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Anti-tumor activity of prepared human alpha-lactalbumin-oleic acid and bovine alpha-lactalbumin-oleic acid complexes on mice bearing AN3 murine mammary adenocarcinoma

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Abstract

Introduction: Current medical issues include the difficulty of selectively targeting and diminishing cancer cells without impacting normal cells, as seen by traditional therapies like chemotherapy and radiation therapy. Recent research has identified proteins with anticancer capabilities, notably alpha-lactalbumin (α-LA), a major protein in human and bovine milk. α-LA, especially in conjunction with oleic acid, has shown specific cytotoxicity towards cancer cells. This research examines the anticancer properties of HAMLET (human alpha-lactalbumin made lethal to tumor cells) and BAMLET (bovine alpha-lactalbumin made lethal to tumor cells) complexes on AN3 murine mammary adenocarcinoma.

Objectives: This study seeks to evaluate the antitumor effect of human α-LA-oleic acid and bovine α-LA-oleic acid complexes against AN3 murine mammary cancer in mice.

Materials and Methods: In this *in vivo* experimental study, human breast milk was collected from mothers aged 24-28 years in Baghdad, and cow milk was purchased locally. Additionally, α-LA was purified using high-performance liquid chromatography (HPLC), with human α-LA at 1.2597 ppm and bovine α-LA at 1.8352 ppm. Complexes of α-LA with oleic acid were prepared, heated, sonicated, and pH-adjusted. Mice bearing AN3 mammary adenocarcinoma were injected subcutaneously with HAMLET or BAMLET and monitored. Leukocyte counts, interferon-γ levels, and histological analysis of tumors were conducted to assess immune responses and tumor changes.

Results: The HPLC study verified the presence of α-LA in both human and bovine specimens. Mice treated with HAMLET and BAMLET showed significant increases in total leukocyte, lymphocyte, neutrophil, and monocyte counts compared to controls. HAMLET-treated mice exhibited a total leukocyte count of 10920.0±71.14 cells/mL blood, and BAMLET-treated mice showed 10324.0±205.05 cells/mL blood, both significantly higher than the control group's 9556.6±595.4 cells/mL blood. Interferon-γ levels were notably elevated in both treatment groups, Histopathological analysis revealed pronounced necrosis and increased inflammatory cells in treated tumors.

Conclusion: Both HAMLET and BAMLET complexes exhibited significant antitumor effects on mice bearing AN3 murine mammary adenocarcinoma, enhancing innate and adaptive immune responses and inducing high levels of interferon-γ. These findings suggest potential therapeutic applications for α-LA-oleic acid complexes in cancer treatment.

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Introduction

Current medical complications involve the difficulty of treating and reducing cancer cells in individuals with cancer. The available cancer treatments include chemotherapy and radiation therapy, which target both normal cells and cancer cells. Many researchers in cancer cell treatment are inclined to develop treatments that specifically target cancer cells without affecting normal cells (1). Recently, studies have reported many proteins with anti-cancer properties that specifically target cancer cells. One such protein, found in human and bovine milk, plays numerous critical roles from an immunological and physiological perspective by stimulating polymorphonuclear immune cells and pro-inflammatory mediators such as interferon-gamma (2).

Apoptosis-like cell death in tumor cells caused by the interaction of oleic acid with human and bovine alpha-lactalbumin (α-LA) has shown that BAMLET (bovine alpha-lactalbumin made lethal to tumor cells) initiates a caspase-independent, lysosomal cell death pathway, predominantly in cancer cells.

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Key point

HAMLET (human alpha-lactalbumin made lethal to tumor cells) and BAMLET (bovine alpha-lactalbumin made lethal to tumor cells) complexes demonstrate considerable antitumor efficacy against AN3 murine mammary cancer in mice. These complexes enhance both innate and adaptive immune responses, leading to increased leukocyte counts and elevated interferon-γ levels. Histopathological analysis of treated tumors shows significant necrosis and inflammatory cell infiltration, indicating the potential of HAMLET and BAMLET as effective anticancer agents.

