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Protective effects of *Acacia raddiana* gum against pulmonary toxicity induced by urethane: A preclinical study

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ABSTRACT

Introduction: *Acacia raddiana* is a Saharan medicinal plant traditionally used to treat respiratory disorders. This study investigated the protective effects of *A. raddiana* gum against urethane-induced pulmonary alterations in rats.

Methods: Twenty rats were divided into four groups: control, urethane, and urethane plus gum (1 g/kg or 2 g/kg). Urethane was administered at a dose of 0.375 g/kg over 14 weeks, with 3-week intervals between injections (i.p.). The gum was administered daily during the final four weeks of the study. Clinical, macroscopic, histopathological, and oxidative stress parameters were assessed.

Results: Urethane caused epistaxis, palpable thoracic and cervical masses, lung tumors, bronchiolar epithelial hyperproliferation, mucin overproduction, and alveolar wall cellular hyperplasia. Urethane also increased catalase (272.7 ± 19.94; $P < 0.01$) and peroxidase (1.64 ± 0.02; $P < 0.0001$) activities in lung tissue compared with the control group (124.1 ± 27.28 and 0.12 ± 0.0, respectively). Treatment with *A. raddiana* gum (1 g/kg) attenuated lung damage, reducing tumor formation, epithelial hyperproliferation, alveolar hyperplasia, and mucin overproduction. It also significantly increased catalase and peroxidase activities compared to the urethane-treated rats ($P < 0.05$). At 2 g/kg, gum decreased catalase (120.4 ± 14.29; $P < 0.01$) and peroxidase (0.64 ± 0.02; $P < 0.0001$) activities compared to the urethane group. At this dose, dark-red lung coloration indicated potential toxicity.

Conclusion: This study demonstrates that *A. raddiana* gum at 1 g/kg protects against urethane-induced pulmonary carcinogenesis in rats by preserving lung structure, reducing mucin overproduction, and modulating oxidative stress.

Implication for health policy/practice/research/medical education:
Acacia raddiana gum may offer protective effects against toxic pneumonitis resulting from occupational or environmental exposures, including solvents and other inhaled toxins. Additionally, it may serve as a natural adjuvant to mitigate chemically induced pulmonary damage.

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Introduction

Pulmonary diseases remain a leading cause of morbidity and mortality worldwide. These disorders are characterized by persistent inflammation, progressive remodeling of the lung parenchyma, and the development of fibrosis. In many cases, fibrotic changes are irreversible and respond poorly to conventional anti-inflammatory or immunosuppressive therapies, highlighting a critical unmet need for more effective treatment strategies (1-4). The central roles of oxidative stress, pro-inflammatory mediators, and dysregulated cell proliferation in disease pathogenesis further underscore the urgency for novel therapeutic agents capable of targeting these pathogenic mechanisms (5-9).

Urethane is a well-established toxicant commonly used in experimental models to induce lung carcinoma and

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chronic inflammatory pneumonitis in rodents. Prolonged exposure induces pulmonary lesions that closely resemble those observed in humans, including inflammatory cell infiltration, alveolar remodeling, epithelial hyperplasia, and, in some cases, tumor nodule formation (10-12). Consequently, this model has been widely employed to evaluate the therapeutic potential of agents with antioxidant, anti-inflammatory, or anticancer properties.

Lung diseases are challenging to manage effectively. In this context, natural compounds derived from medicinal plants attract considerable interest due to their favorable bioavailability, low toxicity, and abundance of bioactive constituents. Among these, natural gums obtained from the *Acacia* genus have been reported to exhibit a broad spectrum of pharmacological activities, including antioxidant, immunomodulatory, gastroprotective, and antitumor effects (13-16). *Acacia raddiana*, a Saharan medicinal plant species traditionally used in folk medicine to treat respiratory and inflammatory disorders (17-19), possesses a complex phytochemical profile rich in polysaccharides, flavonoids, tannins, saponins, and polyphenols, supporting its evaluation as a promising therapeutic candidate (20). Previous studies have shown that the gum of *Acacia* species possesses antioxidant, anti-inflammatory, and cytoprotective properties. In animal models, it exhibited antinociceptive, antiurolithiatic, and DNA-protective effects, while clinical studies demonstrated improvements in metabolic, cardiovascular, and renal parameters, including reductions in oxidative stress and systemic inflammation. These findings suggest that the gum may offer therapeutic potential in conditions associated with oxidative stress, inflammation, and chemical toxicity, providing a rationale for investigating its protective effects in urethane-induced pulmonary injury (16,20-27). Despite its traditional use and reported antioxidant potential, no studies to date have investigated the effects of the gum of *A. raddiana* in models of chemically induced lung carcinogenesis. Therefore, the present study aimed to evaluate the protective effects of *Acacia raddiana* gum against urethane-induced pulmonary carcinogenesis in rats.

