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Evaluation of the Toxicological Effects of *Senecio aureus* Extract on the Liver and Hematological Parameters in Wistar Rats

Madu Joshua Osuigwe [1, 2,*] and Nadro Margret[1]

[1]*Department of Biochemistry, Modibbo Adama University of Technology Yola, Nigeria*

[2]*Department of Chemistry, American University of Nigeria Yola, Nigeria*

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Abstract

The use of *Senecio aureus* for therapeutic purposes is well known; however, in recent times, much concern has been raised regarding the toxicity of this plant extract used in treatment of gynecological disorders and jaundice. The sub-chronic oral toxicity of *Senecio aureus* was investigated. 16 male wistar rats were divided into four groups: control and treatments (100, 300 and 500 mg/kg body weight). Each group received the graded dose of the extract by gavage daily for 28 days while control received water. The administration of the extract resulted in significantly ($p<0.05$) increased total bilirubin and cholesterol and level from 29.14±1.18mg/dl and 83.00±7.16 mg/dl in the control to 53.19±6.11mg/dl and 166.67±14.03mg/dl, respectively, at dose of 500 mg/Kg body weight. In the hematological analysis, there were no significant changes compared to the control group ($p<0.05$). The present result suggests that the prolonged use of this plant extract at high dose in the treatment of diseases could be detrimental to the liver.

Keywords: : *Senecio auerus*, toxicity, jaundice, liver, hematology.

1. Introduction

The use of herbal remedies for the treatment of diseases has a long history and medicinal plants and their derivatives are still used in different parts of the world in one form or the other (Akhtar et al., 2009; Ekor, 2014). Herbal remedies have also been incorporated and consumed as food because of their acclaimed therapeutic effects and believe that the active principle in these herbs work together synergistically (Perumal-Samy and Gopalakrishnakone, 2010; Kasilo and Trapsida, 2011; Ekor, 2014; Si-Yuan, et al., 2014). The advocates of the consumption of herbals often claim that plant drugs are relatively non-toxic, safe and even free from any serious side effects (Goyal et al., 2007; Akhtar et al., 2009; Kasilo and Trapsida, 2011). However, scientific evaluation of plants often show that irrational consumption of these medicinal plants for their active principle have become one of the major causes hepatotoxicity and mortality around the globe (Gurib-Fakim, 2005; Tagliati et al., 2008; Akhtar et al., 2009; Kalatari and Rastmantsh, 2009).

Although a number of herbals are used in treating liver diseases, reports are accumulating about liver injury after intake of herbals including those advertised for the treatment of liver diseases (Stickel and Schuppan, 2007; Wurochekke et al., 2008). Acute and/or chronic liver damage have been reported after ingestion of some Chinese herbs and herbs that contain pyrolizidine alkaloids, kava, atractylis gummifera, senna alkaloids (Haller et al., 2002). Like many synthetic drugs, herbals undergo metabolic activation to form reactive metabolites often associated with drug toxicity (Zhang et al., 2015). The magnitude of the effect depends on the inherent toxicity of the substance, its route and duration of exposure to a particular organism, (Kenneth, 2000). Therefore, safety continues to be a major issue with the use of herbal remedies, hence, it becomes necessary to put in place appropriate measures to ensure that all herbal medicines are safe and of suitable quality.

The plant *senecio aureus* has a long historical use in some local communities of Adamawa State, Nigeria for the treatment of assorted gynecological disorders, speeding up protracted labor and relief of labor pains. It is also used in the treatment of excessive vaginal discharge as well as several kinds of menstrual problems. The plant is also used in the treatment of jaundice in children and infants. A previous study of the plant revealed that the plant was effective against CCl_4 induced liver damage, in the acute toxicity study single doses of up to 4000mg/Kg body weight was safe and resulted in dose dependent increase in Packed Cell Volume (PCV).

There is a high degree of concern regarding the safe use of this plant as its variant from other parts of the world has been reported to be medicinal while others reported it as toxic even at low doses (Wojcikowski et al., 2004).

* Corresponding author. e-mail: madu.joshua@aun.edu.ng.

However, variability in active ingredients due to environmental/growing conditions is known to affect most herbs; for this reason, the present study evaluated the toxicological impact of the plant extracts on the liver and hematological parameters in animal model.

2. Materials and methods

2.1. Collection of Plants Materials

Fresh *senecio aureus* plants were collected around footpaths by the football field and guest house of Modibbo Adama University of Technology Yola. The plant was authenticated in the Department of Plant Science, Modibbo Adama University of Technology, Yola. They were then air-dried and pulverized to fine powder.