BAMLET-induced cell death is likely due to lysosomal membrane permeabilization (3,4). Research suggests that HAMLET (human alpha-lactalbumin made lethal to tumor cells) binding to α-actinin is crucial for tumor cell death through the p38 pathway. Additionally, the use of p38 inhibitors effectively prevents the death of tumor cells treated with HAMLET (4,5). In human epidermoid larynx cancer cells, the complexes reportedly induced cellular arrest (6,7), as well as in the lung cancer cell line A54 (8) and other tumor cells, selectively sparing established epithelial cells and thereby potentially controlling cancer processes (9).

Objectives

This study seeks to evaluate the antitumor effect of human α-LA-oleic acid and bovine α-LA-oleic acid complexes against AN3 murine mammary cancer in mice.

Materials and Methods

This *in vivo* experimental study was designed to investigate about anti-tumor activity of HAMLET and BAMLET against AN3 murine mammary cancer in mice. The mice were kept at room temperature, a common practice in laboratory settings to ensure a controlled and stable environment for the subjects.

Sample collection and solutions preparation

One liter of human breast milk was collected from mothers aged 24-28 years in Baghdad. Cow milk was purchased from the local market. All reagents and working solutions were prepared according to the following concentrations; 0.015 M NaCl, 7% NaCl, 0.1 M $CaCl_2$, 0.02 M tris-HCl, and 0.7 mM HAMLET or BAMLET in 0.9% NaCl. Human and bovine α-LA was prepared from human and cow milk (8).

Investigation of α-LA using high-performance liquid chromatography (HPLC) technique

This study was conducted in the laboratories of the ministry of science and technology, department of materials of research, and housed and cared for by the center of cancer and medical genetics research under standard conditions. HPLC was conducted to examine the alpha-LA samples and standard using a "Shiseido Proteonavi" C4 column (250 mm × 4.6 mm × 5 µm). Phase A, the organic phase, consisted of 0.1% trifluoroacetic acid (TFA) in acetonitrile, while phase B, the aqueous phase, contained 0.1% TFA in ultrapure water. A gradient elution technique was employed at a flow rate of 1 mL per minute. The detection wavelength was set to 215 nm, with an injection volume of 20 µL. Additionally, the column temperature was maintained at 30 °C throughout the experiment. The sample was prepared by dissolving 10 mg in 250 mL to make a 40 mg/mL standard, and then injecting 20 µL into an HPLC column for analysis.

Preparation of HAMLET and BAMLET complexes

Human and bovine α-lactalbumin (α-LA) was dissolved in 20 mM Tris-HCl buffer at pH 8, resulting in a 600 µM final concentration. After heating the solution to 60 °C in a water bath, 40 mol of oleic acid was added. The mixture was sonicated for two minutes at 30 °C (42 kHz, 130 W). Following this, it was stirred at 60 °C for 30 minutes before being cooled. The mixture was subsequently acidified to a pH of 3.5 and stirred for 24 hours at 4 °C.

The pH was then adjusted to 7 and sonicated for one minute at 400 W. A mixture of ethanol/nanopore water was added at a ratio of 1:1, centrifuged at 8000 rpm at 50 °C to remove unbound oleic acid, lyophilized, and stored at -20 °C.

Tumor treatment with HAMLET and BAMLET

This experiment was conducted to evaluate the anti-tumor effects of HAMLET and BAMLET. Experimental mice bearing AN3 mammary adenocarcinoma transplantable tumor line were divided into three groups. Each group received a subcutaneous injection of 1 mL of HAMLET or BAMLET suspended in physiological saline at a concentration of 0.7 mM daily for 10 days, distributed around the tumor region. The vehicle-control mice received an equivalent volume of physiological saline.

Counting of total leucocyte

Blood samples were obtained from mice by heart-puncture for total WBC counting followed by differential count of leucocytes.

Estimation of serum interferon-gamma

Interferon-gamma (IFN-γ) was estimated by ELISA technique, by using Shanghai Yehuan, Biological Technology Co., Ltd. IFN-γ ELISA kit, china.

Histological analysis of tumors

For all histology slides, images were captured using a digital camera under a light microscope at magnifications of 200× and 400×. Hematoxylin and eosin staining was utilized to highlight the morphological changes.

Statistical analysis

GraphPad Prism 8 and SPSS were used to calculate the mean ± standard error (SE). Duncan's multiple range

test was utilized to determine the *P* value. Statistical significance was determined with a *P* value under 0.05.

