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Safety assessment of therapeutic herbal candies (*Annona senegalensis*, *Pericopsis laxiflora*, *Heliotropium indicum* and *Vitellaria paradoxa*) from Korhogo: An *in vivo* toxicological study in *Rattus norvegicus*

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Abstract

Medicinal plants are key therapeutic resource in sub-Saharan Africa, especially for managing respiratory diseases like asthma. This study formulated therapeutic candies from honey and aqueous extracts of four medicinal plants from Korhogo (*Annona senegalensis*, *Pericopsis laxiflora*, *Heliotropium indicum*, *Vitellaria paradoxa*) and evaluated their safety in Wistar rats. Acute toxicity was assessed per OECD guideline 423, using single oral doses of 300 and 2000 mg/kg, with clinical observation over 14 days. Subacute toxicity followed OECD guideline 407, with repeated oral doses of 125, 250 and 500 mg/kg for 28 days. Body weight, organ weights, biochemical and hematological parameters were monitored. Heart, liver and kidney sections were histologically examined under microscope. No mortality and abnormal clinical signs occurred during acute testing, placing the candies in GHS Category 5 (low toxicity). Subacute testing showed no significant changes ($p > 0.05$) in body weight, organ weights and biochemical markers (urea, creatinine, AST, ALT) compared to normal controls. However, at 500 mg/kg, hematocrit significantly decreased and leukocyte count markedly increased ($p < 0.001$), with no other hematological changes. The absence of histopathological lesions supported the weight, hematology and biochemistry findings confirming non-toxicity at the tested doses. These results indicate that oral consumption of the formulated candies poses no major toxicological risk at tested doses, supporting their potential use in traditional asthma management.

Keywords: Toxicity; Therapeutic Candies; Histological Sections; *Rattus norvegicus.*

1. Introduction

Natural substances have gained considerable interest in recent decades owing to their therapeutic potential and their widespread use in traditional medicine worldwide. According to the World Health Organization (WHO), approximately 80% of the global population relies on medicinal plants as a primary source of healthcare [1]. Beyond the investigation of biological activities of plant extracts, researchers are increasingly focusing on the development of innovative dosage forms capable of improving acceptability, physicochemical stability and therapeutic adherence. Among these emerging approaches, therapeutic candies plant based formulations designed for oral delivery represent a particularly promising alternative [2]. This galenic form incorporates active ingredients of natural origin into a simple, palatable and easy to administer preparation, making it especially suitable for pediatric populations and individuals experiencing difficulty swallowing conventional solid dosage forms such as tablets or capsules [3]. Furthermore, combining several medicinal plants in specific proportions may enhance therapeutic efficacy while reducing the risk of individual plant-associated

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toxicity [4]. This is the case of the plants *Annona senegalensis*, *Pericopsis laxiflora*, *Heliotropium indicum* and *Vitellaria paradoxa* which are used empirically in Korhogo to treat asthma. However, the therapeutic use of herbal based candies without prior toxicological characterization may expose consumers to serious and potentially irreversible adverse effects. In this context, preclinical safety assessment constitutes a critical and mandatory step before any therapeutic application in humans. Therefore, the present study aimed to evaluate the acute and subacute oral toxicity of therapeutic candies formulated from medicinal plants of Korhogo (Côte d'Ivoire), based on behavioral observations and hemato-biochemical parameters in Wistar rats

2. Material and methods

2.1. Plant Material

The plant material consisted of aqueous leaf extracts from four species: *Annona senegalensis* Pers., *Pericopsis laxiflora*, *Heliotropium indicum* L., and *Vitellaria paradoxa* C.F. Gaertn. **(Figures 1A–B, 2C–D, 3E–F, and 4G–H).**

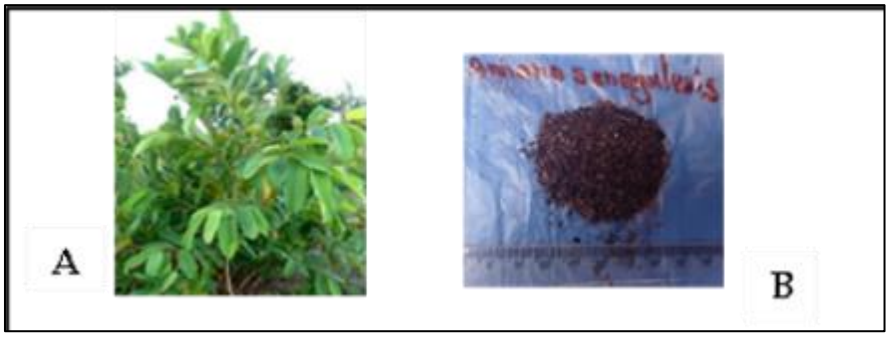


Figure 1 Foliage (A) and Aqueous extract of *Annona senegalesis* pers. leaves (B)