2.2. Animals for the Experiment

Wistar rats (80-100g) were obtained from the National Veterinary Research Institute (NVRI), Vom Plateau State and were allowed to acclimatize for fifteen days prior to the commencement of the experiment. The animals were housed under standard experimental conditions and fed food and water ad libitum, vital feeds from Grand cereals and oil mills Jos were used.

2.3. Preparation of Plant Extract

Five hundred gram (500g) of the pulverized plant material was suspended in 2500 ml of 70% ethanol and allowed for 48 hours after which the mixture was sieved using a cheese cloth and then filtered using Whatman No-1 filter paper. The filtrate was concentrated to dryness in a water bath at 50°C and the yield was calculated as a percentage of the starting material.

2.4. Sub-Chronic Toxicity Study of the Plant Extract

The sub-chronic toxicity study was carried out according to the method described by Hassan et al. (2008). Four groups of rats were used in the study and each group consisted of four rats. The dried extract was dissolved in distilled water as vehicle of administration. The group and treatment were as follows:

Group I: Control group treated with distilled water.

Group II: *Senecio aureus* 100 mg/kg body weight of extract per day.

Group III: *Senecio aureus* 300 mg/kg body weight of extract per day.

Group IV: *Senecio aureus* 500 mg/kg body weight of extract per day.

Animals were fed food and water ad libitum. Each group received the respective treatment orally by gavage, once a day for 28 days and was observed for signs of toxicity.

2.5. Collection of Serum and Blood Samples

After the 28 days of treatment, the rats were fasted overnight and anesthetized using chloroform. Animals were sacrificed by cardiac puncture and blood samples collected. Blood samples were collected in EDTA bottle for hematological analysis and plain bottles for biochemical analysis. Samples for biochemical analysis were centrifuged at 2500 rpm for 10 minutes. The sera obtained were used for biochemical analysis.

2.6. Analysis of Biochemical Indices of Liver Function

Evaluation of liver function, activities of Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP), triglycerides, cholesterol, bilirubin, albumin and total protein in sera were determined using Randox diagnostic kits.

2.7. Hematological Studies

Hematological analyses were performed using automatic hematology analyzer (Coulter USA) on the whole as described by the manufacturer.

2.8. Statistical Analysis

Results are expressed as Mean ± SEM. Statistical analysis was performed by one way Analysis of Variance (ANOVA) followed by Tukey multiple comparison tests using graph pad prism 5. p values < 0.05 were considered significant.

3. Results and Discusson

Senecio aureus is utilized locally by some communities and indigenous healers to treat liver diseases especially jaundice as well as gynecological disorders. The safety of *Senecio aureus* on the liver was evaluated by determining its effects on enzyme and non-enzyme markers of the liver as well as hematological parameters. The results of this experiment showed that groups treated with *Senecio aureus* and control showed no visible changes in behavior and signs of intoxication during the 28-day period. However, at the end of the experiments, the percentage increase in weight of the animals receiving 300 and 500 mg/kg body weight of the extract when compared to the control were significantly ($p<0.05$) different as shown in Table 1.

Table 1: Showing the initial average weight, final average weight and percentage weight increase at the end of the experiment

Treatment	Control	100 mg/kg	300 mg/kg	500 mg/kg
Initial weight (g)	106.5±6.05	108.68±7.95	116.98±9.90	119.90±7.03
Final weight (g)	189.78±8.32	172.65±6.43	170.00±10.53	161.60±8.43
Weight increase (%)	78.19±7.81	58.86±5.91	45.32±9.00*	34.78±7.03*

Values are Mean ± SEM, n=4. Values with * significantly decreased relative to the control ($p<0.05$).

The assay of liver enzymes is an important index in liver diagnosis, disease investigation and assessment of drugs or plant extracts for safety/toxicity risk (Hassan et al., 2008).The greater the degree of damage in the liver, the higher the activities of these enzymes in the serum (Cheesbrough, 1991). In the present study, the administration of *Senecio aureus* extract for 28 days resulted in increased levels of AST and ALT, the increased levels of AST was not significant ($p<0.05$) as to suggest liver damage. This is very useful as more people are utilizing this plant as a traditional medicine today than they were a few years ago. Although some herbal medicines have a promising potential, many of them remain untested and their uses are usually not monitored.

This makes knowledge of their potential adverse effects very limited (Ekor, 2014). Levels of marker enzymes of liver injury increased significantly whenever the liver is compromised (Trung et al., 2010). The results of the enzyme and non-enzyme markers of the liver function after 28 days of treatment are shown in Tables 2 and 3. The results show that there was a dose-dependent increase in ALT, AST and ALP but these increases were not significant ($p<0.05$) compared to the control group as to suggest any damage to the liver. This dose-dependent increase suggests that a dose greater than 500 mg/kg for prolong periods, *Senecio aureus* may not be safe for the treatment of the diseases. The ALP activities generally increased during the experiment (Table 2) but not significant ($p<0.05$) as to suggest any damage. Increased ALP may be due to intra hepatic obstruction of the bile flow (Nwachukwu and Iweala, 2009).