Materials and Methods

Plant material

Gums of *A. raddiana* were collected from the southern region of Morocco. The plant material was taxonomically authenticated by Professor Ahmed Ouhammou, a botanist at the Faculty of Sciences Semlalia, Marrakesh, Morocco, and a voucher specimen (No. 13956) was deposited in the Laboratory of Environment and Ecology. The gum was air-dried, ground to a fine powder, and stored under appropriate conditions. For experimental use, the crude powder was freshly prepared daily and administered orally to the animals.

Experimental design and animal grouping

Sprague-Dawley rats were allocated to the experimental groups as follows. The control group consisted of five healthy animals maintained under standard laboratory conditions without any treatment. The sample size (n = 5) was chosen in accordance with ethical guidelines and was supported by pilot data indicating its adequacy for detecting relevant biological differences. The remaining fifteen rats (n = 15) were used to induce the pulmonary toxicity model. Four intraperitoneal injections of urethane (0.375 g/kg) were administered to these animals at three-week intervals over 14 weeks. The induction regimen was adapted from published protocols using validated rat models of chronic urethane-induced pulmonary toxicity (28).

Fourteen weeks after the initial urethane injection, the urethane-exposed rats were randomly allocated to three groups:

- Urethane group (n = 5): No further treatment was applied.
- Urethane plus 1 g/kg gum group (n = 5): *A. raddiana* gum was administered by oral gavage at 1 g/kg/day for four weeks.
- Urethane plus 2 g/kg gum group (n = 5): *A. raddiana* gum was administered by oral gavage at 2 g/kg/day for four weeks.

The doses of 1 and 2 g/kg/day of *A. raddiana* gum were selected based on previously published toxicological and pharmacological studies (20,29,30).

Monitoring and sample collection

Animals were monitored daily for clinical signs of health and disease progression. At the study endpoint, animals were euthanized under deep anesthesia, and lungs were collected immediately.

Histological processing

Lungs were fixed in 10% neutral-buffered formalin for 24–48 hours, dehydrated through graded ethanol, cleared in xylene, and embedded in paraffin. Sections (4 μm) were cut using a rotary microtome.

Hematoxylin and eosin staining of lung sections

For general histology, sections were stained with hematoxylin for 10 minutes, rinsed, and counterstained with eosin for 2 minutes. Slides were then dehydrated, cleared, and mounted. Slides were examined under light microscopy at ×40 and ×400 magnifications.

Periodic acid–Schiff staining of lung sections

Periodic acid–Schiff staining was performed to detect mucin. Briefly, sections were deparaffinized, rehydrated, and oxidized in 0.5% periodic acid for 5 minutes. After rinsing, slides were incubated with Schiff's reagent for 15 minutes in the dark, washed in running water,

counterstained with hematoxylin, dehydrated, cleared, and mounted. Slides were examined under light microscopy at ×100 magnification.

Biochemical analysis

Peroxidase activity

Peroxidase activity was measured using a validated spectrophotometric assay (31). Lung tissue was homogenized in cold 0.1 M phosphate buffer (pH 7.4). The homogenate was then centrifuged at 12,000 × g for 10 minutes at 4 °C to separate solids from the supernatant, which contained the active enzyme. For the assay, 0.1 mL of the lung tissue homogenate was added to a spectrophotometric cuvette containing 2.9 mL of phosphate buffer (pH 7.4), 0.5 mL of guaiacol (0.05 M), and 0.5 mL of hydrogen peroxide (H_2O_2) at 0.03%. The change in absorbance was recorded at 470 nm every minute for 3 minutes. The slope of the absorbance curve, expressed as ΔA/minute, was used to calculate enzyme activity according to the Beer-Lambert law. This calculation determined the amount of guaiacol oxidized per minute per gram of tissue (U/g tissue). The following equation was used:

$$Peroxidase\ activity = \frac{\Delta A / \min}{\varepsilon \times l \times V}$$

Where:

ε: molar extinction coefficient of oxidized guaiacol (26.600 M^{-1} cm^{-1}) at 470 nm.