Results

HPLC analysis of α-lactalbumin

The HPLC analysis indicated a major peak at 3.657, suggesting the presence of α-lactalbumin (Figure 1). This peak showed the same retention time (RT) as the standard α-lactalbumin at 3.491 ppm (Figure 2), with a concentration of 1.2597 ppm, correlating to an immortality rate of 41; 27.3% of the total cases. Additionally, the HPLC examination revealed a main peak at 3.627, representing the presence of the extracted α-lactalbumin (Figure 3). This peak also had the same retention time as the standard α-lactalbumin at 3.491 ppm (Figure 2), with a concentration of 1.8352 ppm.

Treatment with HAMLET and BAMLET

Mice treated with HAMLET showed a significant increase in total leukocyte count (10920.0 ± 71.14 cells/ μL blood, $P < 0.05$) compared to controls (9556.6 ± 595.4 cells/μL blood). Similarly, another group of mice treated with BAMLET exhibited a significant increase in total leukocyte count (10 324.0 ± 205.05 cells/μL blood) compared to the

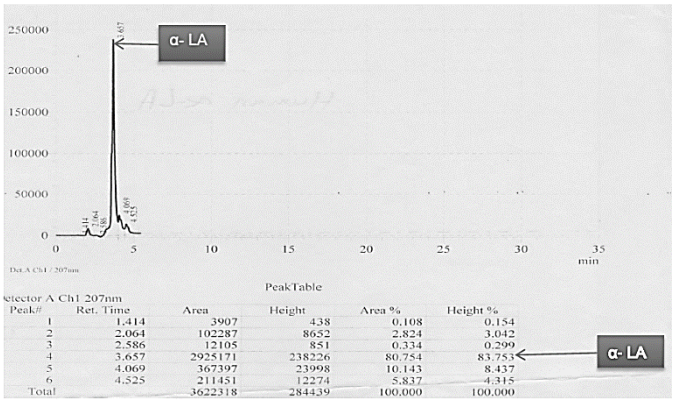

Figure 1. HPLC results of human alpha-lactalbumin.

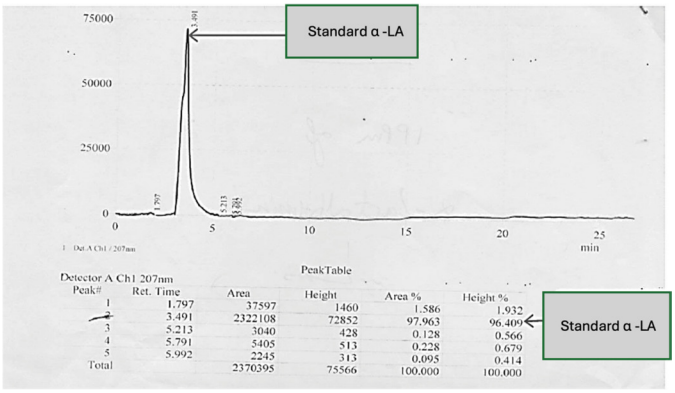

Figure 2. HPLC results of standard alpha-lactalbumin.

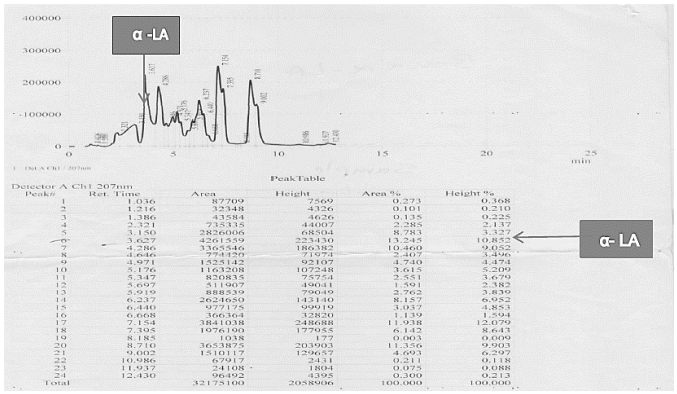

Figure 3. HPLC results of bovine alpha-lactalbumin.

control group (9556.6 ± 595.4 cells/µL blood) (Table 1).

Mice treated with HAMLET exhibited a considerable increase in total lymphocyte count (4216.0 ± 15.1 cells/µL) compared to controls (4047.7 ± 22.18 cells/µL). Another group of mice treated with BAMLET showed a significant increase in lymphocyte count (4817.3 ± 101.7 cells/µL) compared to the control group (4047.7 ± 22.18 cells/µL; Table 2).