Table 2: Results of post treatment of rats with ethanolic extract of *Senecio aureus* on some enzyme markers of liver function

Groups	AST(U/L)	ALT(U/L)	ALP(U/L)
Control	35.00±2.92	12.25±1.44	50.00±3.00
100 mg/kg	42.75±4.52	14.00±2.12	47.22±4.70
300 mg/kg	44.50±6.59	16.00±1.96	57.64±4.99
500 mg/kg	49.00±6.68	18.25±0.96	61.11±5.07

Values are Mean ± SEM, n=4. No significant changes were observed compared to the control group ($p<0.05$)

The decreasing serum albumin concentration resulting from the administration of the extract as the dose of the extract increase (Table 3) suggests that high doses of these extracts may impair the absorption of protein in the intestine or even liver damage (Grant and Kachmar, 1987; Ozaki et al., 1991). Bilirubin is mainly formed form the breakdown of hemoglobin in the cells of the liver, spleen and bone marrow. As the liver becomes irritated, the total bilirubin becomes elevated which may be a result of liver cell damage or bile duct damage within the liver itself (Ochei and Kolhatkar, 2005). In the present study there was a significant ($p>0.05$) increase in total bilirubin at dose of 500mg/kg indicating possible damage to the liver.

The cholesterol and triglyceride levels increased in the entire treated group but the increase in triglyceride was not significant ($p<0.05$) compared to the control group but the increase in cholesterol was significant compared to the control at 500 mg/Kg. The liver has a major role in controlling the plasma level of LDL cholesterol; it synthesizes cholesterol, removes cholesterol from lipoprotein remnant. Increased level of serum cholesterol may be a result of the impaired liver function (Vasudevan and Sreekumari, 2007).

Table 3: Results of non-enzyme markers of liver function after 28 days of administration of extract of *Senecio aureus*

Groups	C.B (µmol/L)	T.B (µmol/L)	Albumin (mg/dl)	T.G (mg/dl)	Cholesterol (mg/dl)
Control	25.22± 3.68	29.14± 4.43	29.46± 1.18	85.40± 13.15	83.00± 7.16
100 mg/kg	25.83± 2.56	35.08± 1.20	28.26± 1.95	102.08± 13.77	131.25± 26.65
300 mg/kg	28.91± 4.20	46.25± 5.75	28.53± 0.96	106.25± 15.73	125.00± 11.28
500 mg/kg	35.06± 1.85	53.19± 6.11*	25.45± 1.12	116.67± 9.00	166.67± 14.03*

Values are Mean ± SEM; n=4, values with * significantly increased relative to the control ($p<0.05$), C.B: Conjugated bilirubin, T.B: Total bilirubin, and T.G: Triglycerides

Although the PCV of the *Senecio aureus* treated groups increased as the dose increased but this increase was not significantly different from the control ($p<0.05$). The present study, therefore, does not reveal significant effects on hematological parameters (Table 4), suggesting that the extract may not have had any effect on the blood production system of the body. The results of the present study suggest that there could be hepatotoxicity of the biliary cirrhosis when the extract is taken for a longer period, at higher dose.

Table 4: Results of hematological parameters of treated and control animals after 28 days of treatment with ethanolic *Senecio aureus* extract

Groups	PCV %	T. WBC Cells/mm^3	Neutrophils %	Monocytes %	Lymphocytes %
Control	41.50± 3.48	23333± 6467	18.33± 4.41	3.00± 1.53	75.33± 2.60
100 mg/kg	39.75± 1.38	18466± 3525	15.00± 2.89	2.33± 1.77	82.67± 2.19
300 mg/kg	43.00± 1.08	23000± 9800	25.00± 5.00	Not detected	75.00± 5.00
500 mg/kg	48.00± 1.08	20700± 2506	21.25± 3.15	2.75± 1.31	76.00± 3.94

Values are Mean ± SEM, n=4. Basophils and Eosinophils were not detected in any of the samples during differential count. None of the hematological parameters showed any significant difference relative to the control ($p<0.05$)

4. Conclusion

From the results of the present study, the use of *Senecio aureus* for the treatment diseases at high dose and prolonged periods will have an adverse effect on the liver. Therefore, the persistent use of the plant in the treatment of the diseases should be discouraged.

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