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Toxicological Studies of Two Compounds Isolated from *Loranthus globosus* Roxb

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Abstract: The sub-acute toxicities of two compounds 3,4-dimethoxycinnamyl alcohol (1) and 3,4,5-trimethoxycinnamyl alcohol (2) isolated from the plant *Loranthus globosus* Roxb were studied on long Evan's rats. The studies included the gross general observation such as changes in body weight, haematological profiles [total count of Red Blood Cells (RBC) and White Blood Cells (WBC), differential count of WBC, platelet count and Haemoglobin (Hb) %], biochemical parameters of blood [Serum Glutamate Oxaloacetate Transaminase (SGOT), Serum Glutamate Pyruvate Transaminase (SGPT), Serum Alkaline Phosphatase (SALP), urea and creatinine) and histopathology of the liver, kidney, heart and lung of both control and experimental groups of rats. The changes in haematological and biochemical parameters were statistically not significant after the administration of compounds 1 and 2 in a dose of 300 μg/rat/day for consecutive 14 days. No abnormality was found in the histopathology of the liver, kidney, heart and lung in the experimental groups of rats following same dose when compared with control group. This preliminary study suggests that the isolated compounds may be used safely for clinical trial.

Key words: Toxicological studies, cinnamyl alcohol, *Loranthus globosus*

INTRODUCTION

The importance of plant in human civilization is very great. Human being and other living organisms are to depend, to every great extent, on the plant kingdom for many of their daily necessities of life since the beginning of life on earth. Today standing in the twenty-first century, in the age of massive development of modern science, mankind still depends on nature for its survival. Interestingly people back to use natural products rather than synthetic products to cure diseases and relieve physical sufferings. Therapeutic agents may be of plants, animals or mineral origin. Among these plants are potent sources. They are popularized for thousands of years and continue to rely on them for health care due to their effectiveness, easy availability, low cost and comparatively being devoid of serious toxic effects. Plants contain a large number of chemically diverse and biologically interesting compounds. The past century has seen the increasing importance of plants in the development of drugs for the treatment of diseases ranging from bacterial infection to cardiovascular problems and cancer. An impressive number of drugs have been isolated from plants.

Attempts were taken to find out new and more bioactive compounds from the plant *Loranthus globosus* (Synonym: *Macrosolen chochinsinensis*). The plant, a parasitic shrub, locally known as Choto Banda belongs to the family Loranthaceae, is widely distributed in Bangladesh Tropical Himalaya; Nepal, Wallich, Sikkim, alt. 1-4000 ft., J.D.H. Bengal, Cachar, Khasia Mts., Pegu, Penang, Malacca and Java (Kirtikar and Basu, 1994; Alam, 1986). The whole plant was collected from a host mango tree (*Mangifera indica* L.) during April 2001 from Rajshahi, Bangladesh. The plant was authenticated by Professor ATM Naderuzzaman, Department of Botany, University of Rajshahi where a voucher specimen (Collection Number 98) has been preserved. The water extract of bark is used in the treatment of menstrual abnormalities and to check abortion (Information gathered from a herbalist of Northern District, Bangladesh). A decoction of bark and leaves is given for the management of acute and chronic diarrhoea (Hooker, 1890). The ethyl acetate extract of the bark of this plant showed significant antimicrobial and cytotoxic effects (Islam *et al*., 2004). Bark is also used in headache and itch (Kirtikar *et al*., 1994). Various species of Loranthaceae family are reported to possess antihypertensive effect (Alam, 1986), antiviral effect (Hasan, 1993; Lohezic-Le *et al*., 2002), antihepatotoxic action (ISI, 2002), antidiabetic property (Harvala *et al*., 1984; Obatoni *et al*., 1994), immunobiologic response (Fernandez *et al*., 2003), anticancer effect (Ohashi *et al*., 2003), antitumor activity (Zarkovic *et al*., 1998; Yoon *et al*., 1999), antimicrobial and anticonvulsant

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activity (Amabeoku *et al.*, 1998) and for the treatment of schizophrenia (Block and Stevenson, 1971). We previously isolated two compounds 3,4-dimethoxycinnamyl alcohol and 3,4,5-trimethoxycinnamyl alcohol from the plant *Loranthus globosus* by column and preparative thin layer chromatography and characterized by spectral analysis (Sadik *et al.*, 2003). These compounds showed significant antimicrobial and cytotoxic effects.

