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Acute and Subacute Skin Toxicity of Shea Butter (*Vitellaria paradoxa* C.F. Gaertn.) Based Milk and Body Cream Formulations in Mice Naval Medical Research Institute

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Abstract

The study aimed to evaluate the acute and subacute skin toxicity of the milk and body cream formulations based on shea butter on male and female Naval Medical Research Institute mice. The study was conducted in Burkina Faso. Two formulations (natural and stable body milk and cream) and a control (shea butter) were applied only on the first day for the acute skin toxicity test and daily from day 1 to day 28 for the subacute skin toxicity test. The animals were observed daily to note any abnormal signs or behavior, and their weight was measured weekly. For each test, the mice were euthanized using diethyl ether, blood was collected by cardiac puncture, and the major organs (heart, lungs, liver, kidneys, and spleen) were removed for macroscopic observations, weighing, and histological analysis. The blood samples were used for hematological and biochemical analyses. No mortality or signs of toxicity were observed in the animals following application of the formulations. Furthermore, application of the shea butter-based formulations did not negatively impact the animals' weight in either the acute or subacute toxicity tests. Macroscopic observations of the major organs revealed no lesions, which was confirmed by histological analyses. In addition, there was no significant difference between the weight of these organs in the treated groups compared to the control group.

The hematological parameters of mice treated with milk and body cream were normal compared to those of controls to which shea butter was applied ($P > 0.05$). The same trend was observed for biochemical parameters, with no significant differences between the groups of mice used for acute and subacute skin toxicity testing ($P > 0.05$). The results demonstrate the safety of shea butter-based milk and body cream formulations in NMRI mice and encourage the use of these formulations in cosmetics, although further studies are still needed.

Keywords

Shea Butter, Body Lotion and Cream, Toxicity, Burkina Faso

1. Introduction

Shea butter, extracted from the nuts of the *Vitellaria paradoxa* tree, occupies a crucial place in the global market, particularly in the cosmetics and pharmaceutical industries [1]. This vegetable oil is gaining popularity due to its unsaturated fatty acid composition and the potential usefulness of its unsaponifiable fraction, now used in cosmetic, pharmaceutical, and nutraceutical applications [2]. In traditional medicine, it can also be used to treat skin conditions and improve people's appearance, personality, or hygiene [3] [4]. Interest in these various compounds in cosmetics is growing due to their ability to protect the skin from harmful external and internal substances. It also contributes to the resolution of many skin diseases [5]. Although several studies have been conducted on shea butter, there is no experimental evidence of its value or acute and subacute skin toxicity in natural and stable body lotion and cream formulations. Cosmetic formulations based on shea butter have often been abandoned in research because they focus primarily on their medicinal values or properties and their uses as food [6].

Recently, interest in body cosmetics made from natural extracts has grown. These formulations, which are natural and traditionally used, are considered safe and harmless. However, their natural origin does not guarantee their safety, as highlighted by the risks associated with the use of products made from natural extracts [7]. Therefore, it is essential to have scientific information on the application of this milk and body cream formulation. Acute and subacute toxicological evaluations of the shea butter-based milk and body cream formulation are essential to understand its side effects, particularly in people who use it. The use of cosmetic products is becoming increasingly indispensable in our societies. Individuals are under social pressure to stay in the game by maintaining a dynamic appearance for as long as possible. The keys to this well-being are diet and the use of natural and wellness cosmetics. Therefore, this acute and subacute toxicity study on laboratory animals will determine the toxicity of the natural milk and body cream formulation made from shea butter.

2. Materials and Methods

2.1. Milk and Body Cream

The products used were milk and body cream made from shea butter. Shea butter was extracted from shea nuts (*Vitellaria paradoxa*) through the churning process [8]. The one that meets the quality criteria of category I of the *Codex Alimentarius* was used in the formulation of milk and body cream [9]. It has been used directly as the main raw material. It has antioxidant properties [10] and contains minerals and unsaturated fatty acids, which give the formula softening, moisturizing, protective, and nourishing properties [11]. Raw shea butter was used as a control in the study because it contains no additives that could influence the acute or subacute toxicity test. It also serves as the basis for the various experimental formulations, ensuring consistent comparison and making it easier to determine the effect of the added substances. Unlike the control sample, which consists solely of raw shea butter, the milk (E2) and cream (E3) formulations include additional ingredients. E2 milk is characterized by a fluid texture, due to the incorporation of water and emulsifiers that ensure the homogeneous dispersion of the lipid phase. E3 cream, produced using a reverse process in which the oil phase is gradually incorporated into the aqueous phase, is characterized by a higher fat content and the use of agents that reinforce its texture. These differences in composition are key factors in interpreting any variations in toxicity between the formulations.

2.2. Mice Management

For the acute and subacute skin toxicity study, 30 NMRI (Naval Medical Research Institute) mice, including 15 males and 15 females, were used. Upon arrival at the animal facility, the mice were weighed and randomly assigned to polypropylene cages. In the animal facility, the mice had free access to food (2918C, Harlan Laboratories, Inc., USA) and water and lived under animal facility conditions for 1 week prior to the experiment. The mice lived under controlled conditions: 22˚C ± 3˚C, 50% ± 20% humidity, and a 12-hour light/dark cycle.

2.3. Acute skin toxicity study

The acute skin toxicity of the milk and body cream formulation was tested on 15 NMRI mice divided into three (03) groups of five (05) mice as follows:

- Group 1 (control 1): application of *Vitellaria paradoxa shea* butter;
- Group 2 (test 1): application of the body milk formulation (E2);
- Group 3 (test 2): application of the body cream formulation (E3).

The mice were shaved before the start of the tests with depilatory cream to facilitate the application of the formulation to their skin. The application was made once (D0), and the mice were monitored for 14 days.

During this period, the mice were monitored, and any suspicious behavior (behavior, signs of distress, alteration in general condition) and skin appearance (er-

ythema, edema, ulceration, dryness) were observed.