V: total volume of the reaction (L).

l: optical path length (1 cm).

Catalase activity

Catalase enzymatic activity was quantified according to the protocol established by Aebi (32). Pulmonary tissue was mechanically disrupted in chilled 50 mM phosphate buffer (pH 7.0) at a weight-to-volume ratio of 1:10, followed by centrifugation at 10,000 × g for 15 minutes at 4 °C. The clarified fraction (supernatant) was collected and utilized as the enzymatic preparation. The reaction mixture, consisting of 0.1 mL enzyme extract, 1.0 mL 50 mM phosphate buffer (pH 7.0), and 0.4 mL 30 mM hydrogen peroxide, was incubated at room temperature in a 1 cm quartz cuvette for 3 minutes. The reaction was stopped by adding 2.0 mL of dichromate-acetic acid reagent (5% potassium dichromate in glacial acetic acid), followed by incubation in a boiling water bath for 10 minutes to allow chromogen development. Following cooling to ambient temperature, absorbance was recorded at 620 nm using a blank devoid of enzymatic fraction as a reference. Catalase activity was quantified as enzymatic units per gram of tissue (U/g), with one unit defined as the catalytic decomposition of 1 µmol hydrogen peroxide per minute under assay parameters. Catalase activity was calculated using the following equation:

$$Catalase\ activity = \frac{\Delta A \times V_{total}}{\varepsilon \times l \times V_{sample} \times t \times m}$$

Where:

ΔA: Absorbance difference between the blank and the sample at 620 nm.

V_{total}: Total reaction volume in the cuvette (mL).

ε: Molar extinction coefficient of the dichromate–H_2O_2 complex at 620 nm (42.6 $M^{-1} \cdot cm^{-1}$).

l: Optical path length of the cuvette (cm).

V_{sample}: Volume of enzyme extract used in the reaction (mL).

t: Reaction time (min).

m: Mass of lung tissue used to prepare the homogenate (g).

Data analysis

All animals were included in the analysis. Numerical data were reported as mean values accompanied by their standard error of the mean (SEM). Comparisons between multiple experimental groups were conducted using one-way ANOVA, with Dunnett's test applied post hoc to identify significant differences relative to the control group. A threshold of $P < 0.05$ was set to determine statistical significance. All statistical evaluations were performed using GraphPad Prism (version 9.0.0).

Results

Clinical observations

Urethane induced epistaxis and palpable masses in the thoracic and cervical regions in three rats, whereas no clinical abnormalities were observed in the control group. In contrast, urethane-exposed rats treated with 1 g/kg *A. raddiana* gum remained clinically normal.

Macroscopic examination of the lung

Macroscopic examination of the lungs revealed the presence of tumors (black arrow) on lung surfaces in urethane-treated rats, whereas no tumors were observed in the control group. Interestingly, treatment with gum from *A. raddiana* completely prevented tumor formation in rats. Moreover, treatment with gum at 2 g/kg resulted in dark red lungs. All results are shown in Figure 1.

Attenuation of urethane-induced rat lung structural damage by *Acacia raddiana* gum

Urethane exposure induced aberrant cell proliferation in the bronchiolar epithelium (blue arrows) and alveolar wall cellular hyperplasia (black rectangle) compared with the control group. Treatment with gum from *A. raddiana* prevented urethane-induced bronchiolar epithelial hyperproliferation and alveolar septal cellular hyperplasia. The results are shown in Figure 2.

Acacia raddiana gum reduces urethane-induced mucin overproduction in the rat lung tissue

Mucin staining was absent in normal terminal bronchioles.