Mice treated with HAMLET exhibited a substantial increase in neutrophil count (2899.7 ± 12.5 cells/ µL) compared to the control group (1601.7 ± 7.6 cells/µL). Similarly, the group of mice treated with BAMLET showed a significant increase in neutrophil count (1830.0 ± 29.8 cells/µL) compared to the control group (1601.7 ± 7.6 cells/µL; Table 3).

Mice treated with HAMLET displayed a significant rise in monocyte count (785.7 ± 5.5 cells/µL blood) likened to control (629.7 ± 3.5 cells/µL blood). An additional group of mice treated with BAMLET exhibited a significant rise in monocyte count (705.3 ± 5.5 cells/µL blood) likened to control (629.7 ± 3.5 cells/µL blood; Table 4).

Table 1. Total leucocytes count (mean ± standard error) in mice treated with HAMLET and BAMLET and control group

Group	Mean ± Standard error (cells/µL blood)	Statistical evaluation
Control	9556.6±595.4	b
HAMLET	10920.0±71.14	a
BAMLET	10324.0±205.05	a

Duncan's multiple range test was performed following ANOVA to identify significant differences between group means at $P < 0.05$. Group means were assigned letters (a, b, c) to indicate statistical differences: means sharing the same letter are not significantly different, while those with different letters are significantly different.

Table 2. Lymphocyte count (mean ± standard error) in mice treated with HAMLET and BAMLET and control group

Group	Mean ± Standard error (cells/µL blood)	Statistical evaluation
Control	4047.7± 22.18	a
HAMLET	4216.0± 15.1	b
BAMLET	4817.3± 101.7	a

Duncan's multiple range test was performed following ANOVA to identify significant differences between group means at $P < 0.05$. Group means were assigned letters (a, b, c) to indicate statistical differences: means sharing the same letter are not significantly different, while those with different letters are significantly different.

Table 3. Neutrophil count (mean ± standard error) in mice treated with HAMLET and BAMLET and control group

Group	Mean ± Standard error (cells/µL blood)	Statistical evaluation
Control	1601.7±7.6	c
HAMLET	2899.7±12.5	a
BAMLET	1830.0±29.8	b

Duncan's multiple range test was performed following ANOVA to identify significant differences between group means at $P < 0.05$. Group means were assigned letters (a, b, c) to indicate statistical differences: means sharing the same letter are not significantly different, while those with different letters are significantly different.

Interferon-γ level

Mice treated with HAMLET displayed a significant increase in interferon-γ levels (364.0 ± 13.11 pg/mL) compared to the control group (188.3 ± 38.55 pg/mL). Similarly, mice treated with BAMLET showed a notable increase in interferon-γ levels (358.0 ± 8.0 pg/mL) compared to the control group (188.3 ± 38.55 pg/mL; Figures 4-6).

Anti-tumor consequences of HAMLET and BAMLET in AN3 murine adeno-carcinoma mice

Tumor sections obtained from mice with AN3 murine mammary adenocarcinoma, treated with 0.7 mM of HAMLET, BAMLET, and a control, revealed a high level of histological diversity. The polyp sections of control mice displayed pleomorphic adenocarcinoma arranged in glandular structures (Figure 7).

Tumor slices from mice treated with HAMLET displayed inflammatory cells and more pronounced necrosis of malignant cells (Figure 8). Mice tumor slice (400 mg/kg) displays extensive necrosis and inflammatory cells (Figure 9).

Discussion

Both HAMLET and BAMLET demonstrate antitumor activity and influence both innate and specific immunity (10). They demonstrate broad-spectrum efficacy against various cancer cell lines, with oleic acid in BAMLET and HAMLET potentially affecting membrane lipids, protein-lipid interactions, and signaling pathways, leading to cytotoxicity in cancer cells while sparing normal cells (11). Studies suggest that HAMLET and BAMLET induce cancer cell death by disrupting ion fluxes or interacting with proteins in cellular signaling pathways, exploiting the similar characteristics of malignant cells (12). Autophagy, the process of degrading cellular proteins and components via autophagosomes and lysosomes, plays a role in cell survival during starvation and is considered part of programmed cell death, promoting cell death in HAMLET-infected cells (13).