Toxicology is the aspect of pharmacology that deals with the adverse effect of bioactive substances on living creature along with their diagnosis and clinical use. In order to develop and establish the safety and efficacy level of a new drug, toxicological studies are very essential experiments in animals like rat, guinea pigs, dog, monkey etc under various conditions of drug. No drug is used clinically without its clinical trial as well as toxicity studies. Toxicological data help to make decision whether a new drug is adopted for clinical use or not. This led to the present investigation on the sub-acute toxicity study of the compounds 3,4-dimethoxycinnamyl alcohol (1) and 3,4,5-trimethoxycinnamyl alcohol (2) at a dose of 300 μg/day/rat on 6 Long Evan's rats for 14 consecutive days.

MATERIALS AND METHODS

The experimental works were done in the department of Pharmacy, University of Rajshahi, Rajshahi, Bangladesh after the collection of plant materials.

Collection of experimental rats: For the purpose of subacute toxicity studies, 12 Long Evan's male rats of about five weeks old weighing 120-140 g were collected from the Animal Branch of International Center for Diarrhoeal Disease Research, Bangladesh (ICDDR, B).

Maintenance of the rats: The rats were kept in properly numbered iron cages individually in a hygienic animal house with an optimum temperature (25-30°C) and were given standard laboratory diet (Hawk *et al.*, 1954). The animals were maintained in this way for 15 days before drug administration and continued up to the end of the experiment.

Grouping of the rats: Individual weight of the rats was taken and they were grouped into three. The rats of group B (4 rats, average weight 56 g) and C (4 rats, average weight 58 g) were used for experiment while those of group A were used as control (4 rats, average weight 51 g).

Administration of the sample: The compounds 1 and 2 were dissolved separately in distilled water using tween-20 as co-solvent, so that 0.3 mL contained 300 μg of the compound. The rats in group A, B and C were injected intraperitoneally with vehicle (300 μL isotonic solution), compound 1 and 2, respectively at a dose of 300 μg/day/rat for 14 consecutive days. On the 15th day blood was collected from external jugular vein under mild ether anaesthesia for the estimation of haematological and biochemical parameters. Then all the rats were sacrificed and liver, kidney, heart and lung were removed for histopathological study.

Gross general observation: During the whole experiment period their behaviour, CNS excitation and depression, reflexes, muscular weakness, salivation, diarrhoea and food intake were observed. The body weight of each rat of groups A, B and C were measured before drug administration, after completion of the treatment and prior to sacrificing the rats.

Investigation of haematological profiles: The haematological parameters like Total Count (TC) of RBC and WBC, Differential Count (DC) of WBC, platelet count and haemoglobin percentage were performed just before drug intake and also on 14th day pf drug administration. For TC, DC and platelet count blood was drawn from the tail veins of the experimental and the control rats of either groups and blood smears were made on glass slides followed by staining with Leisman reagent. Blood was also drawn from each rat with the help of capillary tube for estimating the haemoglobin percentage by Van Kampen-Ziftra's method.

Biochemical parameters of blood: To determine biochemical parameters such as SGOT (Serum Glutamate Oxaloacetate Transaminase), SGPT (Serum Glutamate Pyruvate Transaminase), SALP (Serum Alkaline Phosphatase), serum bilirubin, creatinine and urea blood samples were collected from each rat of either group from their throat vein while they were sacrificed after 14 days of drug administration. The samples were analysed using the usual procedures reported by King and Armstrong (1934), Reitman and Frankel (1957), Fawcett and Scott (1960) and Coulombe and Favreau (1963).

Histopathological investigation: For histopathological investigation, the liver, kidney, lung and heart of all experimental and control rats were isolated after sacrificing them at the end of 14 days of drug administration. These tissues were separately sliced in pieces, fixed in 10% formaline for 3 days, processed, stained, mounted on glass slides and observed under power microscope.

