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# *In Vivo* Subacute Liver Toxicity of "Attoté": A Herbal Drink

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## Abstract

The herbal drink "Attoté" has been widely used in the Abidjan district to treat a number of illnesses, notably erectile dysfunction. Despite the popularity of its therapeutic effects, very few studies have been carried out on its effects on the health of users. The aim of this study was to identify the constituents contained in the phytomedicinal product and to assess their potential adverse effects *in vivo*. Phytochemical screening was conducted to identify the bioactive molecules in "Attoté" and to evaluate its hepatic effects *in vivo*. Forty (40) Wistar rats, randomly divided into 4 groups, with 10 animals per group (5 males and 5 females) were used to study potential hepatotoxic effects. Group 1 animals (control group) received distilled water. Batches I, II and III received by gavage a volume of Attoté extract corresponding to 1 ml/100 g body weight at 200 mg/kg, 400 mg/kg and 800 mg/kg, respectively. Attoté extract was administered daily at the same time for 28 days, and serum was collected every two weeks to assess hepatic biochemical markers by spectrophotometry using a Cobas C311® HITACHI biochemistry system. After one month of study, the rats were euthanized by ether overdose and the livers were harvested for morphological and histopathological analysis. Phytochemical screening revealed the presence of alkaloids, polyphenols, leucoanthocyanes, anthraquinones and quinones. Hepatic biochemical and hematological parameters such as red globular, hemoglobin, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), alkaline phosphatase (ALPs) and gamma glutamyl transferase (GGT) showed no significant change ($p > 0.05$) in the treated rat group compared with controls. However, these variations were moderate and transient, with values remaining almost within their standard limits. Microscopic observations of liver tissue sections from treated rats showed no liver damage or dysfunction. This study merits further investigation, with a view to gaining a better understanding of the

cytotoxic mechanisms of herbal medicinal beverages, with a view to their reformulation as improved traditional medicines (ITMs).

## Keywords

Herbal Drink, Attoté, Toxicity *in Vivo*, Hepatic Biomarkers, Abidjan

## 1. Introduction

The use of medicinal plants for the treatment of various diseases is attracting growing interest among the world's population, particularly in developing countries [1]. Indeed, medicinal plants are a resource for a large proportion of rural populations [2]. They are widely used in traditional African pharmacopoeia for the diagnosis, prevention or elimination of chronic or benign diseases [3]. Today, they are coveted products in both traditional and modern medicine. Moreover, according to WHO data, around 80% of rural populations in developing countries, especially in sub-Saharan Africa, use medicinal plants as their main means of treating various pathologies [2].

In Côte d'Ivoire, as in many sub-Saharan African countries, utilization of herbal medicines is an old practice, and various studies have documented the numerous medicinal plants used by local populations for their anti-malarial and anti-inflammatory properties [4] [5].

However, the increasing use of phytomedicines and their by-products is raising concerns about their potential health effects. In recent years, the population of the Abidjan district has increasingly been using plant or herbal medicines. Some of these phytomedicines take the form of drinks. These include "congnons-mousso-yako", "Atoté" and other derivatives used to treat erectile dysfunction in men [6]. In addition, the risk associated with the use of medicinal plants may stem from direct factors such as the inherent toxicity of their various bioactive compounds, such as alkaloids and glycosides [7] [8]. Also, compositions and mechanisms of action of these herbal products are often unclear, leading to unexpected results [9].

In fact, toxicity studies conducted on aqueous and hydroalcoholic extracts of *Terminalia mantaly* H. have revealed significant variations in liver and heart parameters [10] [11]. Other work on plants of the genus *Aristolochia* used as phytomedicines has revealed the presence of aristolochic acid, a powerful carcinogen and nephrotoxicant [12].

In the case of Attoté, its consumption can cause cardiovascular risks, strokes, heart attacks and even sudden death [13]. In addition, the combination of several medicinal plants in traditional preparations makes it difficult to predict the toxic effect of the mixture [14] [15]. There is an urgent need for toxicological tests to be carried out prior to their use in all forms by Ivorian populations. Thus, the aim of our study is to assess the subacute toxicity of "Attoté", a medicinal plant-based drink, on Wistar rats.