2.4. Subacute Skin Toxicity Study

The subacute skin toxicity of the milk and body cream formulation was tested on 15 NMRI mice divided into three (03) groups of five (05) mice. The mice were divided as follows:

- Group 1 (control 1): application of *Vitellaria paradoxa* shea butter;
- Group 2 (test 1): application of the body milk formulation (E2);
- Group 3 (test 2): application of the body cream formulation (E3).

The mice were also shaved before the start of the test with depilatory cream to facilitate the application of the formulation to the mice's skin. The application was carried out every day for 28 days. During this period, the mice were monitored, and any suspicious behavior (behavior, signs of distress, alteration in general condition) and skin appearance (erythema, edema, ulceration, dryness) were observed. The animals' weights were measured weekly (D0-D7-D14-D21-D28). On the 29th day, *i.e.*, 24 hours after the last application, the mice were euthanized using diethyl ether. Organs such as the heart, lungs, liver, kidneys, and spleen were removed for histological analysis. Blood was collected by cardiac puncture for hematological and biochemical analysis.

3. Data Processing

The data obtained (body weight, biochemical and hematological parameters, and organ weight) were expressed as mean ± standard deviation for each group.

Statistical analysis was performed using R software (version 4.3.2). Comparisons between the groups that received an application of both formulations (milk and body cream) based on shea butter and the control group that received an application of shea butter were performed using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test for parametric data or the Kruskal-Wallis test followed by Dunn's test for non-parametric data (if normality conditions were not met). The statistical significance threshold was set at $P < 0.05$.

4. Results

4.1. Acute Skin Toxicity

4.1.1. Effect of Milk and Body Cream on Behavior

No deaths were recorded among mice treated with milk (E2) and body cream (E3) during the 14 days of the study. No signs of systemic toxicity were observed, and the animals maintained normal behavior throughout the observation period.

No behavioral disorders were noted in mice exposed to the various milk and body cream solutions tested, including:

- normal locomotor activity, without ataxia or tremors;
- intact motor and sensory reflexes;
- no lethargy, convulsions, or coma;

- normal feeding behavior and hydration;
- no signs of stereotypy, self-mutilation, or excessive reaction to handling.

In terms of the skin, no local lesions (erythema, edema, necrosis, ulceration) were observed at the application site, regardless of how the lotion and body cream were applied.

4.1.2. Effect of Milk and Body Cream on the Weight of Mice

The analysis aimed to evaluate the effect of applying two cosmetic formulations based on shea butter (E2 and E3), compared to a control (shea butter), on the change in body weight of mice over time. Average weights were measured on days 0 (D0), 7 (D7), and 14 (D14).

On D0, the initial weights were relatively similar between the groups: 41.0 g ± 2.80 g for the control group, 44.3 g ± 1.76 g for the E2 group, and 45.2 g ± 1.57 g for the E3 group. On D7, an increase in body weight was observed in all groups: 41.6 g ± 2.05 g for the control group, 45.1 g ± 1.54 g for E2, and 45.8 g ± 1.06 g for E3. This increase reflects continuous body growth. On day 14, this trend continued, with an average weight of 42.3 g ± 3.50 g for the control group, 45.4 g ± 2.32 g for group E2, and 46.2 g ± 2.92 g for group E3 (Figure 1).

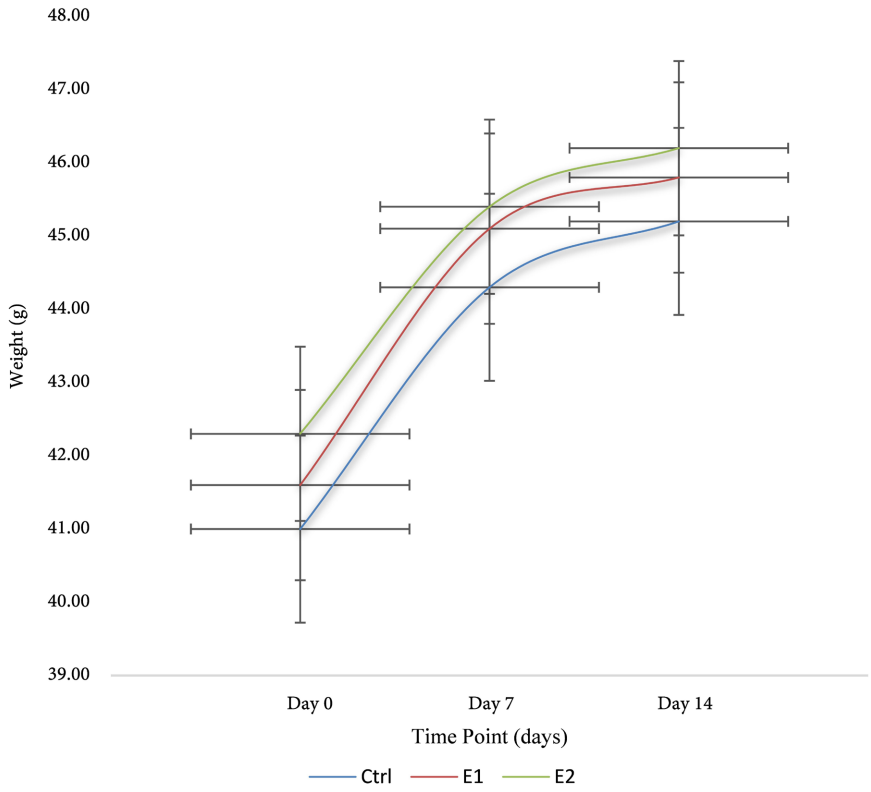

Figure 1. Effect of milk and body cream on the weight of mice.

The analysis of deviation (Type II) showed no significant effect of the application of the formulation on body weight (P = 0.062), as well as an effect of the time factor (P = 0.0546). However, the interaction between application of the cosmetic

formulation and time was not significant, indicating that the effect of application was relatively constant over time and that the mice grew naturally.