Figure 2 Foliage (C) and Aqueous extract of *Vitellaria paradoxa* leaves (D)

Figure 3 Foliage (E) and Aqueous extract of *Pericopsis laxiflora* leaves (F)

Figure 4 Foliage (G) and Aqueous extract of *Heliotropium indicum* leaves (H)

2.2. Animal Material

Albino Wistar rats (*Rattus norvegicus*) were used as the animal model in this study **(Figure 5).**

2.3. Preparation of Aqueous Extracts

Aqueous extracts of *Annona senegalensis* Pers., *Pericopsis laxiflora*, *Heliotropium indicum* L., and *Vitellaria paradoxa* C.F. Gaertn leaves were prepared according to the method described by Guédé-Guina and allies [5].

Briefly, 100 g of dried leaf powder from each plant species were macerated in 1 L of distilled water for 24 hours under continuous magnetic stirring. The resulting macerate was subjected to sequential filtration: a primary filtration through cotton wool, followed by a secondary filtration through Whatman filter paper to remove all residual solid particles. The filtrate, containing the bioactive compounds of interest, was then separated from the residue and evaporated to dryness in an oven at 50°C. The dried residue obtained constituted the total aqueous extract of each plant **(Figure 6**).

Figure 5 Photograph of wistar rats

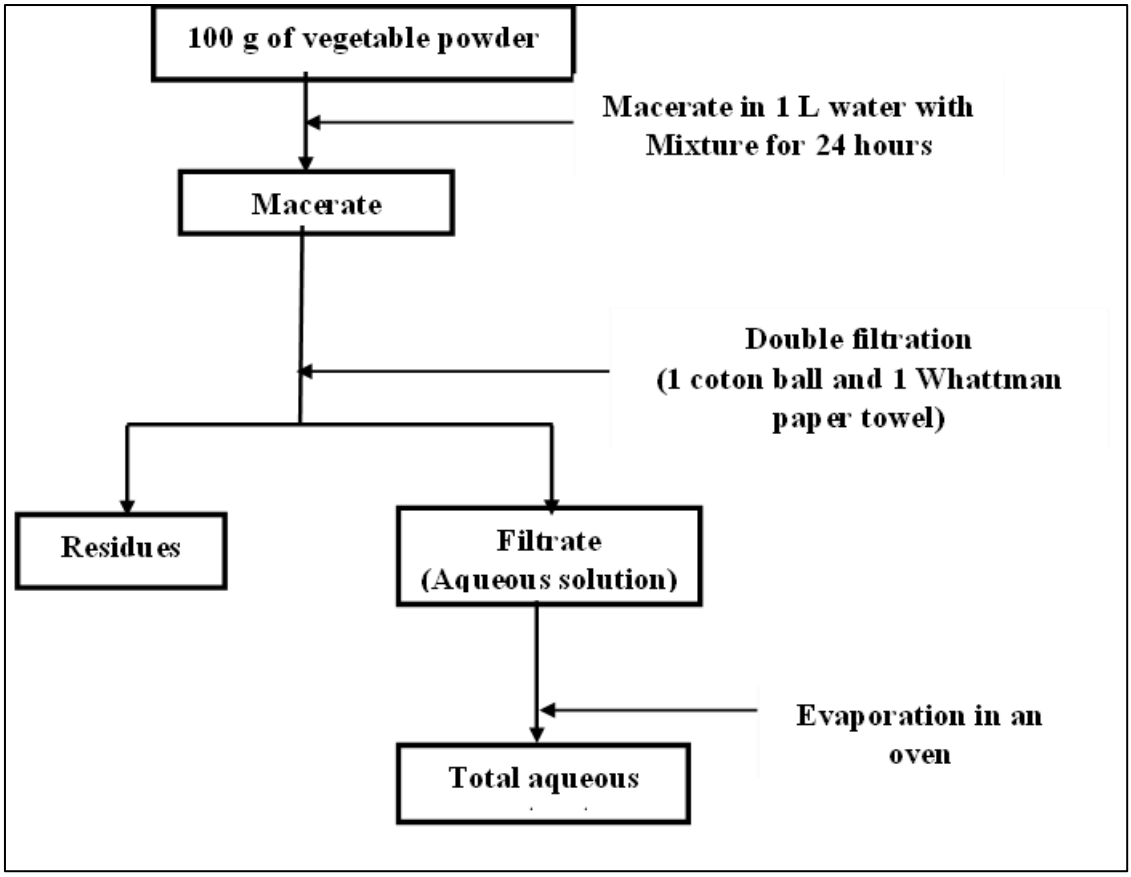


Figure 6 Diagram of preparation of aqueous extracts of the leaves of each plant used