## 2. Materials and Methods

### 2.1. Plant Material

Plant material was lyophilization of the "Attoté", a herbal drink sold in the District of Abidjan. This herbal drink was collected during the ethnomedicinal survey carried out between July and September 2020 in three municipalities of the Autonomous District of Abidjan (Yopougon, Abobo, Plateau).

### 2.2. Phytochemical Screening

Phytochemical tests based on staining, precipitation or turbidity reactions were to detect chemical families of secondary metabolites such as polyphenols, alkaloids, saponosides, indoles, flavonoids, cardiotonic glycosides, catechic tannins, phlobatanins, leucoanthocyanes and quinones [16].

### 2.3. Experimental Animals

The animal selection was in accordance with the Organization of Economic Cooperation and Development (OECD) guidelines No. 423 [17]. Healthy, young, and nulliparous, non-pregnant Wistar rats that weigh 100 - 120 g, were 8 - 10 weeks old, and were obtained from the animal house of pharmaceutical science, Abidjan (Côte d'Ivoire) was selected. The animals are picked randomly, and marked to permit individual identification. Animals were kept in plastic cages with wood shavings that were changed every other day for 5 days before dosing. This allows animals to acclimatise to laboratory conditions (ambient temperature 25˚C ± 3˚C; humidity ranged from 35% to 60%; light and dark period, 12/12 hours, bedding cleaned and sterilized). All animals had a regular supply of drinking water and food [11].

### 2.4. Treatment with Plan Material

A repeated oral dose of toxicity study was carried out according to the OECD Guideline 407 [14]. The rats were divided into four groups of 10 animals each (5 males and 5 females). Group 1 received 1 ml/100g body weight of distilled water and served as the control group. Groups I, II, and III received extract doses of 200, 400, and 800 mg/kg body weight, respectively. Mortality, body weights, food and water consumption, as well as observation for general toxicity signs of the animals were evaluated daily for 28 days.

### 2.5. Blood Sample and Organ Collection

At the end of each week, the animals were anesthetized with diethyl ether. The blood was drawn through cardiac puncture and collected in sterile tubes without anticoagulant. Plasma was obtained in one set by centrifuging the blood at 3000 revolutions/min for 10 min and stored at −20˚C in Eppendorf bottles until it required enzymatic activities and concentration of biochemical metabolites assays. Whole blood was also collected in EDTA-containing tubes and used to perform

hemoglobin, white blood cells and red blood cells analyses. Liver was collected and fixed with 10% buffered formalin for further analysis [10] [18].

### 2.6. Determination of Hepatic Parameters in Rat Serum

Hepatic enzyme activities were determined using a Cobas C311® HITACHI biochemistry system (Roche Diagnostics, France). Tests were performed using commercial kits (Roche Diagnostics, France) based on the manufacturer's instructions, summarized in Table 1.

**Table 1.** Operating parameters for the quantitative determination of serum cardiac markers.

| Hepatic biochemical markers | Methods (Spectrophotometry) | Wavelength (nm) |
|---|---|---|
| Alanine aminotransferase (ALT) | Absorption kinetics (Disappearance of NADH) | 340 |
| Aspartate aminotransferase (AST) | Absorption kinetics (Disappearance of NADH) | 340 |
| gamma-glutamyltransferase (GGT) | Rate of 2-nitro-5-aminobenzoic acid formation | 405 |
| Alkaline phosphatase (ALP) | Absorption kinetics (Rate of p-nitrophenol) | 405 |

### 2.7. Preparation of Tissue Sections and Histopathology

Hepatic tissues were cut into transverse blocks. An automatic processor (RH-12EP Sakura, Fine Technical Co. Ltd., Tokyo, Japan) was used to further process the blocks. About 12 hours were required for dehydration (96% alcohol for one hour × four changes, and 100% alcohol for one hour × one change).

Clearing was done in three changes of toluene for one hour each. Tissues were impregnated in two changes of paraffin wax with a melting point of 50˚C for a period of 2 hours. Embedding of tissue was done in paraffin using L-shaped metallic moulds. These blocks were put in the refrigerator for a period of 4-6 hours. Each block was cut on a rotary microtome (MicromGmbh, Waldorf, Germany). About 5-micrometer-thick tissue section was obtained and placed in the water bath with a temperature of 50˚C below the melting point of paraffin wax. The cut ribbons of tissues were placed on the albumenized glass slide. The sample slides were subsequently stained with haematoxylin-eosin (HE) and examined under a light microscope; photomicrographs of the samples were recorded [10] [11] [19].