RESULTS AND DISCUSSION

Table 1 showed that the rats of group A, B and C being treated with vehicle, compound 1 and 2, respectively exhibited no signs of tremor, convulsions and reflex abnormalities. The body weights of all the rats in each group were increased after treatment. Moreover, no muscular numbness of the hind and fore legs, salivation or diarrhoea was observed. The food intake per day was also found normal. So, from the results, it is decided that the drug has no effect on normal growth.

Table 2-4 showed haematological profiles that were studied on experimental rats in compared to control rats and 14 days of treatment. Each time the value of the

Table 1: Effect of the compounds 1 and 2 on body weight of rats

Group	Dose (i.p.) µg/rat/day	Body weight (g) before drug administration n = 4, $M_1 \pm SD_1$	Body weight (g) after drug administration n = 4, $M_2 \pm SD_2$	% of change	t_c	t_s	Remark
A	300 µL vehicle	51, 53, 50, 50 51±1.22	54, 55, 51, 52 52±1.87	+1.96	0.896	2.447	NS
B	300 µg compound 1	56.1, 58, 54, 57.1 56.3±1.49	58, 61, 56, 59 58.5±1.80	+3.91	1.883	2.447	NS
C	300 µg compound 2	59, 57.6, 60, 56.2 58.2±1.44	61, 58, 62, 60 60.25±1.48	+3.52	1.986	2.447	NS

t_c indicates calculated value; t_s indicates t-value at 5% level of significance; M_1 and M_2, sample mean value; SD_1 and SD_2, standard deviation; n, number of rats; NS, not significant; +, increase; -, decrease

Table 2: Haematological profiles of group A (rat treated with vehicle)

	Normal rat	Treated with vehicle	
Haematological parameters	1st day n = 4, $M_1 \pm SD_1$	7th day n = 4, $M_2 \pm SD_2$	14th day n = 4, $M_3 \pm SD_3$
Total RBC count (million/cc)	3.8, 3.9, 3.8, 3.7 3.8±0.07	4.0, 4.1, 4.0, 3.9 4.0±0.07	4.0, 4.1, 3.9, 3.9 3.975±0.08
Total WBC count (thousand/cc)	5.9, 6.1, 5.7, 5.7 5.85±0.17	6.1, 6.2, 5.6, 5.9 5.95±0.23	6.2, 6.3, 5.8, 5.6 5.975±0.29
Differential count of WBC in %			
a. Neutrophil	47, 46, 49, 50 48±1.58	46, 48, 50, 48 48±1.41	46, 45, 47, 46 46±0.71
b. Lymphocyte	39, 36, 41, 38 38.5±1.80	38, 37, 40, 39 38.5±1.12	42, 40, 44, 41 41.75±1.48
c. Monocyte	2, 0, 1, 1 1±0.71	1, 1, 2, 1 1.25±0.43	2, 2, 3, 3 2.5±0.5
d. Eosinophil	4, 3, 2, 3 3±0.71	4, 2, 3, 4 3.25±0.83	5, 2, 4, 3 3.5±1.12
Platelet count (no./cc)	270000, 285000, 265000, 269000 272250±7595.2	281000, 283000, 269000, 273000 276500±5722.8	288000, 291000, 278000, 281000 284500±5220.2
Haemoglobin (%)	58, 57, 61, 59 58.75±1.48	60, 58, 61, 61 60±1.22	63, 58, 62, 63 61.5±2.06
ESR (mm/1st h)	21, 22, 19, 20 20.5±1.12	21, 21, 20, 22 21±0.71	22, 21, 21, 22 21.5±0.5

Table 3: Haematological profile of group B (rat treated with compound 1)