2.4. Formulation of Candies for Therapeutic Purposes

The **figure 7** presents the formulation diagram for the therapeutic candies. For preparation, 3 g of extract from each of the four plant extracts (at concentration of 0.1 g/mL) were introduced into 50 mL of demineralized water previously placed in a stainless steel pot. Subsequently, 100 g of unheated honey and 10 g of lemon juice were added to the mixture. The preparation was then placed on a hot plate set at 60°C and maintained under continuous magnetic stirring for 30 minutes to promote complete dissolution of the components and ensure a homogeneous mixture. During heating, additional homogenization was performed using a wooden spatula to obtain a uniform solution. Thereafter, 20 g of gelatin and 2 g of *Curcuma longa* essential oil were gradually incorporated into the mixture, followed by brief homogenization. The resulting mixture was poured into molds and allowed to solidify by freezing at −18°C for one hour [2].

2.5. Acute Toxicity of Formulated Candies

The acute toxicity study was conducted in accordance with OECD Guideline 423 [6], which consists of administering the test product as single dose over a 24-hour period. For this purpose, 12 female rats were randomly subdivided into four groups of three animals each, as follows :

- Group I: Animals received the candies at a dose of 300 mg/kg body weight.
- Group II: Animals also received 300 mg/kg body weight, with the specific objective of confirming or refuting the results obtained in Group I.
- Group III: Animals received the candies at an elevated dose of 2000 mg/kg body weight.
- Group IV: Animals received the same dose of 2000 mg/kg body weight, in order to validate or refute the results obtained in Group III.

Following administration, a rigorous monitoring phase was implemented, during which animal behavior was observed over a 14-day period to record any clinical signs manifested **(Figure 8).** The median lethal dose (LD_{50}) and the hazard category of the candies according to the Globally Harmonized System (GHS) were also determined using the acute toxicity decision diagram outlined in OECD Guideline 423 [6].