## 3. Results

### 3.1. Phytochemical Screening

Table 2 shows the results of phytochemical analysis of the aqueous extract of Attoté. The results show the presence of alkaloids, polyphenols, quinones, anthraquinones and leucoanthocyanes. However, the analysis did not reveal the presence of compounds such as saponosides, indoles, flavonoids, and cardiotonic glucosides.

**Table 2.** Phytochemical constituents of Attoté.

| Different Compounds | Presence (+) | Absence (−) |
|---|---|---|
| Polyphenols | + | |
| Alkaloids | + | |
| Saponosides | | − |
| Indoles | | − |
| Flavonoids | | − |
| Cardiotonic glucosides | | − |
| Catechic tannins | | − |
| Phlobatanins | | − |
| Leucoanthocyane | + | |
| Anthraquinones | + | |
| Quinones | + | |
| Anthracenosides | | − |

Presence (+), Absence (−).

## 3.2. Hematological Results

### 3.2.1. Effect of Attoté on the Level of Hemoglobin

Hematological results are presented in Figures 1-3 and Table 3. Figure 1 shows hemoglobin level of treated animals compared to control groups. Results show a slight non-significant decrease in hemoglobin at J28. Similar variations are observed for red blood cell levels (Figure 2). A similar slight non-significant decrease in white blood cell levels was observed in rats on J28 of treatment (Figure 3).

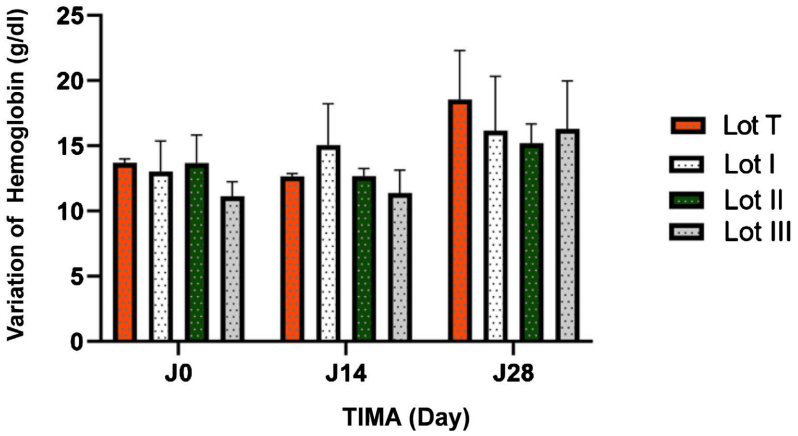


**Figure 1.** Variation of hemoglobin (g/dl) versus time. Each bar represents the mean ± SD, n = 10, T = control with batch; lot I = 200 mg/kg; Lot I = 400 mg/kg batch III = 800 mg/kg body weight of the animal on the days (J0, J14, J28). *p < 0.05: Significant difference compared with the control.