Regarding the effect of time, the estimated marginal means were 43.5 g ± 0.74 g on D0, 44.2 g ± 0.78 g on D7, and 44.5 g ± 0.72 g on D14. A slight and gradual increase in mouse weight was observed between D0 and D14. However, post-hoc findings show no significant difference for multiple comparisons (Tukey).

These results indicate that during the application of formulations E2 and E3, the mice's weight increased. Application of the formulation to the skin did not influence the mice's weight gain over time. **Figure 1** shows the effect of milk and body cream on the mice's weight.

4.1.3. Effect of Milk and Body Cream on Organ Weight

Macroscopic post-mortem examination of organs revealed no abnormalities during necropsy of major organs, which appeared normal in all animals regardless of the formulation application group. These results suggest that application of shea butter-based milk and body cream does not cause any visible alteration of organs to the naked eye.

To supplement this observation, the relative weights of several major organs were measured and compared between groups. The mean relative weight of the heart was 0.230 g ± 0.014 g in the control group, 0.213 g ± 0.015 g in the E2-treated group, and 0.232 g ± 0.060 g in the E3-treated group. No significant differences were detected between the groups ($P = 0.84$).

The average relative weight of the lungs was also measured to assess the potential toxicity of the application. It was 0.375 g ± 0.120 g in the control group, 0.277 g ± 0.047 g in the E2 group, and 0.372 g ± 0.105 g in the E3 group. No significant differences were observed between the groups ($P = 0.34$).

The mean relative liver weight was 2.90 g ± 0.04 g in the control group, 2.37 g ± 0.20 g in the E2 group, and 2.47 g ± 0.25 g in the E3 group. No significant differences were observed between the groups ($P = 0.065$). However, adjusted multiple comparisons (Tukey's method) revealed no significant differences between the groups taken two by two.

The mean relative weight of the spleen was 0.71 g ± 0.01 g in the control group, 0.70 g ± 0.09 g in the E2 group, and 0.76 g ± 0.06 g in the E3 group. No significant differences were detected between groups ($P = 0.37$).

The mean relative weight of the kidneys was 0.385 g ± 0.30 g in the control group, 0.193 g ± 0.03 g in the E2 group, and 0.205 g ± 0.06 g in the E3 group. No significant differences were observed between the groups ($P = 0.21$).

4.1.4. Effect of Milk and Body Cream on Hematological Parameters in Mice

The various hematological parameters analyzed revealed no statistically significant differences between the experimental groups ($P > 0.05$ for all cases).

Analysis of red blood cell (RBC) count revealed no significant differences between the experimental groups ($P = 0.68$). The means observed were $7.94 \times 10^6/\mu L \pm 1.57$

$\times 10^6$/µL for the control group, 9.13×10^6/µL ± 0.51×10^6/µL for the E2 group, and 7.54×10^6/µL ± 3.61×10^6/µL for the E3 group. Although a slight increase was observed in the E2 group, no significant difference was found between the milk and body cream applications.

The number of white blood cells (WBC) showed no significant difference between the groups (P = 0.491). The mean values were 2.39×10^3/µL ± 0.67×10^3/µL in the control group, 3.10×10^3/µL ± 0.38×10^3/µL in group E2, and 2.62×10^3/µL ± 1.03×10^3/µL in group E3.

A slight upward trend was observed in group E2, but it did not reach statistical significance.

Regarding hemoglobin (HB) levels, the averages were 15.09 g/dL ± 3.44 g/dL for the control group, 17.13 g/dL ± 1.02 g/dL for the E2 group, and 13.58 g/dL ± 6.14 g/dL for the E3 group. Statistical analysis (P = 0.5693) showed no significant difference between the groups.

Similarly, hematocrit (HCT) had mean values of 50.09% ± 10.71% in the control group, 57.25% ± 4.13% in the E2 group, and 47.00% ± 23.10% in the E3 group. No significant variation was observed between groups (P = 0.6869), although the values in the E3 group showed greater interindividual variability.

As for platelet count (PLT), the means were 592.92×10^3/µL ± 162.00×10^3/µL for the control group, 620.00×10^3/µL ± 155.56×10^3/µL for the E2 group, and 440.42×10^3/µL ± 170.01×10^3/µL for the E3 group. Again, statistical analysis (P = 0.6997) revealed no significant differences.

Analysis of mean corpuscular volume (MCV) revealed no significant differences between the experimental groups (P = 0.76). The mean MVC values were 62.9 fL ± 1.81 fL in the control group, 62.7 fL ± 1.45 fL in the E2 group, and 61.9 fL ± 1.95 fL in the E3 group. Although slight variations were observed between groups, these were not statistically significant.

Analysis of lymphocyte count (LYM) showed no significant differences between the experimental groups (P = 0.28). The mean lymphocyte counts were 1.82×10^6/µL ± 0.62×10^6/µL in the control group, 2.47×10^6/µL ± 0.17×10^6/µL in the E2 group, and 2.09×10^6/µL ± 0.85×10^6/µL in the E3 group. Although some variations were observed between groups, these were not statistically significant.

Table 1. Effect of milk and body cream on the hematological parameters of mice.

Parameter (unit)	Control	E2	E3	P-value
GR ($\times 10^6$/µL)	7.94 ± 1.57	9.13 ± 0.51	7.54 ± 3.61	0.68
GB ($\times 10^3$/µL)	2.39 ± 0.67	3.10 ± 0.38	2.62 ± 1.03	0.49
HB (g/dL)	15.09 ± 3.44	17.13 ± 1.02	13.58 ± 6.14	0.57
HCT (%)	50.09 ± 10.71	57.25 ± 4.13	47.00 ± 23.10	0.69
PLT ($\times 10^3$/µL)	592.92 ± 162.00	620.00 ± 155.56	440.42 ± 170.01	0.70
MVC (fL)	62.9 ± 1.81	62.7 ± 1.45	61.9 ± 1.95	0.76
LYM ($\times 10^6$/µL)	1.82 ± 0.62	2.47 ± 0.17	2.09 ± 0.85	0.28
BAS ($\times 10^6$/µL)	0.35 ± 0.05	0.49 ± 0.33	0.38 ± 0.11	0.66

Analysis of basophil counts (BAS) revealed no significant differences between the experimental groups (P = 0.66). The mean basophil counts were 0.35×10^6/µL ± 0.05×10^6/µL in the control group, 0.49×10^6/µL ± 0.33×10^6/µL in the E2 group, and 0.38×10^6/µL ± 0.11×10^6/µL in the E3 group. Although variations are apparent between groups, they are not statistically significant. The effect of milk and body cream on the hematological parameters of mice is shown in Table 1.