Figure 7 Formulation diagram of therapeutic candies

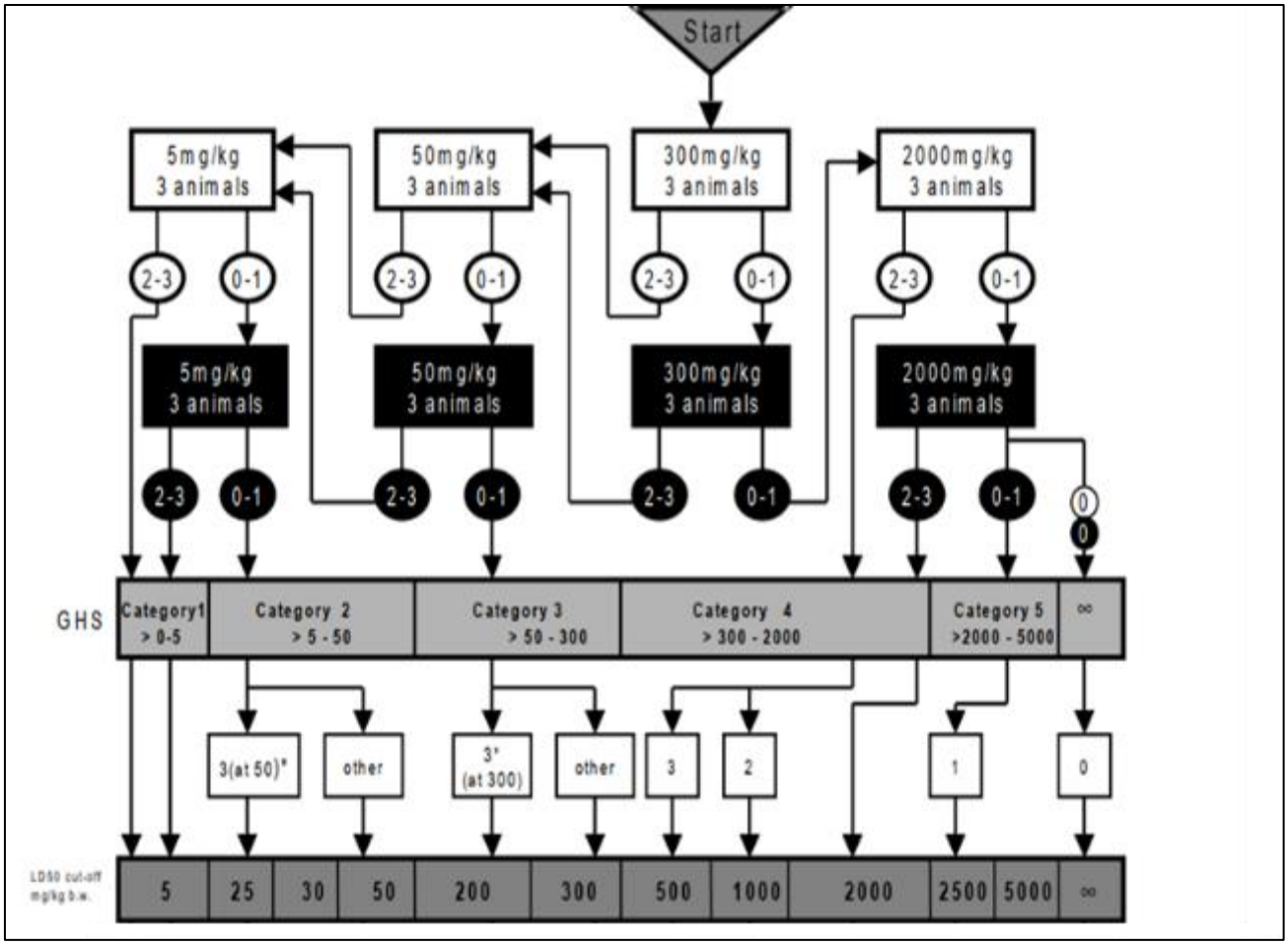


Figure 8 Diagram of the acute toxicity study of therapeutic candies in Wistar rats

2.6. Subacute Toxicity of Formulated Candies

The subacute toxicity study aims to assess the health risks resulting from repeated exposure to the product over a 28-day period. This study was conducted by daily oral administration in rats Wistar.

2.6.1. Experimental design

A total of 12 female rats were randomly assigned to four groups of three animals each, as follows:

- Control group : Animals received distilled water daily by gavage.
- Group 1: Animals received the candies by gavage at a dose of 125 mg/kg body weight.
- Group 2: Animals received the candies by gavage at a dose of 250 mg/kg body weight.
- Group 3: Animals received the candies by gavage at a dose of 500 mg/kg body weight.

Each animal received 1 mL of the candy daily preparation for 28 days, adjusted according to body weight (per 100 g). Body weight was recorded weekly throughout the four-week treatment period. At the end of the study, the animals were sacrificed, and the vital organs (liver, kidneys and heart) were harvested and weighed. The organs were subsequently preserved in 10% formalin solution [2].

2.6.2. Blood and vital organ sampling

Blood samples were collected into EDTA tubes (purple-top tubes) for complete blood count (CBC) analysis, and into dry tubes (red-top tubes) for biochemical analyses, including urea, creatinine, and transaminase levels. Vital organs from anesthetized rats were harvested, weighed, and fixed in 10% formalin. Hematological parameters were determined using an *Alfa* hematological analyzer, and biochemical parameters were measured sequentially using an *Erba* biochemistry analyzer.

2.6.3. Histopathology evaluation

The organs were washed in an isotonic solution, fixed in 10% formalin, and embedded in paraffin to ease the slicing. The samples were stained with hematoxylin-eosin dye and then examined microscopically [7].

2.7. Statistical Evaluation

The results were expressed as mean ± standard deviation for 3 rats in each group. Statistical analysis was performed using a one-way ANOVA. The results of the experimental groups were compared to their respective controls, and a p-value < 0.05 was considered statistically significant.

3. Results and discussion

3.1. Effect of Single Dose of Formulated Candy on Survival and General Behavior of Rats

The formulated candies are illustrated in **Figure 9**. The **Table 1** summarizes the clinical signs recorded over the 14 days observation period of the acute toxicity study.