### 3.2.2. Effect of Attoté on the Level of Red Blood Cells

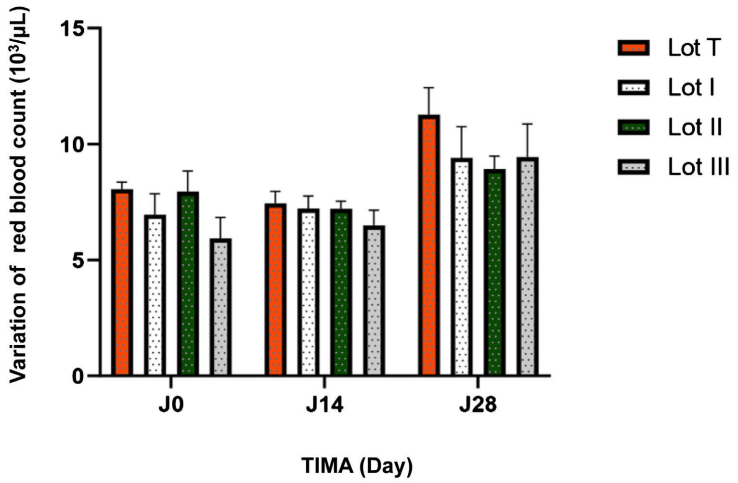


**Figure 2.** Variation of the red blood cell count ($10^3/\mu$) versus time. Each bar represents the mean ± SD, n = 10, T = control with batch; lot I = 200 mg/kg; Lot I = 400 mg/kg; Lot III = 800 mg/kg body weight of the animal on the days (J0, J14, J28). *p < 0.05: **S**ignificant difference compared with the control.

### 3.2.3. Effect of Attoté on the Level of White Blood Cells

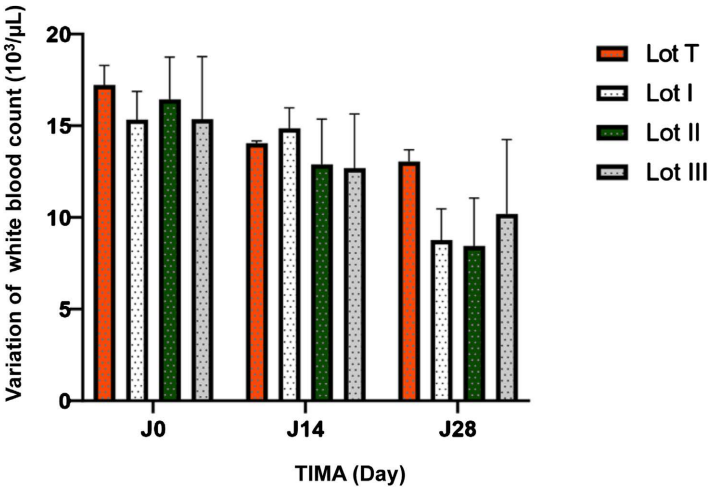


**Figure 3.** Variation of the red blood cell count ($10^3/\mu$) versus time. Each bar represents the mean ± SD, n = 10, T = control with batch; lot I = 200 mg/kg; Lot I = 400 mg/kg; Lot III = 800 mg/kg body weight of the animal on the days (J0, J14, J28). *p < 0.05: **S**ignificant difference compared with the control.

## 3.3. Biochemistry and Results

### 3.3.1. Effect of Attoté on the level of ALAT

Results of hepatic biochemical parameters are presented in **Figures 4-7** and **Table 3**.

Results of the effect of "Attoté" on alanine aminotransferase activity are shown in **Figure 4**. ALAT activity mean values ranged from 80.25 ± 1.35 IU/L to 268.8 ± 4.6 IU/L in control animals, and from 111.87 ± 25.13 IU/L to 226.47 ± 21.45 IU/L in Attoté-treated rat batches. At J14, ALAT activity in these treated rats was almost

similar to that in control rats. However, at J28, rats treated with different concentrations of Attoté showed an increase in alanine aminotransferase activity. However, this increase in enzyme activity showed no significant difference ($p > 0.05$) compared with controls.

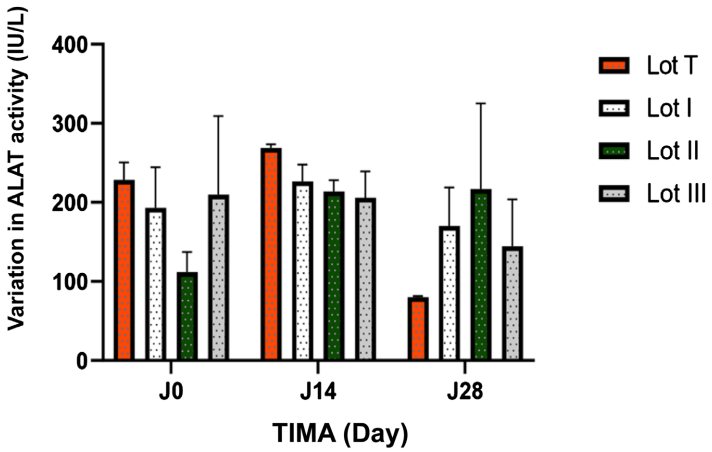


**Figure 4.** Effects of Attoté on ALT activities as a function of time. Each bar represents the mean ± standard deviation, n = 10 with Lot T = control; Lot I = 200 mg/kg; Lot II = 400mg/kg; Lot III = 800 mg/kg of body weight of the animal; the asterisk indicates the significant differences of each group of animals treated according to the time of each week (*$p < 0.05$).