A previous meta-analysis showed a modest decrease in the incidence of childhood malignancies, including

Table 4. Monocyte count (mean ± standard error) in mice treated with HAMLET and BAMLET and control group

Group	Mean ± Standard error (cells/µL blood)	Statistical evaluation
Control	629.7±3.5	b
HAMLET	785.7±5.5	a
BAMLET	705.3±5.5	a

Duncan's multiple range test was performed following ANOVA to identify significant differences between group means at $P < 0.05$. Group means were assigned letters (a, b, c) to indicate statistical differences: means sharing the same letter are not significantly different, while those with different letters are significantly different.

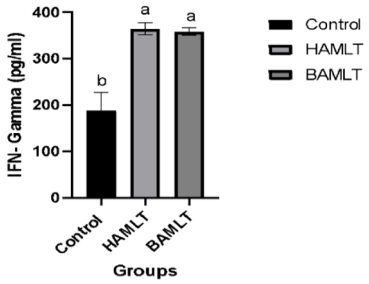

Figure 4. The mean of interferon –γ in mice treated with HAMLET and BAMLET and control group.

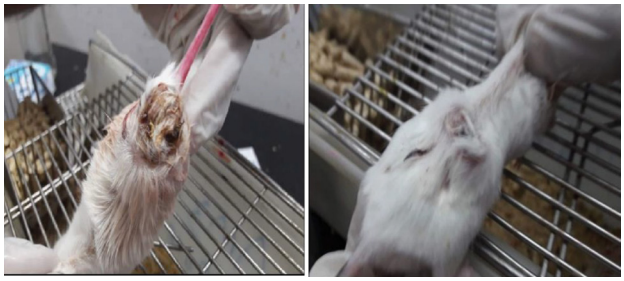

Figure 5. Sign of tumor recovery in mice treated with HAMLET and BAMLET (inflammation and formation of pus tissue around the tumor, bleeding may also be seen).

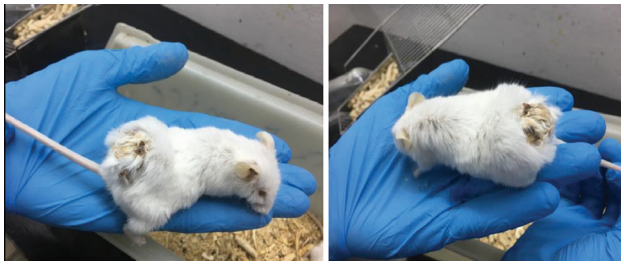

Figure 6. Final stage of tumor recovery in mice treated with HAMLET and BAMLET shows that the tumor tissue is completely recovered as it showed to be Take-off or snatched from the body of mice.

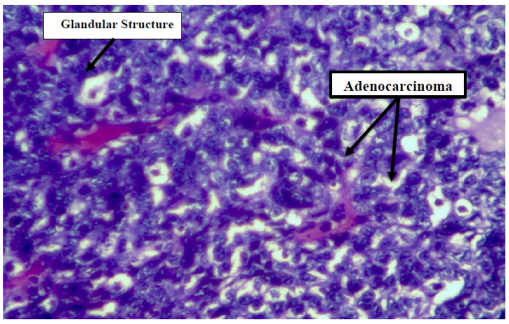

Figure 7. A tumor slice from a mouse with AN3 murine mammary adenocarcinoma reveals malignant pleomorphic cells organized granularly (adenocarcinoma) (arrows) (H&E; 400×).

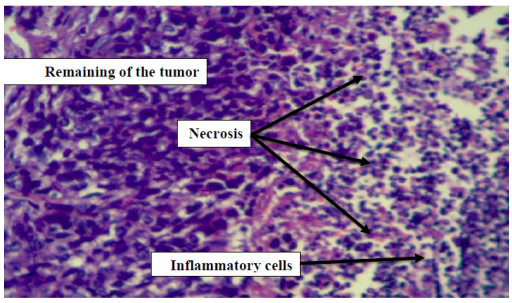

Figure 8. Tumor sections from AN3 murine adenocarcinoma mice treated with HAMLET reveal the presence of inflammatory cells and more pronounced necrosis of cancerous cells (arrows) (H&E; 400×).