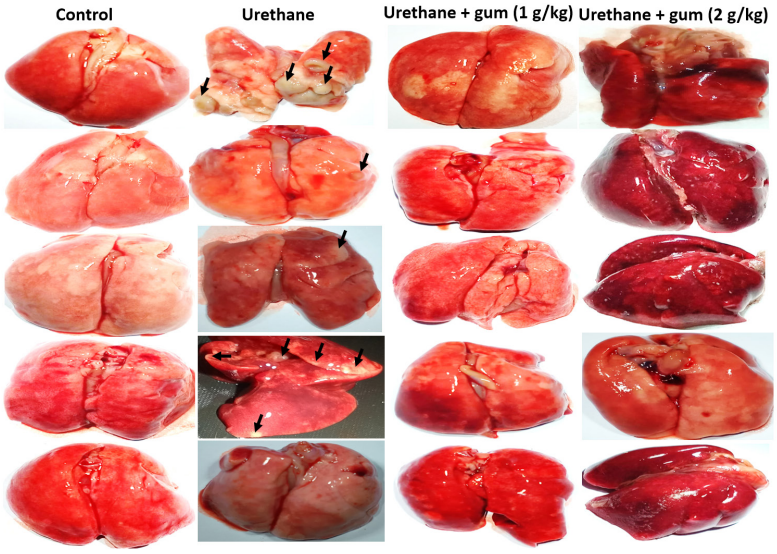

Figure 1. Macroscopic evaluation of pulmonary morphology. Rats received four doses of urethane at three-week intervals. Eighteen weeks later, tumors (black arrow) were observed on the lung surfaces of urethane-treated rats (urethane). Administration of *A. raddiana* gum during the last four weeks completely prevented urethane-induced tumor formation (urethane + 1–2 g/kg gum), and lungs from rats treated with 2 g/kg gum appeared dark red (urethane + 2 g/kg gum). No tumors or anomalies were detected on the lung surfaces of urethane-untreated rats (control).

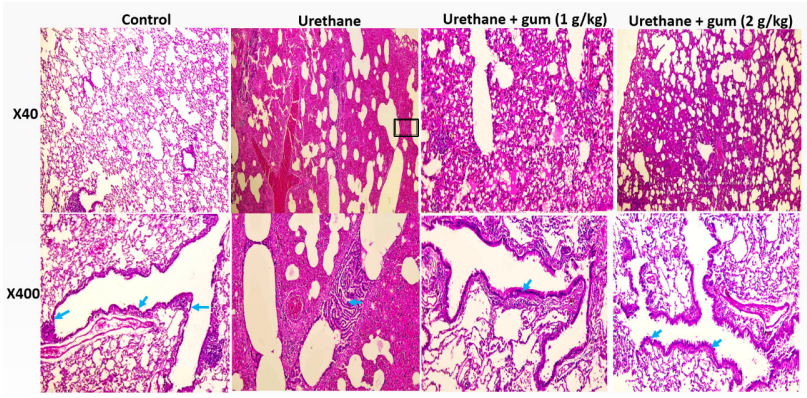

Figure 2. Lung tissue morphology assessed by hematoxylin–eosin staining at 40× and 400× magnifications. Blue arrows: bronchiolar epithelium. black rectangle: alveolar wall cellular hyperplasia.

In contrast, abundant mucin staining was observed in the terminal bronchioles following urethane exposure (yellow circle). In animals pretreated with urethane and subsequently treated with gum derived from *A. raddiana*, mucin staining was markedly reduced compared with the urethane-only group. The results are shown in Figure 3.

Modulation of catalase and peroxidase activities by *Acacia raddiana* gum attenuates urethane-induced oxidative stress in the rat's lung

Urethane exposure significantly increased catalase ($P<0.01$) and peroxidase ($P<0.0001$) activities compared with the control group (Table 1). In contrast, treatment with gum derived from *A. raddiana* markedly attenuated these effects, resulting in a significant reduction in catalase ($P<0.01$ and $P<0.05$) and peroxidase ($P<0.0001$) activities compared with the urethane group.