	Normal rat	Treated with vehicle	
Haematological parameters	1st day n = 4, $M_1 \pm SD_1$	7th day n = 4, $M_2 \pm SD_2$	14th day n = 4, $M_3 \pm SD_3$
Total RBC count (million/cc)	3.2, 3.4, 3.3, 3.0 3.225±0.148	3.4, 3.6, 3.7, 3.3 3.5±0.158	3.6, 3.7, 3.6, 3.5 3.6±0.07
Total WBC count (thousand/cc)	5.4, 5.1, 5.8, 5.3 5.4±0.255	5.6, 5.4, 6.1, 5.4 5.625±0.286	5.7, 5.3, 6.3, 5.8 5.775±0.356
Differential count of WBC in %			
a. Neutrophil	43, 46, 44, 46 44.75±1.299	45, 47, 46, 48 46.5±1.118	46, 49, 46, 49 47.5±1.5
b. Lymphocyte	34, 34, 28, 31 31.75±2.487	32, 31, 33, 30 31.50±1.118	30, 34, 32, 32 32±1.414
c. Eosinophil	2, 3, 4, 4 3.25±0.829	4, 3, 2, 2 2.75±0.829	1, 2, 2, 0 1.25±0.829
d. Monocyte	2, 1, 0, 1 1±0.707	3, 2, 1, 1 1.75±0.829	3, 2, 2, 3 2.5±0.5
Platelet count (no/cc)	245000, 250000, 246000, 242000 245750±2861.38	251000, 253000, 248000, 245000 249250±3031.1	249000, 255000, 251000, 248000 250750±2680.95
Haemoglobin (%)	50, 51, 56, 50 51.75±2.487	51, 53, 56, 51 52.75±2.046	52, 50, 59, 55 54±3.391
ESR (mm/1st h)	24, 25, 24, 22 23.75±1.089	25, 26, 24, 24 24.75±0.829	25, 25, 24, 24 24.5±0.5

Table 4: Haematological profile of group-C (Rat treated with Compound 2)

	Normal rat	Treated with vehicle	
Haematological parameters	1st day n = 4, $M_1 \pm SD_1$	7th day n = 4, $M_2 \pm SD_2$	14th day n = 4, $M_3 \pm SD_3$
Total RBC count (million/cc)	4.1, 3.9, 4.2, 3.7 3.975±0.192	4.2, 4.3, 4.1, 4.0 4.15±0.112	4.4, 4.6, 4.5, 4.4 4.475±0.083
Total WBC count (thousand/cc)	5.4, 5.2, 5.6, 5.4 5.4±0.141	5.7, 5.5, 5.5, 5.1 5.45±0.218	5.8, 5.6, 5.7, 5.5 5.65±0.112
Differential count of WBC in %			
a. Neutrophil	52, 50, 55, 51 52±1.87	55, 53, 52, 54 53.5±1.112	56, 51, 54, 56 54.25±2.046
b. Lymphocyte	33, 37, 35, 35 35±1.414	36, 36, 38, 40 37.5±1.658	37, 38, 40, 39 38.5±1.118
c. Eosinophil	4, 2, 5, 2 3.25±1.299	3, 4, 4, 2 3.25±0.829	3, 5, 3, 4 3.75±0.829
d. Monocyte	2, 0, 1, 2 3±0.829	1, 2, 3, 2 2±0.707	2, 1, 3, 3 2.25±0.829
Platelet count no/cc	300000, 320000, 290000, 300000 302500±10897.2	320000, 300000, 300000, 300000 305000±8660.3	340000, 310000, 290000, 300000 310000±18708.3
Haemoglobin (%)	58, 54, 57, 55 56±1.58	57, 58, 61, 56 58±1.87	60, 59, 62, 58 59.75±1.48
ESR (mm/1st h)	19, 17, 20, 18 18.5±1.112	21, 16, 22, 19 19.5±2.291	22, 19, 23, 22 21.5±1.5

Table 5: Effect of compound 1 on biochemical parameters of rat's blood after i.p. administration of 300 μg/rat/day for 14 consecutive days