### 3.3.2. Effect of Attoté on the Level of ASAT

**Figure 5** shows the results of Attoté's effect on ASAT. From J0 to J28, ASAT activity mean values ranged from 192.35 ± 12.15 IU/L to 289.3 ± 9.4 IU/L in Lot T, and from 162.47 ± 33.92 IU/L to 363.87 ± 121.32 IU/L in Lot I, II and III. At the end of J14, results showed no variation of ASAT activity in the exposed rats compared with controls. However, at J28, an increased value of ASAT was observed, but this difference is not significant ($p > 0.05$).

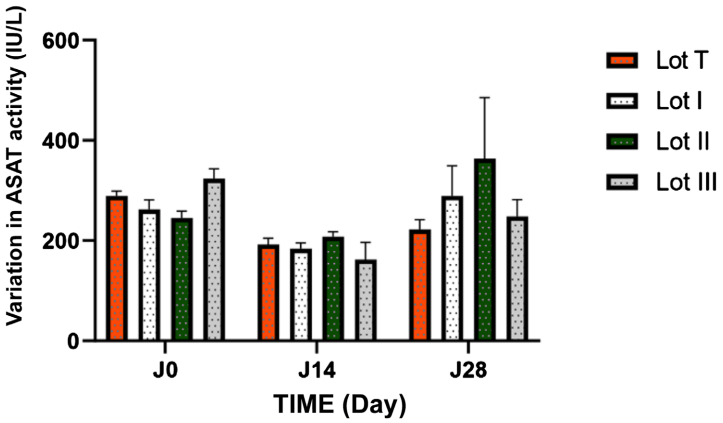


**Figure 5.** Effects of Attoté on ASAT activity as a function of time. Each bar represents the mean ± standard, n = 10 with Lot t = control; Lot I = 150 mg/kg; Lot II = 300 mg/kg; Lot III = 600 mg/kg of body weight of the animal; S1; S2; S3; S4: weeks of study, The differences observed between batches and over time are not significant: $p > 0.05$.

### 3.3.3. Effect of Attoté on the Level of ALPs

Figure 6 shows the results of the influence of the phytomedicinal Attoté on alkaline phosphatase (ALP) activity. The mean values of PAL activity obtained from J0 to J28 ranged from 521.5 ± 125.5 IU/L to 831.5 ± 3.5 IU/L in Lot T, while they oscillated between 339.33 ± 51.82 IU/L and 762.75 ± 64.47 IU/L in Lot I, II and III. These results showed no significant variation in the concentration of ALP activity in treated rats.

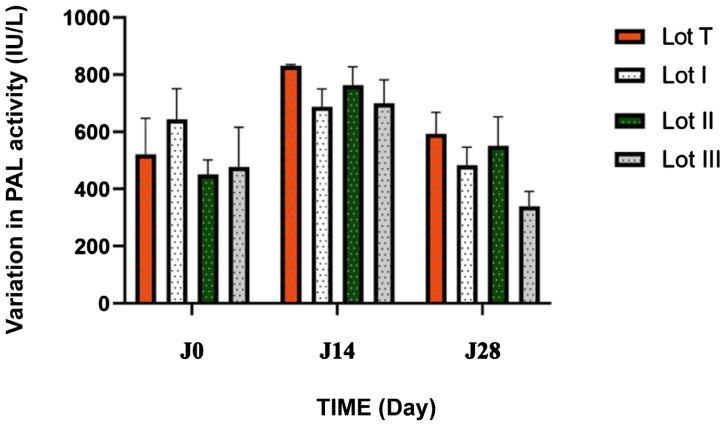


Figure 6. Effects of Attoté on ALPs activity as a function of time. Each bar represents the mean ± standard, n = 10 with Lot t = control; Lot I = 150 mg/kg; Lot II = 300 mg/kg; Lot III = 600 mg/kg of body weight of the animal; S1; S2; S3; S4: weeks of study; the asterisk indicates the significant differences of each group of animals treated according to the time of each week (*p < 0.05).

