes containing heparin (John *et al.*, 2011). All the experimental animals were kept under constant observation during entire period of study. Experimental protocol was approved by institutional ethics committee.

Assay procedure

The collected blood samples were centrifuged at 3000 rpm for 15 min and the plasma was harvested in clean sterile glass test tubes and stored at -20°C till further analysis. Activities of alanine aminotransaminase (ALT), aspartate aminotransaminase (AST), gamma glutamyl transpeptidase (GGT) and lactate dehydrogenase (LDH-P) and levels of total protein, albumin, blood urea nitrogen (BUN), creatinine (CR), unconjugated and conjugated bilirubin in plasma were determined by standard kits from Transasia Bio-Medicals by using chemistry analyzer (Kayto). Values of globulin were determined by subtracting albumin from total protein.

Statistical analysis

The results were subjected to analysis of variance (ANOVA) in completely randomized design (CRD) with statistical significance at $p < 0.05$ being tested using the Duncan Multiple Range Test.

RESULTS

Table 1 show the protective effects of acetone and n-hexane extracts of *Ageratum conyzoides* on activities of different specific biomarker for the liver damage like ALT, AST, LDH-P, and GGT in control and treated animals. ALT, AST, and GGT were significantly $p < 0.05$ increased whereas activity of LDH-P was significantly reduced ($p < 0.05$) in APAP treated group as compared to control animals. Treatment with silymarin significantly reduced the activity of GGT, AST, ALT and significant increased LDH-P activity as compared to APAP treated animals. Pretreatment with acetone and n-hexane extracts of *A. conyzoides* restore the values of ALT, GGT and LDH-P as compared to control whereas the values of AST are not restored by administration of both of the plant extracts.

Total protein, albumin, globulin and A/G ratio in control and acetone and n-hexane extracts of *A. conyzoides* group of rats were presented in table 2. Values of total protein, albumin and globulin were significantly reduced ($p < 0.05$) whereas A/G ratio was significantly increased ($p < 0.05$) in APAP treated animals as compared to control animals. Pre exposure with silymarin significantly increased ($p < 0.05$) total protein, albumin, globulin as compared to APAP exposed group and values are comparable to control group rats. Pre-exposure with the n-hexane extract restore the albumin and globulin but fails to maintain the globulin and A/G ratio as compared to control values.

Table 1: Protective effects of acetone and n-hexane extracts of *Ageratum conyzoides* on activities of ALT, AST, GGT and LDH-P in plasma of control and experimental groups of rats.

Group	AST(IU/L)	ALT(IU/L)	GGT (U/L)	LDH-P (IU/L)
I. Control	71.22 ^a ± 5.51	46.54 ^a ± 3.79	1.82 ^a ± 0.05	598.47 ^a ± 29.30
II. APAP	130.26 ^b ± 13.58	114.77 ^b ± 5.01	4.33 ^b ± 0.52	150.86 ^b ± 15.12
III. Silymarin + APAP	94.21 ^a ± 3.51	93.21 ^b ± 4.57	2.03 ^a ± 0.75	242.74 ^d ± 26.70
IV. Acetone Ext of AC	99.53 ^a ± 6.53	62.20 ^a ± 7.15	2.65 ^c ± 0.34	242.99 ^d ± 17.61
V. n-hexane Ext of AC	105.57 ^b ± 5.70	62.18 ^a ± 4.10	1.98 ^a ± 0.56	384.27 ^c ± 55.96
VI. Acetone Ext of AC + APAP	104.13 ^b ± 4.95	59.35 ^a ± 2.28	1.93 ^a ± 0.63	322.88 ^c ± 29.20
VII. n-hexane Ext AC + APAP	119.46 ^b ± 7.75	53.60 ^a ± 4.09	2.01 ^a ± 0.67	481.29 ^a ± 53.14

Values are given as mean ± SE of six animals in each groups. Values having different superscripts (a, b, c) in a column are statistically differ significantly p < 0.05. (APAP - Acetaminophen, AC - *Ageratum conyzoides*)

Table 2: Protective effects of acetone and n-hexane extracts of *Ageratum conyzoides* on total protein, albumin, globulin, A/G ratio in plasma of control and experimental groups of rats.