4.1.5. Effect of Milk and Body Cream on Biochemical Parameters in Mice

Analysis of AST levels revealed no significant differences between the experimental groups (P = 0.20). The mean values observed were 366 IU/L ± 268 IU/L for the control group, 188 IU/L ± 233 IU/L for the E2 group, and 62.5 IU/L ± 43.8 IU/L for the E3 group. Although an apparent decrease in AST levels was observed in the E2 and E3 groups compared to the control group, this variation did not reach statistical significance. Variability was particularly high in the control group, suggesting considerable individual heterogeneity.

Analysis of ALT levels revealed no statistically significant difference between the experimental groups (P = 0.075). The mean values observed were 115 IU/L ± 31 IU/L for the control group, 116.5 IU/L ± 12 IU/L for group E2, and 119 IU/L ± 23 IU/L for group E3.

Analysis of creatinine levels (CREA) revealed no significant differences between the experimental groups (P = 0.48). The mean values observed were 9.0 mg/dL ± 3.97 mg/dL for the control group, 10.5 mg/dL ± 6.87 mg/dL for the E2 group, and 14.0 mg/dL ± 4.33 mg/dL for the E3 group. Although a trend toward increased creatinine levels was noted in the E3 group, no statistically significant differences were found between the cosmetic applications.

Analysis of urea levels (UREA) showed a trend close to significance between the experimental groups (P = 0.065). The observed means were 11.6 mmol/L ± 1.35 mmol/L for the control group, 11.2 mmol/L ± 2.87 mmol/L for the E2 group, and 14.5 mmol/L ± 0.87 mmol/L for the E3 group. Although an increase was noted in the E3 group, this difference is not statistically significant. The effect of milk and body cream on the biochemical parameters of the mice is shown in Table 2.

Table 2. Effect of milk and body cream on biochemical parameters in mice.

Parameter (unit)	Control (Ctrl)	E2 Treatment	E3 Treatment	P-value
ASAT (U/L)	366 ± 268	188 ± 233	62.5 ± 43.8	0.1954
ALAT (U/L)	115 ± 30.8	116.5 ± 12.2	119 ± 23	0.0755
Creatinine (µmol/L)	9 ± 3.97	10.5 ± 6.87	14 ± 4.33	0.4844
Urea (mmol/L)	11.6 ± 1.35	11.2 ± 2.87	14.5 ± 0.87	0.0649

4.2. Subacute Skin Toxicity

4.2.1. Effect of Milk and Body Cream on Behavior

No mortality or signs of distress were observed following application of formulation E2 or E3 throughout the duration of the experiment (28 days). We also ob-

served no abnormal behavioral changes in mice treated with body cream (E3) or milk (E2).

Mice subjected to repeated application of the formulation for 28 days exhibited normal activity throughout the experiment. More specifically, we observed:

- preserved locomotor activity, with no signs of ataxia, tremors, or hypoactivity;
- normal motor and sensory reflexes;
- no signs of stress, lethargy, aggression, or self-mutilation;
- unchanged eating and drinking behavior;
- preserved grooming and interaction with other mice.

As for local irritation (erythema, edema, desquamation, ulceration), no signs were observed at the site of application of the milk and body cream (E2 and E3) in mice during the 28 days of the subacute skin toxicity experiment.

4.2.2. Effect of Milk and Body Cream on the Weight of Mice

The analysis aimed to evaluate the effect of two formulations (E2 and E3) based on shea butter, compared to a control (shea butter), on the change in body weight of mice over a period of 28 days. Weights were measured on days 0, 7, 14, 21, and 28.

On D0, the initial weights were relatively comparable between the groups: 52.6 g ± 2.32 g for the control group, 49.9 g ± 1.28 g for the E2 group, and 47.2 g ± 1.36 g for the E3 group (Figure 2). Weight variations over time differed between groups. The control group showed a gradual increase in body weight until D28: 53.1 g ± 2.56 g on D7, 53.8 g ± 2.53 g on D14, 54.0 g ± 2.55 g on D21, and 54.5 g ± 2.42 g on D28.

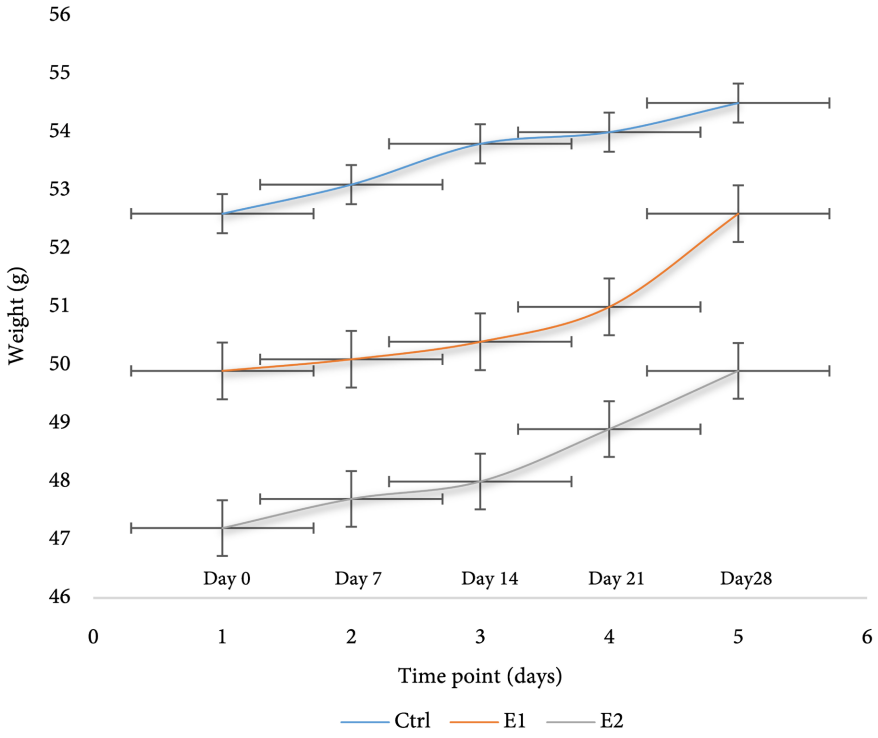

Figure 2. Effect of milk and body cream on the weight of mice.