### 3.3.4. Effect of Attoté on the Level of GGT

Similar values were observed of gamma glutamyl transferase (GGT) activity. GGT Mean values (J0 to J28) range from 1 ± 2 IU/L and 2.5 ± 3.5 IU/L in Lot T, while they ranged from 2 ± 1.915 IU/L to 11 ± 10.42 IU/L in Lot I, II and III (Figure 7).

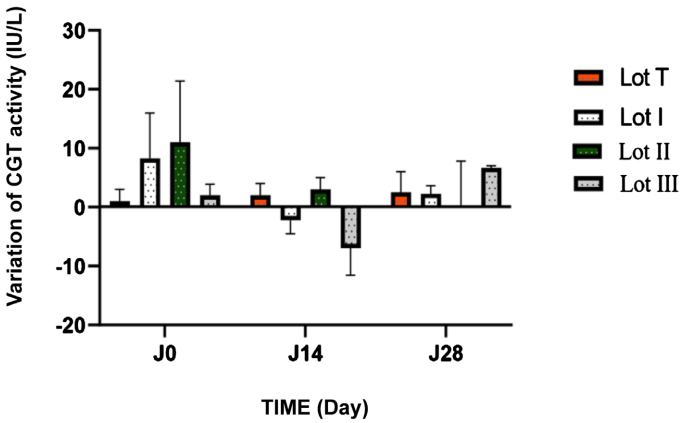


Figure 7. Effect of Attoté on GGT activity according to the time. Each bar represents the mean ± standard, n = 10 with Lot T = control; Lot I = 200 mg/kg; Lot II = 400 mg/kg; Lot III = 800 mg/kg of body weight of animal Jo; J14 and J28: days of study; the asterisk indicates the significant differences of each group of animals treated according to the time of each week (*p < 0.05).

**Table 3.** Biochemistry parameters.

| | | Lot T | Lot I | Lot II | Lot III |
|---|---|---|---|---|---|
| Hemoglobin | Initial | 13.7 ± 0.28 | 13.025 ± 2.34 | 13.67 ± 2.13 | 11.12 ± 1.11 |
| | p-value | | 0.9717 | >0.9999 | 0.4524 |
| | J14 | 12.65 ± 0.21 | 15.05 ± 3.16 | 12.67 ± 0.59 | 11.37 ± 1.77 |
| | p-value | | 0.5035 | >0.9999 | 0.8527 |
| | J28 | 18.55 ± 3.75 | 16.15 ± 4.17 | 15.2 ± 1.47 | 16.3 ± 3.67 |
| | p-value | | 0.5182 | 0.3103 | 0.6011 |
| Red blood cells | Initial | 8.055 ± 0.305 | 6.95 ± 0.90 | 7.95 ± 0.89 | 5.93 ± 0.90 |
| | p-value | | 0.8356 | 0.9998 | 0.3929 |
| | J14 | 7.44 ± 0.52 | 7.22 ± 0.54 | 7.21 ± 0.33 | 6.49 ± 0.65 |
| | p-value | | 0.9983 | 0.998 | 0.8878 |
| | J28 | 11.27 ± 1.17 | 9.41 ± 1.35 | 8.92 ± 0.56 | 9.44 ± 1.42 |
| | p-value | | 0.5048 | 0.3543 | 0.5631 |
| White blood cells | Initial | 17.22 ± 1.5 | 15.34 ± 3.06 | 16.45 ± 4.59 | 15.37 ± 6.80 |
| | p-value | | 0.9169 | 0.9929 | 0.9197 |
| | J14 | 14.05 ± 0.16 | 14.86 ± 2.22 | 12.89 ± 4.94 | 12.69 ± 5.91 |
| | p-value | | 0.9921 | 0.9775 | 0.9645 |
| | J28 | 13.05 ± 0.91 | 8.77 ± 3.39 | 8.46 ± 4.51 | 10.19 ± 7.02 |
| | p-value | | 0.5514 | 0.5381 | 0.8134 |
| ASAT | Initial | 289.3 ± 9.4 | 262.2 ± 18.86 | 245.05 ± 13.83 | 323.8 ± 19.38 |
| | p-value | | 0.9428 | 0.8101 | 0.8939 |
| | J14 | 192.35 ± 12.15 | 183.77 ± 11.42 | 207.75 ± 9.79 | 162.47 ± 33.92 |
| | p-value | | 0.998 | 0.9888 | 0.9384 |
| | J28 | 222.2 ± 19.5 | 289.4 ± 59.87 | 363.87 ± 121.32 | 248.27 ± 33.39 |
| | p-value | | 0.5914 | 0.1221 | 0.9591 |
| ALAT | Initial | 228.65 ± 21.85 | 193.25 ± 51.15 | 111.87 ± 25.13 | 209.7 ± 99.39 |
| | p-value | | 0.948 | 0.3969 | 0.991 |
| | J14 | 268.8 ± 4.6 | 226.47 ± 21.45 | 213.7 ± 14.48 | 205.7 ± 33.34 |
| | p-value | | 0.9205 | 0.8482 | 0.8166 |
| | J28 | 80.25 ± 1.35 | 170.27 ± 48.66 | 216.67 ± 108.40 | 144.43 ± 59.29 |
| | p-value | | 0.5986 | 0.3334 | 0.8152 |