During the acute toxicity test, no mortality was observed in any of the animals treated with doses of 300 or 2000 mg/kg body weight. Furthermore, no abnormal clinical signs were recorded including immobility, respiratory distress, locomotor disturbances and abdominal constriction. Normal behavior was maintained throughout the 14 days observation period, demonstrating the absence of immediate toxic effects attributable to the administration of the candies. With an estimated LD_{50} exceeding 2500 mg/kg body weight, the formulated candies can be classified under Category 5 of the Globally Harmonized System (GHS) for classification of hazardous substances. In accordance with OECD guidelines, these candies belong to the group of substances with low acute toxicity [1,8]. These findings are consistent with those reported by Murwanti and allies [7], who investigated herbal formulation combining Piper crocatum Ruiz and Pav., *Typhonium flagelliforme (*Lodd.) Blume, and *Phyllanthus niruri* L., as well as those of Ramdas and allies [9], who similarly demonstrated the low acute toxicity of preparation derived from medicinal plants of the Indian pharmacopoeia.

Figure 9 Photograph of formulated therapeutic candies

Table 1 Clinical signs observed over 14 days during the acute toxicity study in Wistar

18 rats treated							
Treated and non-treated groups	Number of rats treated	Number of rats dead	Clinical signs observed				
			Food	Immobility	Rapid breathing	Difficult movement	Abdominal constriction
Distilled water							
Control	6	00	Normal	No	Normal	Normal	No
Candy with therapeutic properties							
Group 1 (300 mg/kg bw)	6	00	Normal	No	Normal	Normal	No
Group 2 (2000 mg/kg bw)	6	00	Normal	No	Normal	Normal	No

3.2. Effect of Candy on the Body Weight of Rats

The change in body weight of rats receiving the candy by gavage for 28 days is presented in the **table 2**. With respect to body weight, a progressive increase was recorded across all groups, including the control group. No weight loss or growth retardation was noted in any animal. This trend suggests that the candies did not disrupt energy metabolism or impair the nutritional status of the animals. Body weight change is recognized by the OECD [10] as an important indicator of systemic dysfunction; its absence here reinforces the safety profile of the formulation. These findings are in agreement with those of Abebe [11], who demonstrated that repeated administration of *Rhamnus prinoides* extract over four weeks did not adversely affect food consumption or weight gain in rats. Moreover, Naseri and allies [12] reported that certain plant extracts may stimulate appetite, which could partly account for the weight gain observed in the treated groups. Collectively, these results indicate that the animals maintained normal food intake throughout the treatment period and that the candies formulated from the four plant extracts did not induce any metabolic stress or anorexigenic effects. Similar observations were reported by Gnahoué and allies [13], who demonstrated that the consumption of certain plant extracts does not necessarily affect body weight. Sengupta [14] further indicated that the observed weight gain confirms the adequacy of the experimental conditions employed in this study.

3.3. Effect of Candies on the Absolute Organ Mass and Histological Sections in Study Animals

The **table 3** presents the absolute organ masses (g) of the kidneys, liver and heart in control rats and rats treated with candies for 28 days.

Analysis of the absolute organ masses including the liver, kidneys and heart revealed no statistically significant difference between the treated groups and the control group ($p > 0.05$). This stability suggests the absence of organ hypertrophy or atrophy, two morphological changes frequently associated with toxic damage. The liver and kidneys play a central role in the biotransformation and elimination of xenobiotics; maintaining their structural integrity therefore constitutes an important indicator of toxicological safety, as highlighted by Hilaly and allies [15].

Histological examination is shown in the **Figure 10.** Histological examination of sections of the heart, liver and kidneys revealed normal architecture in control rats (healthy rats). Cardiac fibers and vessels were well-organized in the myocardium. Hepatocyte trabeculae and the portal tract were regular in the liver. Glomeruli and convoluted tubules were well defined in the kidney. In rats treated with the candies (at doses of 125, 250, and 500 mg/kg body weight), the architecture of the three organs remained broadly similar to that of the controls. Histopathological examination is intended to detect any abnormalities in gross pathology and organ histology [11]. No major necrotic, inflammatory, or degenerative lesions were observed in the organs of the treated rats. These results are consistent with those of Gnamien and allies [16], who reported that an extract inducing no histological changes in rats confirms its relative safety at the tested dose. Other authors have emphasized that renal tubular alterations or hepatocyte atrophy observed at certain doses highlight the importance of dose and exposure duration in assessing the subacute toxicity of medicinal plants. The histopathological evaluation of the vital organs thus confirmed normal architecture, with no microscopic alterations observed in the heart, kidneys or liver [17].