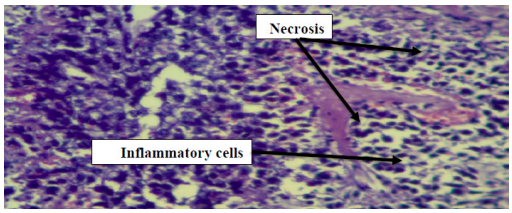

Figure 9. A tumor slice of BAMLT-treated AN3 murine adenocarcinoma mice displayed a large area of necrosis and inflammatory cells (arrows) (H&E; 400×).

leukemia, Hodgkin's disease, neuroblastoma, and non-hematological cancers, among those who were breastfed as infants. However, this tenuous link is likely due to confounding variables rather than a true correlation (14). Few modifications to the lipid enable HAMLET-like cytotoxicity (13), and it is generally believed that oleate is the primary active component of HAMLET-like compounds, regardless of its source (14). Studies on HAMLET-like substances indicate that the protein-lipid combination exhibits greater cytotoxicity than equivalent amounts of oleic acid or sodium oleate alone. Additionally, cytotoxicity varies with different protein carriers of oleic acid. These variations in results are likely due to challenges in solubilizing oleic acid for use in aqueous cellular systems, impacting the accuracy and precision of measuring oleic acid in HAMLET-like compounds that induce cytotoxic effects (15).

Up to 10% of cells exposed to HAMLET undergo necrosis, characterized by disrupted plasma membranes, loss of cellular contents, and the amalgamation of nuclear and cytoplasmic components (9). HAMLET targets numerous cancer cell types through various mechanisms. Research indicates that HAMLET affects membrane lipids, protein-lipid packing, and signaling, which can be toxic to all cells except for their specific cancer targets (16). Oleic acid, a component of HAMLET, may increase membrane fluidity, making membrane proteins more sensitive and promoting cell death (17). The signaling pathways of oleic acid and free fatty acids have been extensively studied (15), and oleic acid signaling is associated with promoting cell death (18). Early negative characteristics of HAMLET may involve specific signals from evolutionarily developed biological mechanisms (19).

Conclusion

Human and bovine α-LA – oleic acid complexes exhibit an anti-tumor effect on mice bearing the AN3 Mammary Adenocarcinoma cell line. Both HAMLET and BAMLET demonstrate immunomodulatory activities by inducing high levels of interferon-gamma production.

Limitations of the study

This research did not receive any specific funding from public, commercial, or non-profit sectors, which may limit the resources available for more extensive investigations. Additionally, the study was conducted on a specific murine model, and results may not directly translate to human cancers. Further research is needed to confirm the findings and explore the mechanisms in diverse biological systems.

Acknowledgments

We would like to express our deepest gratitude to all those who provided us with the possibility to complete this research. Also, all thanks to the ministry of science and technology, department of materials of research.

Conflicts of interest

The authors state that they have no recognized challenging financial benefits or personal associations that might have looked to influence the work stated in this paper.

Authors' contribution

Conceptualization: Omar A. Mahmoud
Data curation: Omar A. Mahmoud
Formal analysis: Omar A. Mahmoud
Funding acquisition: Omar A. Mahmoud
Investigation: Omar A. Mahmoud
Methodology: Omar A. Mahmoud.
Project administration: Omar A. Mahmoud, Shahlaa M. Salih, Zahraa K. Zedan.
Resources: Omar A. Mahmoud
Software: Omar A. Mahmoud
Supervision: Shahlaa M. Salih, Zahraa K. Zedan
Validation: Omar A. Mahmoud
Visualization: Omar A. Mahmoud
Writing–original draft: Omar A. Mahmoud.
Writing–review & editing: Omar A. Mahmoud, Shahlaa M. Salih, Zahraa K. Zedan.

Ethical issues

The research and protocol for this study adhered to the guidelines for animal studies and received approval from the Ethics Committee of AL-Nahrain University, Department of Molecular Genetics and DNA Fingerprint Forensic DNA Center for Research and Training (Ref# MG2324). In accordance with this approval, the study followed the guidelines for animal experiments established by the United States National Institutes of Health (NIH, 1978). This research also forms part of the thesis of Omar A. Mahmoud at the Department of Molecular Genetics and DNA Fingerprint Forensic DNA Center for Research and Training (Thesis #MG2324, dated 9/10/2023).

Conflicts of interest

The authors declare that they have no competing interests.

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