**Continued**

| | | | | | |
|---|---|---|---|---|---|
| GGT | Initial | 1 ± 2 | 8.25 ± 7.72 | 11 ± 10.42 | 2 ± 1.915 |
| | p-value | | 0.6973 | 0.484 | 0.9985 |
| | J14 | 2 ± 2 | 2.25 ± 2.286 | 3 ± 2 | -7 ± 4.58 |
| | p-value | | 0.912 | 0.9985 | 0.6028 |
| | J28 | 2.5 ± 3.5 | 2.25 ± 1.38 | 0 ± 7.81 | 6.67 ± 0.33 |
| | p-value | | >0.9999 | 0.9827 | 0.9298 |
| PAL | Initial | 521.5 ± 125.5 | 644 ± 106.02 | 451.5 ± 49.39 | 477 ± 138.91 |
| | p-value | | 0.6649 | 0.9014 | 0.9704 |
| | J14 | 831.5 ± 3.5 | 688 ± 61.610 | 762.75 ± 64.47 | 700.67 ± 81.59 |
| | p-value | | 0.5692 | 0.9095 | 0.6646 |
| | J28 | 594 ± 74 | 482.75 ± 63.72 | 551.67 ± 100.26 | 339.33 ± 51.82 |
| | p-value | | 0.7351 | 0.9797 | 0.2043 |

*: p-value is significant ($p < 0.05$).

### 3.4. Histological Study of Liver

Figure 8 shows histological sections of the liver in animals. These sections show an almost identical normal anatomical structure in the liver of rats from Lot T to Lot III. Hepatic cells show no alteration in tissue structure compared with controls.