Group	Total protein (gm/dl)	Albumin(gm/dl)	Globulin (gm/dl)	A/G ratio
I. Control	6.19 ^a ± 0.28	5.60 ^a ± 0.29	1.63 ^a ± 0.37	3.48 ^a ± 0.67
II. APAP	5.06 ^c ± 0.34	5.12 ^b ± 0.18	1.24 ^b ± 0.36	7.88 ^b ± 3.79
III. Silymarin + APAP	5.95 ^a ± 0.22	5.41 ^a ± 0.20	1.53 ^a ± 0.35	3.56 ^a ± 0.91
IV. Acetone Ext of AC	5.52 ^b ± 0.29	4.01 ^c ± 0.38	1.68 ^a ± 0.21	2.48 ^a ± 0.33
V. n-hexane Ext of AC	4.99 ^b ± 0.36	4.50 ^c ± 0.25	0.91 ^c ± 0.20	5.45 ^b ± 1.12
VI. Acetone Ext of AC + APAP	5.84 ^a ± 0.26	4.77 ^c ± 0.25	1.07 ^c ± 0.14	4.86 ^b ± 0.75
VII. n-hexane Ext AC + APAP	6.10 ^a ± 0.48	5.32 ^a ± 0.35	1.08 ^c ± 0.20	5.18 ^b ± 0.68

Values are given as mean ± SE of six animals in each groups. Values having different superscripts (a, b, c) in a column are statistically differ significantly p < 0.05. (APAP - Acetaminophen, AC - *Ageratum conyzoides*)

Table 3: Protective effects of acetone and n-hexane extracts of *Ageratum conyzoides* on BUN, CR, unconjugated and conjugated bilirubin in plasma of control and experimental groups of rats.

Group	BUN(mg/dl)	CR (mg/dl)	Unconjugated bilirubin (mg/dl)	Conjugated bilirubin (mg/dl)
I. Control	37.27 ^a ± 4.19	0.81 ^a ± 0.10	0.88 ^a ± 0.03	0.68 ^a ± 0.03
II. APAP	60.56 ^b ± 6.35	0.89 ^b ± 0.04	1.44 ^b ± 0.15	0.52 ^b ± 0.01
III. Silymarin + APAP	75.97 ^c ± 4.51	0.85 ^a ± 0.03	0.72 ^a ± 0.08	0.53 ^b ± 0.01
IV. Acetone Ext of AC	79.64 ^c ± 2.66	0.69 ^c ± 0.05	0.66 ^c ± 0.04	0.52 ^b ± 0.01
V. n-hexane Ext of AC	83.94 ^c ± 3.43	0.80 ^a ± 0.05	0.82 ^a ± 0.08	0.54 ^b ± 0.02
VI. Acetone Ext of AC + APAP	80.30 ^c ± 3.69	0.86 ^b ± 0.04	0.95 ^a ± 0.08	0.64 ^a ± 0.07
VII. n-hexane Ext AC + APAP	80.87 ^c ± 3.66	0.99 ^b ± 0.05	0.93 ^a ± 0.08	0.71 ^a ± 0.04

Values are given as mean ± SE of six animals in each groups. Values having different superscripts (a, b, c) in a column are statistically differ significantly p < 0.05. (APAP - Acetaminophen, AC - *Ageratum conyzoides*)

Table 3 shows the protective effects of acetone and n-hexane extracts of *Ageratum conyzoides* on blood urea nitrogen (BUN), creatinine, unconjugated and conjugated bilirubin in blood of control and exposed animals. Significant increased (p < 0.05) levels of BUN, CR and unconjugated bilirubin and significant reduction (p < 0.05) in conjugated bilirubin was observed in APAP exposed group as compared to control animals. Pre-exposure to acetone and n-hexane extracts restore the unconjugated and conjugated bilirubin whereas values of BUN and CR were not restored by pre-exposure of extracts.

DISCUSSION

Herbal preparations have recently attracted much attention as alternative medicines useful for treatment and prevention of wide variety of disorders primarily induced by chemicals and/or stress exposure (Raj Kapoor *et al.*, 2008; Gillette, 2000). Several plant products have been examined which have potential to minimize the hepatic damage induced by different chemical agents (Subramonium and Puspangadan, 1999; Hatem *et al.*, 2010). Various studies have been also shown that aqueous and alcoholic extracts of different parts of *A. conyzoides* don't have

potential to produce toxicity in animal models upto 2gm/kg on oral administration (Ita *et al.*, 2009; Adebayo *et al.*, 2010; Sumalatha, 2012).