In comparison, groups E2 and E3 had significantly lower weights. Both groups showed a gradual increase in weight. For E2, the average weights ranged from 50.4 g ± 2.32 g on day 14 to 52.6 g ± 2.70 g on day 28, while for E3, they ranged from 48.0 g ± 2.13 g on day 14 to 49.9 g ± 3.42 g on day 28.

Statistical analysis revealed no significant effect of cosmetic application on body weight ($P < 0.07$), indicating that the groups differ significantly in terms of average weight. However, no significant effect of the time factor ($P = 0.15$) or application × time interaction ($P = 0.98$) was observed, suggesting that weight differences between groups remained constant over time.

Regarding the effect of the time factor, although a slight and gradual increase in weight was observed between D0 and D28, none of the comparisons were statistically significant for multiple comparisons (all $P > 0.2$), confirming the absence of a time effect in this model.

In summary, these results show that the application of the E2 and E3 shea butter-based cosmetic formulation did not result in a reduction in body weight throughout the 28 days of the experiment. **Figure 2** shows the effect of the milk and body cream on the weight of the mice.

4.2.3. Effect of Milk and Body Cream on Organ Weight

Post-mortem macroscopic examination of internal organs revealed no visible abnormalities in any of the animals treated with repeated applications of shea butter formulations. All organs examined, including the heart, lungs, liver, spleen, and kidneys, appeared normal, with no lesions, discoloration, or signs of hypertrophy or atrophy. These observations suggest good overall tolerance to the application of the cream and body lotion, with no detectable macroscopic toxic effects after 28 days of repeated daily application of the shea butter-based formulation to the skin.

The mean relative heart weight was 0.237 g ± 0.038 g in the control group, 0.263 g ± 0.055 g in the E2 group, and 0.250 g ± 0.018 g in the E3 group. No significant differences were observed between the groups ($P = 0.69$).

The mean relative lung weight was 0.393 ± 0.167 g in the control group, 0.417 g ± 0.099 g in the E2 group, and 0.370 g ± 0.084 g in the E3 group. No significant differences were observed between the groups ($P = 0.87$).

The mean relative weight of the liver was 3.27 g ± 0.23 g in the control group, 3.78 g ± 0.17 g in the E2 group, and 3.44 g ± 0.32 g in the E3 group. No significant differences were observed between the groups ($P = 0.89$).

The mean relative weight of the spleen was 0.82 g ± 0.03 g in the control group, 0.85 g ± 0.06 g in the E2 group, and 0.77 g ± 0.10 g in the E3 group. No significant differences were observed between the groups ($P = 0.37$).

The mean relative weight of the kidneys was 0.213 g ± 0.0139 g in the control group, 0.217 g ± 0.0139 g in the E2 group, and 0.235 g ± 0.0120 g in the E3 group. No significant difference was observed between the groups ($P = 0.69$).

4.2.4. Effect of Milk and Body Cream on Hematological Parameters in Mice

Analysis of red blood cell (RBC) counts showed no significant differences between

the experimental groups (P = 0.589). The means were $9.93 \times 10^6/\mu L \pm 1.97 \times 10^6/\mu L$ for the control group, $11.4 \times 10^6/\mu L \pm 0.64 \times 10^6/\mu L$ for the E2 group, and $10.8 \times 10^6/\mu L \pm 2.26 \times 10^6/\mu L$ for the E3 group. Although a slight increase was observed in the E2 group, this variation remains statistically insignificant.

Analysis of white blood cell (WBC) counts revealed no significant difference between the experimental groups (P = 0.491). The means observed were $3.32 \times 10^3/\mu L \pm 0.92 \times 10^3/\mu L$ for the control group, $4.31 \times 10^3/\mu L \pm 0.54 \times 10^3/\mu L$ for group E2, and $3.65 \times 10^3/\mu L \pm 1.43 \times 10^3/\mu L$ for group E3. Although a slight increase was observed in the E2 group, this variation was not statistically significant.

Analysis of hemoglobin (HB) levels revealed no significant difference between the experimental groups (P = 0.569). The means were 21 g/dL ± 4.79 g/dL for the control group, 23.8 g/dL ± 1.43 g/dL for group E2, and 18.9 g/dL ± 8.54 g/dL for group E3. Despite a downward trend in group E3, this variation was not statistically significant.

The hematocrit (HCT) analysis showed no significant difference between the groups (P = 0.687). The mean values observed were 69.7% ± 14.9% for the control group, 79.7% ± 5.75% for the E2 group, and 65.4% ± 32.1% for the E3 group. Despite a slight increase in the E2 group, this variation did not reach statistical significance.

Analysis of platelet count (PLT) revealed no significant difference between the experimental groups (P = 0.700). The means were $826 \times 10^3/\mu L \pm 452 \times 10^3/\mu L$ for the control group, $863 \times 10^3/\mu L \pm 54 \times 10^3/\mu L$ for group E2, and $613 \times 10^3/\mu L \pm 501 \times 10^3/\mu L$ for group E3. No statistically significant variation was observed despite a downward trend in group E3.