Biochemical parameters	Group A, n = 4, $M_1 \pm SD_1$	Group B, n = 4, $M_2 \pm SD_2$	% of change	t_c	t_s	Remark
SGPT (IUL^{-1})	8, 9, 10, 8 8.75±0.829	9, 9, 11, 7 9±1.414	+2.86	0.305	2.447	NS
SGOT (IUL^{-1})	10, 11.9, 10.6, 11 10.875±0.69	9.5, 12, 11, 10.5 10.75±0.901	-1.15	0.220	2.447	NS
SALP (IUL^{-1})	44, 41, 37, 42 41±2.55	42, 42, 39, 43 41.5±1.5	+1.22	0.338	2.447	NS
Serum bilirubin (mmol L^{-1})	0.23, 0.29, 0.27, 0.31 0.275±0.03	0.25, 0.27, 0.28, 0.31 0.2775±0.022	+0.91	0.134	2.447	NS
Creatinine (mg %)	0.62, 0.59, 0.65, 0.56 0.605±0.034	0.64, 0.58, 0.66, 0.59 0.6175±0.033	+2.07	0.528	2.447	NS
Urea (mmol L^{-1})	18, 19, 19, 16 18±1.22	18, 17, 20, 18 18.25±1.09	+1.39	0.306	2.447	NS'

NS' indicates not significance

Table 6: Effect of Compound 2 on biochemical parameters of rat's blood after i.p. administration of 300 μg/rat/day for 14 consecutive days

Biochemical parameters	Group A, n = 4, $M_1 \pm SD_1$	Group B, n = 4, $M_2 \pm SD_2$	% of change	t_c	t_s	Remark
SGPT (IUL^{-1})	8, 9, 10, 8 8.75±0.829	9, 10, 11, 10 10±0.707	+14.29	2.295	2.447	NS
SGOT (IUL^{-1})	10, 11.9, 10.6, 11 10.875±0.69	11, 12.5, 11, 10.5 11.25±0.75	+3.45	0.736	2.447	NS
SALP (IUL^{-1})	44, 41, 37, 42 41±2.55	46, 43, 38, 41 42±2.915	+2.44	0.516	2.447	NS
Serum bilirubin (mmol L^{-1})	0.23, 0.29, 0.27, 0.31 0.275±0.03	0.22, 0.30, 0.29, 0.30 0.2775±0.033	0.91	0.112	2.447	NS
Creatinine (mg%)	0.62, 0.59, 0.65, 0.56 0.605±0. 034	0.64, 0.62, 0.63, 0.59 0.62±0.02	+2.48	0.761	2.447	NS
Urea (mmol L^{-1})	18, 19, 19, 16 18±1.22	20, 18, 20, 18 19±1.0	+5.56	1.268	2.447	NS

NS = Not Significance

parameters in each rat was changed slightly. However, the parameters remained within normal range.

Table 5 and 6 showed biochemical parameters on control group and treatment groups of rats. The parameters remained within the normal range. This indicates that the compounds 3,4-dimethoxycinnamyl alcohol (1) and 3,4,5-trimethoxycinnamyl alcohol (2) have no adverse effect on liver and kidney function.

After the 14th day of drug treatment, the animals of both control and experimental groups were sacrificed and the organs such as liver, kidney, heart and lung were isolated and histopathological experiments were done. No abnormality was observed between the control and the drug treated rats when the tissue slides were examined under microscope. This indicates that both compounds have no effect on cellular structure i.e., the compound does not cause degeneration of cells of these organs (Table 7).

As a part of our continuous research for novel plant metabolite, we isolated the active metabolites 3,4-dimethoxycinnamyl alcohol and 3,4,5-trimethoxycinnamyl alcohol. The present study is the continuation of this

Table 7: Effect of compounds 1 and 2 on histopathology of rat's kidney, heart, liver and lung tissue after i.p., administration of 300 μL/rat/day for 14 consecutive days

		Observation of histopathological change			
Group	Dose (i.p.) μL/rat/day	Kidney	Liver	Heart	Lung
A	300 μL (Vehicle)	NAD	NAD	NAD	NAD
B	300 μL (Compound 1)	NAD	NAD	NAD	NAD
C	300 μL (Compound 2)	NAD	NAD	NAD	NAD

NAD = No abnormality detected

toxicological study. The results of present study demonstrate that the compounds possess no adverse effect on Long Evan's rats at a dose of 300 μg/rat/day. Thus the findings of this investigation and previous investigation would give valuable support to make clinical trial of the isolated compounds to get a more potent bioactive agent.

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