Drug induced liver injury is responsible for 5% of all hospital admissions and 50% of all acute liver failures (Ostapowicz *et al.*, 2002). Damage in liver primarily adversely affect the metabolism of endogenous & xenobiotics, fat digestion, glycogen storage, production of cholesterol and plasma proteins, etc leading to disturbance in homeostasis. In general, the extent of liver damage is assessed by levels of hepatic enzymes such as ALP, SGOT, SGPT and bilirubin release in circulation (Plaa and Charbonneau, 1994). The estimation of GGT is an important screening test with a high negative predictive value for hepatic disease (Nemesanszky, 1996). In present study elevated levels of AST, ALT, GGT and reduced levels of total protein, albumin has been attributed to the damaged structural integrity of the liver, because these cytoplasmic contents released into circulation after cellular damages (Sallie *et al.*, 1991). Similar results were also observed on different types of hepatotoxicants exposure (Singh *et al.*, 1998; Kim *et al.*, 1977). Pretreated group with acetone and n-hexane extracts of *A. conyzoides* has a reduced level of these enzymes compared with APAP exposure group showing that

extracts maintains the membrane integrity and functional capacity of the liver. These biochemical restoration by the plant extracts may be due to either inhibitory effects on cytochrome P-450 or/and promotion of its glucuronidation of toxic metabolites or directly scavenging activity of reactive intermediate molecules responsible for the hepatocytes insert.

Bilirubin (unconjugated) is a yellow pigment produced when heme is catabolized. Hepatocytes render bilirubin water-soluble and therefore easily excretable by conjugating it with glucuronic acid (conjugated bilirubin) prior to secreting it into bile. During exposure of hepatotoxicants levels of unconjugated bilirubin increased due to inability of hepatocytes for conjugation process.

Increased bilirubin may result from either production of more bilirubin than the liver can process; damage or obstruction of excretory ducts of the liver impairs its ability to excrete normal amounts of bilirubin.

Serum bilirubin is considered to be one of the true tests of liver functions since it reflects the ability of the liver to take-up and process bilirubin into bile. High levels of total bilirubin in the APAP-induced toxicity in rats may indicate severe illness attributed to the damaged structural integrity of the liver, because they are cytoplasmic in location and released into circulation after cellular damages (Sallie *et al.*, 1991).

Pretreated group with acetone and n-hexane extracts of *A. conyzoides* has a reduced level of these enzymes significantly compared with APAP exposure group showing that extracts maintains the functional capacity of the liver. Silymarin, a standardized extract of *Silybum marianum* (Compositae) is also a known potent hepatoprotective agent. It reverses hepatotoxin-induced alterations of biochemical parameters and has so far been the most thoroughly investigated of all the plant substances in prevented liver damage induced by carbon tetra chloride, D-galN and APAP in rat models (Ramellini and Meldoles, 1976; Bahati *et al.*, 2006).

The total protein, albumin and globulin level may decrease due to liver dysfunction, malnutrition, diarrhea, nephrosis, acute hemolytic anemia and pregnancy. Prolonged destruction of the hepatic cells results in more hepatic releases to exacerbate hepatic dysfunction and causes decrease in the serum levels of total protein, albumin and globulin.

Similar observations were also reported by Hattori *et al.*, (1990) and Emmanuel *et al.*, (1995) against acetaminophen-induced hepatic damage. The increased concentration of BUN and CR in group given APAP may be linked to protein metabolism. Among the negative acute-phase proteins, of which the synthesis and secretion are decreased, are albumin, transferrin and transthyretin (Trey and Kushner, 1995). The results of this study equally showed decreased concentrations of albumin and total protein in group given APAP alone when compared with control animals. However, administration of extracts of *Ageratum conyzoides* ameliorated the effect. It is evident from observation that acetone and n-hexane extracts of *A. conyzoides* was able to

restore the levels of SGPT, SGOT, LDH and bilirubin as an indication of the stabilization of plasma membrane as well as repair of hepatic tissue damages caused by APAP.

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