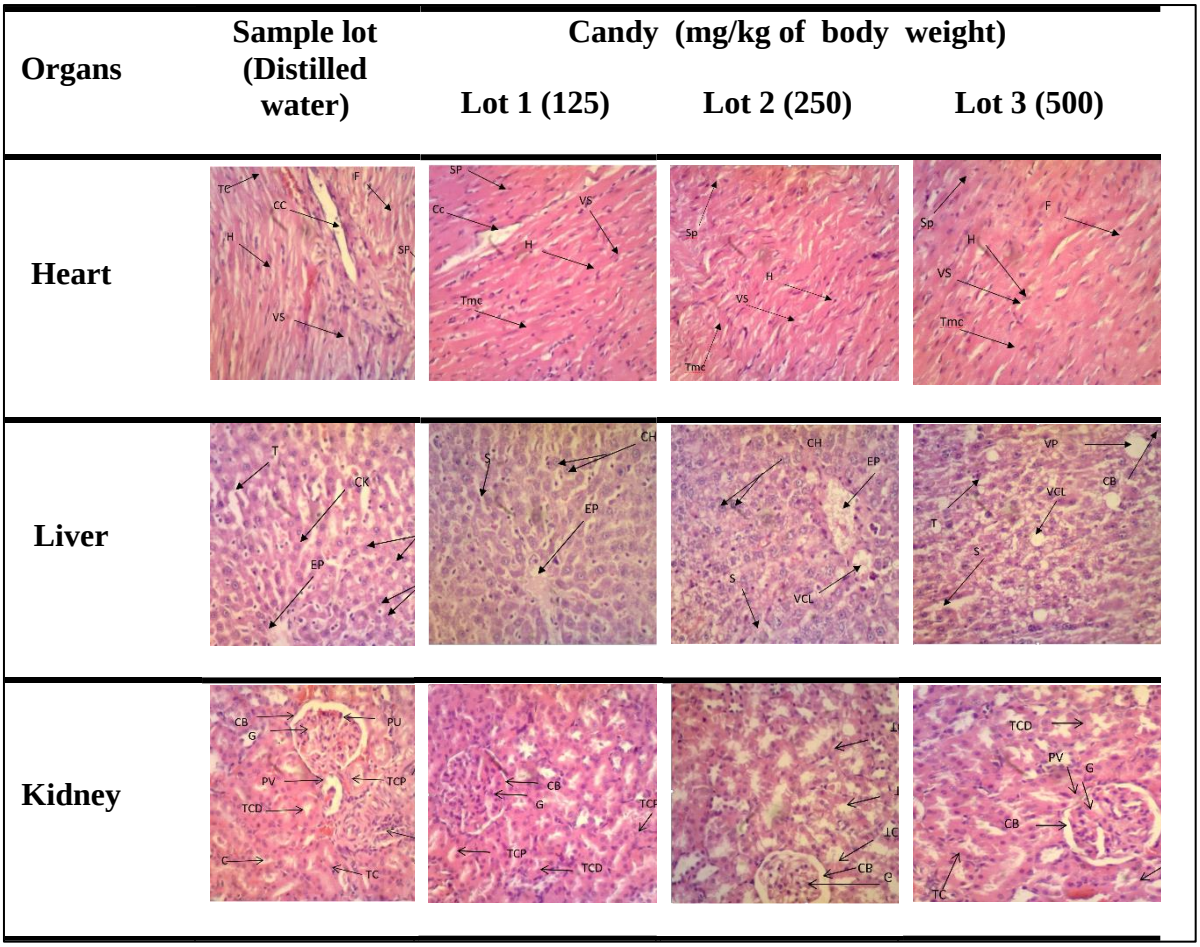
Table 2 Mean change in body mass in control rats and rats treated with the candies for 28 days

Body mass of rats (g) / **Groups of Untreated rats and rats treated with doses of candy**	**Day 0**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Earnings**
Control (distilled water)	132.0 ± 4.4	153.0 ± 2.3**	174.0 ± 3.9***	179.0 ± 5.3***	189.0 ± 1.5***	57.0 ± 5.3
Lot 1 (125 mg/ kg of body weight)	147.3 ± 4.7	155.3 ± 2.1ns	163.0 ± 4.0ns	170.3 ± 7.4ns	194.7 ± 3.0***	53.7 ± 1.9
Lot 2 (250 mg/ kg of body weight)	151.0 ± 5.2	174.0 ± 3.6ns	192.0 ± 3.6**	205.0 ± 4.0***	212.0 ± 1.5***	61.0 ± 6.6
Lot 3 (500 mg/ kg of body weight)	141.0 ± 5.5	163.0 ± 4.4*	166.0 ± 2.3**	169.0 ± 3.1**	184.0 ± 5.7***	43.0 ± 4.4