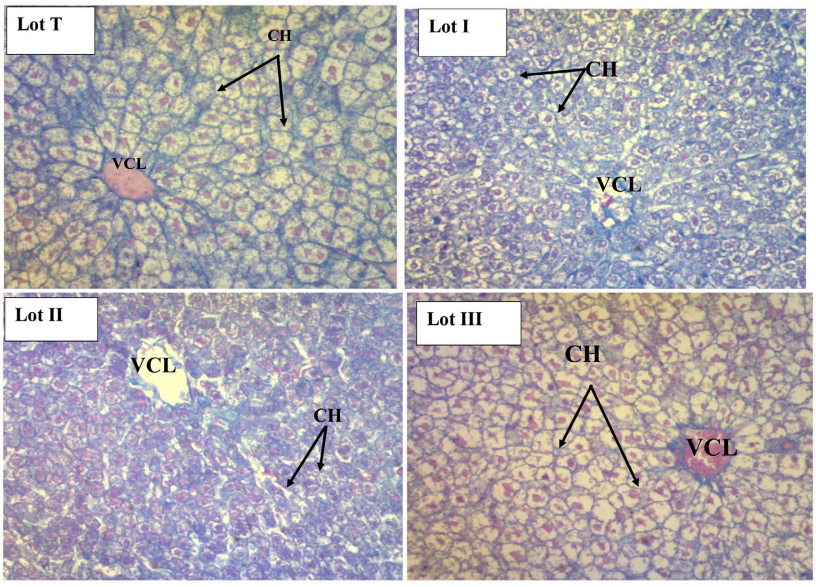


Figure 8. Portion of the liver of rats treated by Attoté. Hemalun-eosin stain; magnification: ×100 T-lot (control): portion of control rat liver tissue; Lot I (200 mg/kg PC), Lot II (400 mg/kg PC), and Lot III (800 mg/kg PC); portions of liver tissue from rats treated at different doses. CH: Hepatic Cells, VCL: Centro-Lobular Vein.

## 4. Discussion

Several cases of cerebrovascular accidents (CVA), heart attacks and even sudden death have been reported following its consumption [13]. Following this observation, the aim of our study was to evaluate the potential adverse effect of Attoté on human health through acute and subacute toxicity.

Phytochemical analysis of Attoté extract reveals the presence of alkaloids, polyphenols, quinones, anthraquinones and leucoanthocyane. Alkaloids can have medicinal, analgesic and antitumor properties, but they can also be toxic, and their use must be controlled. The presence of polyphenols also reflects the antioxidant, anti-inflammatory and cardioprotective properties of the Attoté phytomedicinal [13]. Variations in haematological parameters obtained in animals treated with Attoté extract may be predictive of intoxication in humans exposed to drug substances [19]. Our study showed a slight, non-significant decrease in red blood cell count in rats on day 28 of treatment. These results are similar to those of Gbogbo *et al.* and Kamo *et al.* who reported a significant decrease in red blood cell count and hemoglobin level, as well as an increase in blood platelets in rats treated with [20] [21].

Attoté toxicity to the liver was assessed by measuring enzyme activity such as aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and gamma glutamyl transpeptidase. These enzymes are commonly analyzed to assess liver damage [22]. The ASAT and ALAT enzymes originate from the mitochondria and cytoplasm of cells. In the event of cell death, liver damage or increased permeability of hepatocyte membranes, these enzymes can be released into the bloodstream, leading to an increase in their serum concentration [23] [24]. During the treatment of rats treated with different concentrations of Attoté, the activity of the GGT and PAL enzymes did not vary. However, those of ALAT and ASAT showed an increase in their activity, and statistical analysis showed no significant difference ($p > 0.05$) in the rates of variation between the control and treated batches, irrespective of the dose administered on day 28 of exposure.

Results obtained in the present study show that the four weeks of treatment of animals with Attoté did not induce lesions in liver tissue. In contrast, Lamchouri *et al.* showed that chronic treatment (12 weeks) with Peganum harmala alkaloid extracts significantly increased the activities of these enzymes in rats. Results showed that after 4 weeks of treatment, ALAT activity was non-significantly reduced in animals treated with the 800 mg/kg dose [25].

Histological sections of liver tissue showed almost identical normal anatomical structures in the livers of rats from Lot T to Lot III. Liver cells showed no alteration in tissue structure compared with controls. These results suggest that Attoté extract does not interfere with liver function or integrity; these results are similar to those of Kamo *et al.* who observed an absence of lesions, oedema or necrosis in the hearts of rats treated with hydroalcoholic extract of *Terminalia mantaly* [11].

## 5. Conclusion

The aim of this study was to assess the hepatotoxic effects of the Attoté medicated

drink. The hepatic biochemical parameters ALT, ASAT, ALP and GGT showed no significant change ($p > 0.05$) in the group of treated rats compared with controls. However, moderate variations in the direction of an increase in the biochemical parameters measured were evidenced, albeit transient, as the values remained almost within the standard reference limits. Moreover, microscopic observations of liver tissue sections from treated rats showed no lesions, oedema or necrosis. These results suggest that Attoté did not interfere with liver function or alter liver integrity. The study should be further investigated to understand Attté's toxic mechanisms on human cell lines (HepG2) and thus contribute to its reformulation as an improved traditional medicine (ITM) for modern herbal medicine.

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## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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