Analysis of mean corpuscular volume (MCV) showed no significant differences between groups (P = 0.761). The mean values observed were 87.6 fL ± 2.52 fL for the control group, 87.3 fL ± 2.02 fL for the E2 group, and 86.2 fL ± 2.72 fL for the E3 group. The values, therefore, remain stable and comparable between the different cosmetic applications.

Table 3. Effect of milk and body cream on hematological parameters in mice.

Parameter (Unit)	Control Group	Group E2	Group E3	P-value
Red blood cells ($10^6/\mu L$)	9.93 ± 1.97	11.40 ± 0.64	10.80 ± 2.26	0.589
White blood cells ($10^3/\mu L$)	3.32 ± 0.92	4.31 ± 0.54	3.65 ± 1.43	0.491
Hemoglobin (g/dL)	21.00 ± 4.79	23.80 ± 1.43	18.90 ± 8.54	0.569
Hematocrit (%)	69.70 ± 14.90	79.70 ± 5.75	65.40 ± 32.10	0.687
Platelets ($10^3/\mu L$)	826 ± 452	863 ± 54	613 ± 501	0.700
Mean corpuscular volume (fL)	87.60 ± 2.52	87.30 ± 2.02	86.20 ± 2.72	0.761
Lymphocytes ($10^3/\mu L$)	2.54 ± 0.86	3.43 ± 0.24	2.91 ± 1.18	0.290
Basophils ($10^3/\mu L$)	0.48 ± 0.07	0.68 ± 0.45	0.53 ± 0.15	0.655

Analysis of lymphocyte count (LYM) revealed no statistically significant difference between the groups (P = 0.290). The means were $2.54 \times 10^3/\mu L \pm 0.86 \times 10^3/\mu L$

in the control group, 3.43 × 10^3/µL ± 0.24 × 10^3/µL in the E2 group, and 2.91 × 10^3/µL ± 1.18 × 10^3/µL in the E3 group. The values observed remain comparable between cosmetic applications.

Analysis of the number of basophils (BAS) showed no significant difference between the experimental groups (P = 0.655). The means were 0.48 × 10^3/µL ± 0.07 × 10^3/µL for the control group, 0.68 × 10^3/µL ± 0.45 × 10^3/µL for the E2 group, and 0.53 × 10^3/µL ± 0.15 × 10^3/µL for the E3 group. No notable variation was observed between treatments. The effects of milk and body cream on the hematological parameters of the mice are shown in Table 3.

4.2.5. Effect of Milk and Body Cream on Biochemical Parameters in Mice

Analysis of AST (aspartate aminotransferase) levels revealed no significant differences between the experimental groups (P = 0.195). The mean values observed were 610 U/L ± 447 U/L for the control group, 614 U/L ± 389 U/L for the E2 group, and 604 U/L ± 73 U/L for the E3 group. Despite an apparent decrease in the E2 and E3 groups, this variation was not statistically significant.

Analysis of ALT (alanine aminotransferase) levels did not reveal any statistically significant difference between the experimental groups. The control group had a mean of 192 U/L ± 51.4 U/L, compared to 192.6 U/L ± 20.4 U/L for group E2 and 198.3 U/L ± 38.3 U/L for group E3.

Analysis of creatinine (CREA) levels revealed no significant difference between the experimental groups (P = 0.484). The means observed were 15 µmol/L ± 6.61 µmol/L for the control group, 15.5 µmol/L ± 11.5 µmol/L for the E2 group, and 16.3 µmol/L ± 7.22 µmol/L for the E3 group. Although a slight increase in creatinine levels was noted in the E3 group, it was not statistically significant.

Analysis of urea levels (UREA) showed a trend close to significance between the experimental groups (P = 0.065). The observed means were 19.2 mmol/L ± 2.25 mmol/L for the control group, 18.7 mmol/L ± 4.78 mmol/L for the E2 group, and 19.8 mmol/L ± 1.44 mmol/L for the E3 group. Although an increase was noted in the E3 group, this difference did not reach statistical significance. The effect of milk and body cream on the biochemical parameters of the mice is shown in Table 4.

Table 4. Effect of milk and body cream on the biochemical parameters of mice.

Parameter (Unit)	Control Group	Group E2	Group E3	P (ANOVA)
AST (U/L)	610.0 ± 447.0	614.0 ± 389.0	604.0 ± 73.0	0.195
ALT (U/L)	192.0 ± 51.4	192.6 ± 20.4	198.3 ± 38.3	0.066
UREA (mmol/L)	19.2 ± 2.25	18.7 ± 4.78	19.8 ± 1.44	0.065
Creatinine (µmol/L)	15.0 ± 6.61	15.5 ± 11.5	16.3 ± 7.22	0.484

4.2.6. Effect of Milk and Body Cream on Target Organ Tissues

Histological sections of major organs show no lesions, confirming the macroscopic observations made previously (Figure 3). More specifically, there is no congestion or inflammatory infiltrates in the heart (Figures 3(A)-(C)). In the