Values are expressed as mean ± standard deviation (n = 3 rats per group).; ns: no significant difference at $p > 0.05$; *: slightly significant difference at $p < 0.05$; **: significant difference at $p < 0.01$; ***: highly significant difference at $p < 0.001$

Table 3 Absolute mass of organs in control rats and treated rats with candy for 28 days

Organs / **Sample lot and Batches processed**	**Kidneys**	**Liver**	**Heart**
Control (distilled water)	1.07 ± 0.63	5.86 ± 0.88	0.55 ± 0.14
Lot 1 (125 mg/kg of body weight)	1.10 ± 0.40ns	5.91 ± 0.57ns	0.53 ± 0.11ns
Lot 2 (250 mg/kg of body weight)	1.09 ± 0.19ns	5.72 ± 0.57ns	0.59 ± 0.09ns
Lot 3 (500 mg/kg of body weight)	1.43 ± 0.11ns	6.17 ± 0.81ns	0.62 ± 0.14ns



Heart: CC: cardiac cavity; TC: connective tissue; F: cardiac fiber; H: red blood cell; VS: blood vessel; Liver : CK: Kupffer cell; TR: Remak's trabecula; T: trabecula; VCL: centrilobular vein; CB: bile duct; CH: hepatocyte; S: sinusoid; EP: portal tract; VP: portal vein.Kidney:G: glomerulus; CB: Bowman's capsule; PV: vascular pole; TCP: proximal convoluted tubule; TCD: distal convoluted tubule; TC: collecting duct; A: arteriole; PU: urinary pole; C: capillary

Figure 10 Hematoxylin and eosin-stained histological sections of the Heart, Liver and Kidney (200 x magnification) of the control rats and those exposed to 125, 250 and 500 mg/kg b.w.

3.4. Effect of Candies on Hematological and Biochemical Parameters

The hematological and biochemical parameters (control and treated rats) following 28 days of treatment are presented respectively in **Tables 4** and **5**.

Hematological evaluation provided additional evidence regarding the safety of this formulation. The majority of parameters assessed including red blood cell count (RBC), hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) were not significantly altered in the treated groups compared to the control. This stability suggests that the formulated candies did not adversely affect the erythrocyte lineage. However, a statistically significant decrease in hematocrit was observed at doses of 250 mg/kg ($p < 0.01$) and 500 mg/kg ($p < 0.001$), which could be attributable to a slight disruption of erythropoiesis or a hemodilution phenomenon, as proposed by Adebayo and allies [18]. In addition, the significant increase in leukocyte count observed at the 500 mg/kg dose may reflect stimulation of the immune system or a moderate inflammatory response. Similarly, the significant increase in platelet count could result from activation of hematopoietic function by the bioactive compounds present in the candies. Nevertheless, the absence of significant variation in other erythrocyte indices and in the leukocyte differential count suggests that no major toxicological consequence occurred in the treated rats, consistent with the findings reported by Maru and Belemkar [19].

The biochemical parameters assessed namely urea, creatinine, AST, and ALT showed no statistically significant variation between the treated groups and the control group ($p > 0.05$). Urea and creatinine concentrations serve as established markers of renal function, whereas ALT and AST activities are commonly used to evaluate hepatic integrity. The liver and kidneys are the primary organs involved in the metabolism and elimination of xenobiotics and are therefore particularly vulnerable to toxic insult from various substances, including medicinal plants and pharmaceutical

compounds [20]. The results obtained in this study indicate that both renal and hepatic functions were preserved in all treated animals, implying that the formulated candies did not induce nephrotoxicity or hepatotoxicity at the doses tested.

Table 4 Values of biochemical parameters (M ± SD) of control rats and treated rats with the candies for 28 days

Settings biochemicals	Sample lot (Distilled water)	Candy (mg/kg of body weight)		
		Lot 1 (125)	Lot 2 (250)	Lot 3 (500)
Urea	5.8 ± 0.9	5.9 ± 0.9^{ns}	5.8 ± 0.7^{ns}	6.2 ± 0.9^{ns}
Creatinine	10.8 ± 2.2	11.0 ± 1.0^{ns}	10.5 ± 0.5^{ns}	11.3 ± 1.3^{ns}
ASAT	97.0 ± 4.0	98.0 ± 5.0^{ns}	95.0 ± 5.5^{ns}	101.0 ± 4.2^{ns}
ALAT	48.0 ± 4.1	51.0 ± 5.0^{ns}	47.0 ± 4.1^{ns}	52.0 ± 5.0^{ns}

Table 5 Hematological parameters values in treated and untreated rats after 28 days

Hematological parameters	Sample lot (Distilled water)	Candy (mg/kg of body weight)		
		Lot 1 (125)	Lot 2 (250)	Lot 3 (500)
Red blood cells : RBCs (10^3/mm^3) (erythrocytes)	6.4 ± 0.3	6.5 ± 1,1^{ns}	6.6 ± 0.5^{ns}	5.3 ± 0.9^{ns}
Hemoglobin : HGB (g/dL)	15.3 ± 0.5	15.4 ± 1.0^{ns}	15.5 ± 1.4^{ns}	14.9 ± 0.9^{ns}
Hematocrit : HCT (%)	37.9 ± 1.5	33.7 ± 1.5^{ns}	29.1 ± 3.0**	25.3 ± 2.0***
Mean corpuscular Volume : MCV (μ^3)	52.8 ± 5.2	56.0 ± 4.0^{ns}	48.5 ± 4.5^{ns}	58.0 ± 5.0^{ns}
Mean corpuscular HGB content: MCHC (pg)	18.3 ± 1.1	29.4 ± 9.5^{ns}	26.5 ± 2.5^{ns}	25.5 ± 4,0^{ns}
Mean corpuscular concentration: MCC (g/dL)	35.8 ± 4.9	30.7 ±5.0^{ns}	34.4 ± 3.5^{ns}	39.5 ± 5.5^{ns}
Platelets : PLQ (10^3/mm^3)	229.7 ± 5.3	294.7 ± 4.3***	239.0 ± 5.0^{ns}	271.7 ± 3.5**
White blood cells : (Leukocytes) (10^3/mm^3)	7.23 ± 1.7	4.89 ± 1.05^{ns}	8.27 ± 1.15^{ns}	22.6 ± 3.5***
Leukocyte formulas				
Neutrophils : PMN (10^3/ mm^3)	17.0 ± 2.6	17.0 ± 2.0^{ns}	12.0 ± 3.0^{ns}	16.0 ± 4.0^{ns}
Lymphocytes (10^3/mm^3)	74.0 ± 5.3	74.0 ± 4.5^{ns}	76.3 ± 5.1^{ns}	75.0 ± 4.0^{ns}
Monocytes (10^3/mm^3)	7.0 ± 1.7	9.0 ± 2.0^{ns}	5.0 ± 2.0^{ns}	8.0 ± 3.0^{ns}
Eosinophils	2.0 ± 1.7	1.0 ± 0.0^{ns}	2.0 ± 1.0^{ns}	1.0 ± 0.0^{ns}

4. Conclusion

This study established the toxicological profile of candies formulated from four medicinal plants (*Annona senegalensis, Pericopsis laxiflora*, *Heliotropium indicum*, and *Vitellaria paradoxa*), traditionally used to treat asthma in Korhogo. The acute toxicity assessment determined an LD50 of 2500 mg/kg body weight, classifying these candies as having low toxicity according to OECD guidelines. Repeated administration over a 28-day period did not induce any significant changes in mean body weight, absolute organ weight (heart, liver and kidneys), hematological parameters (white blood cell count, red blood cell count, platelet count, MCC, MCHC, MCV, Hb, and HCT), or clinical biochemical parameters (Urea,

Creatinine, AST and ALT). Furthermore, histopathological examination of the vital organs revealed no microscopic alterations in the heart, kidneys and liver, confirming the structural integrity of these organs. Taken together, these results demonstrate the safety of the formulated candies under the tested experimental conditions and provide a solid scientific basis for their potential use as a therapeutic alternative in the management of asthma.

5. Compliance with ethical standards

Acknowledgments

Authors are thankful to Peleforo GON COULIBALY University for providing their facility and for helping the tests for analysis. We also thank the ethics committee of Félix HOUPHOUËT-BOIGNY University for the follow-up.

Disclosure of conflict of interest

Authors declare no conflict of interest.

Statement of ethical approval

The experimental procedures and protocols used in this study were approved by the ethics committee, Health Sciences Committee, Félix HOUPHOUËT-BOIGNY University. These guidelines were in accordance with those of the European Council Legislation 87/607/EEC for the protection of experimental animals. Every effort has been made to minimize animal suffering and reduce the number of animals used.

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