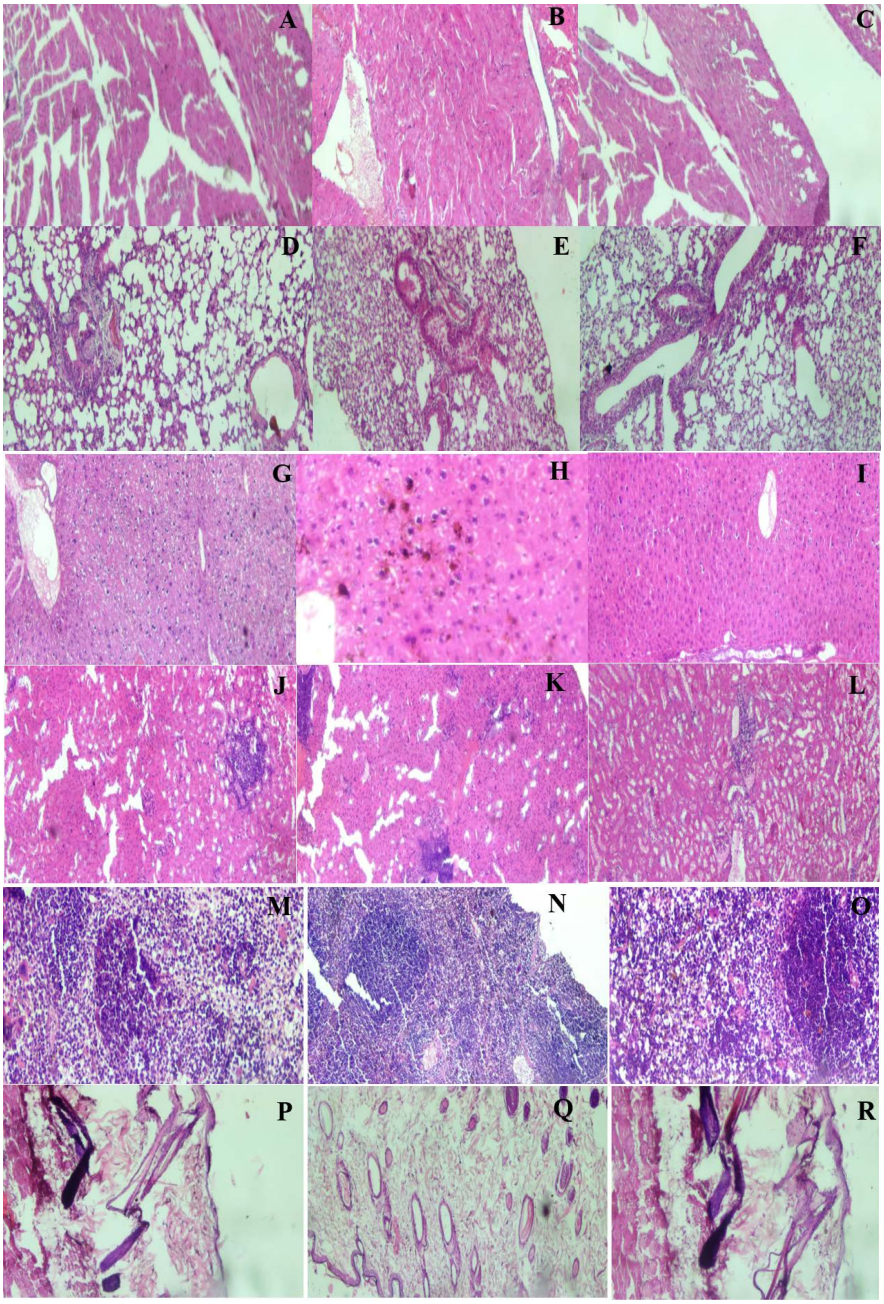

Figure 3. Effect of formulations on target organ tissues. (A)-(C): Heart; (D)-(F): Lungs; (G)-(I): Liver; (J)-(L): Kidney; (M)-(O): Spleen; (P)-(R): Skin.

lungs, the alveoli and bronchioles are subnormal in morphology with no congestion, hemorrhages, or inflammatory infiltrates (**Figures 3(D)-(F)**)). In the liver, the portal spaces and centrilobular veins are regular with no steatosis, necrosis, apoptosis, or portal inflammation (**Figures 3(G)-(I)**). In the kidneys, the cortical area rich in glomeruli and tubules is subnormal in morphology with no necrosis (**Figures 3(J)-(L)**). In the spleen, the white and red pulp are regular, with no congestion or necrosis (**Figures 3(M)-(O)**). The skin at the application site of the formulations shows a regular epidermis and dermis, rich in appendages, with no

inflammation, edema, or necrosis (**Figures 3(P)-(R)**). **Figure 3** shows the effect of the formulations on the tissues of the target organs.

5. Discussion

5.1. Effect of Milk and Body Cream on Behavior

The application of shea butter-based milk and body cream to mice showed no signs of systemic toxicity, behavioral disorders, or mortality. Observation of the mice showed that they maintained their normal behavior throughout the period of application of the formulations. During the 14 days of acute skin toxicity analysis and 28 days of subacute skin toxicity analysis, no local skin lesions (erythema, edema, necrosis, ulceration) were observed at the site of application of the milk and body cream formulation. This indicates that the application of the milk and body cream formulations has no toxicity on the behavior of male and female mice and does not present any form of lethality.

Authors have demonstrated that the application of shea butter-based ointments had no effect on animal behavior and did not induce lethality or systemic toxicity. Akan *et al.* (2023) showed that a mixture of ketamine and shea butter did not induce any form of toxicity but, on the contrary, improved anxiety behavior without altering general locomotor activity [12]. Elsewedy *et al.* (2022) showed that incorporating shea butter and fusidic acid into a solid lipid nanoparticle did not cause any behavioral disorders or irritation reactions such as edema or erythema in rats throughout the duration of the experiment [13]. Israel (2014) showed that topical and dietary use of shea butter on animals does not cause any behavioral disorders in laboratory animals [14]. The results obtained with the milk and shea butter cream formulations corroborate those of these authors and partially confirm the absence of toxicity in shea butter.

5.2. Effect of Milk and Body Cream on Weight

Animal weight is considered a major indicator of substance toxicity, and significant weight gain or loss can be considered a form of toxicity. For this reason, the weight of the mice was measured between D0 and D14 for the acute skin toxicity test and between D0 and D28 for the subacute skin toxicity test. The cutaneous application of the milk and body cream formulations based on shea butter did not significantly influence the weight of the mice over time compared to the control. This result suggests that the formulations do not contain any compounds whose systemic absorption could have a negative effect on the weight gain or loss of the treated mice. It also confirms the safety of these formulations in terms of weight, which is a marker of substance toxicity.

Several authors have used extracts other than cosmetic formulations based on shea butter (*Vitellaria paradoxa*) in studying weight variation in toxicity tests. For example, Nurul *et al.* (2018) in Malaysia worked with ethanolic extracts from Mariposa *christia vespertilionis* leaves and observed continuous weight gain in rats in groups A, B, C, D, and E from the first to the fourth week. All animals showed a

normal increase in body weight, with no significant differences between groups, indicating that the application of the extract did not affect the animals' growth [15]. Similarly, Harizal *et al.* (2010), in Malaysia, using a standardized methanolic extract of *Mitragyna speciosa* Korth, showed that there was no significant effect on body weight after 14 days of treatment [16]. In contrast, Baldrick *et al.* (2001) in the United Kingdom reported a slight decrease in body weight gain in rats fed shea olein and hardened shea olein [17]. These effects were observed in two separate toxicological studies, where the extracts were administered in the diet before mating, during gestation, and until the offspring were weaned.

5.3. Effect of Milk and Body Cream on Organ Weight

Post-mortem macroscopic observation, organ weight analysis, and histological examination revealed no abnormalities in the animals, regardless of treatment group or organ studied. No significant differences were observed between groups in terms of major organ weights. In this study, the liver, kidneys, spleen, lungs, heart, and skin at the site of application of the shea butter-based formulations were evaluated histologically. These organs were selected because of their essential role in physiological function and survival. Both macroscopic and microscopic observations revealed no lesions that could be attributed to the specific toxicity of the formulations on any organ. These results support the safety of the tested formulations with regard to the organs studied. Several studies have examined the effect of various extracts, other than cosmetic formulations based on shea butter, on organ weight. For example, Wang *et al.* (2011) in China administered an extract of Pu-erh black tea orally to Sprague-Dawley rats for 91 days and observed no significant changes in organ weight or macroscopic or clinical alterations [11]. Similarly, Gome *et al.* (2012), in Côte d'Ivoire, reported that subchronic oral treatment with aqueous extract of *Passiflora foetida* Linn. (Passifloraceae) did not cause any significant variation in the relative weights of the liver, kidneys, lungs, and heart [18]. In contrast, Fodouop *et al.* (2017) in Cameroon showed that oral treatment with aqueous extract of *Vitellaria paradoxa* leaves administered to rats infected with *Salmonella typhimurium* resulted in a significant decrease in relative organ weights [19]. The weight of organs is an important indicator of physiological or pathological status. In particular, it can be used to assess whether an organ is damaged [20], enlarged, or swollen [21]. The heart, lungs, liver, kidneys, and spleen are among the main organs that can be affected by metabolic reactions induced by toxic compounds [22].

5.4. Effect of Milk and Body Cream on Hematological Parameters in Mice

The interaction of a toxin or its metabolites with cellular components can cause significant adverse effects and alter hematological parameters. These disturbances, whether rapid or gradual, often affect the structure and function of the tissues concerned. Thus, the evaluation of hematological indices is an important di-

agnostic tool for detecting the deleterious effects of foreign compounds on the blood [23]. Analysis of hematological parameters, including red blood cell (RBC) count, white blood cell (WBC) count, hemoglobin (HB) level, hematocrit (HCT), platelet count (PLT), mean corpuscular volume (MCV), lymphocyte count (LYM), and basophil count (BAS) as part of the assessment of acute and subacute skin toxicity of shea butter-based milk and body cream formulations revealed no significant differences between the experimental groups. This result supports the absence of toxicity of these formulations on hematopoietic cells.

Previous studies have reported similar results with other extracts than cosmetic formulations of milk and body cream based on shea butter. For example, Djerrou *et al.* (2013) in Algeria, using *Pistacia lentiscus* oil on New Zealand rabbits, showed that no significant differences were observed in hematological parameters after skin and eye irritation tests [24]. Similarly, Shivanna *et al.* (2019) in India, working with albino mice treated orally with leaf extracts, observed no significant elevation in blood parameters [25]. However, these results differ from those obtained by Jasper *et al.* (2012) in Brazil, who reported significant hematological alterations in mice of both sexes treated orally with the herbicide glyphosate-Roundup, including a decrease in red blood cell count, hematocrit, and hemoglobin, as well as an increase in MCV [26].

5.5. Effect of Milk and Body Cream on Biochemical Parameters in Mice

The evaluation of biochemical parameters, including alanine aminotransferase (ALT), creatinine (CREA), aspartate aminotransferase (AST), and urea (UREA) levels, as part of the acute and subacute skin toxicity analysis, revealed no significant differences in male and female mice, confirming the absence of toxicity with respect to these measured parameters, although the analysis showed a trend close to significance for urea levels, with an increase observed in group E3, while AST levels showed an apparent decrease in groups E2 and E3, without these variations reaching statistical significance. Similar results with the oral use of other extracts, such as cosmetic formulations of milk and body cream based on shea butter, were reported by Mbosso *et al.* (2022) in Cameroon, who, when administering an ethanolic extract of *Canarium schweinfurthii* Engl. (Burseraceae) trunk bark orally to rats, observed no significant variation in biochemical parameters compared to controls [27]. Conversely, Folarin *et al.* (2020) in Nigeria, working on rats of both sexes that had been given an oral dose of an ethanolic extract of *Vitellaria paradoxa* leaves, observed a significant increase in serum liver enzymes (ALT and AST) after acute and prolonged exposure compared to the control group [28]. Similarly, Chin *et al.* (2010) in Malaysia, studying the toxic effect of carambola juice on serum biochemical parameters in rats, reported an increase in ALT levels in animals treated and observed for three hours [29]. The kidneys and liver are two major organs involved in metabolic detoxification. Estimating blood biochemical values is therefore an essential tool in toxicological assessment [30].

6. Conclusions

The application of milk and body cream containing shea butter to male and female mice for 14 days for acute skin toxicity and 28 days for subacute skin toxicity did not result in any deaths. Furthermore, no significant differences were observed in body or organ weight, and no abnormalities were found at autopsy. In addition, all hematological and biochemical blood values in the treated groups were within normal ranges.

No acute or subacute toxicity was therefore observed. In conclusion, our shea butter-based body milk and cream can be considered free of any toxic risk.

Conflicts of Interest

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

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