Discussion

Lung cancer continues to be the leading cause of cancer-related death globally, and adenocarcinoma has emerged as the most prevalent histological subtype of lung cancer worldwide (33,34). Although many synthetic drugs have been developed for cancer treatment, their side effects and limited efficacy highlight the need for novel, safer, and more effective therapies. Plant gums, such as acacia gum, contain polysaccharides and bioactive compounds that may support the immune system, reduce inflammation and oxidative stress, and help improve tolerance to cancer treatments (13). However, there is no clinical evidence of a direct effect on lung cancer. Thus, this study evaluated the anticancer activity of gum derived from *A. raddiana*.

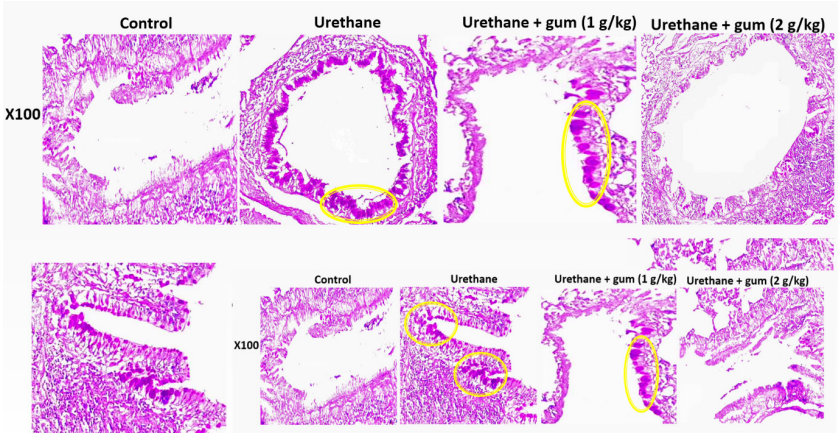

Figure 3. Histochemical evaluation of pulmonary mucin using periodic Acid–Schiff (PAS) staining at 100× magnification. Yellow circle: mucin deposit in the terminal bronchioles.

Rats were exposed to four intraperitoneal injections of urethane, a well-established chemical carcinogen known to induce lung adenocarcinoma, to initiate lung tumorigenesis. Eighteen weeks after the initial urethane administration, three rats developed severe clinical manifestations, including epistaxis and palpable masses in the thoracic and cervical regions. To confirm lung cancer induction, macroscopic and histopathological lung examinations were performed. In this study, urethane exposure induced visible tumors on the lung surface, aberrant bronchiolar epithelial cell proliferation, and alveolar wall cellular hyperplasia compared with non-urethane-exposed controls. These findings are consistent with previous studies demonstrating that urethane induces lung tumors, bronchiolar epithelial cell proliferation, and alveolar epithelial hyperplasia in rodent models (10,35,36).

In the present study, *A. raddiana* gum prevented urethane-induced severe clinical manifestations, inhibited cellular proliferation in the bronchiolar epithelium, and attenuated alveolar wall thickening caused by alveolar cell hyperplasia. However, dark-red lung coloration at the highest dose (2 g/kg) may indicate potential toxicity. The inhibition of excessive cellular proliferation suggests modulation of cell cycle regulation and tissue remodeling, thereby protecting pulmonary tissue against urethane-induced pathological alterations. The reduction in clinical signs further suggests potential systemic protective effects that may contribute to lung protection. These findings are consistent with previous studies reporting that therapeutic strategies targeting lung cell proliferation are associated with reduced tumor growth and improved antitumor responses in experimental models of lung cancer (37-42).

Mucin 5AC (MUC5AC) has been associated with lung adenocarcinoma. MUC5AC is a high molecular weight, gel-forming secreted mucin produced primarily by goblet cells of the respiratory and gastric epithelium. Under normal conditions, MUC5AC staining is scant or absent in terminal bronchioles. In contrast, lung adenocarcinoma tissues, which are considered to be of bronchoalveolar origin, exhibit abundant MUC5AC expression. Furthermore, Muc5ac gene deficiency has been associated with reduced tumor burden in urethane-induced carcinogenesis models, supporting a significant role for MUC5AC in the progression of lung adenocarcinoma (43). Thus, in the present study, we evaluated MUC5AC expression in rat lung tissue using periodic Acid–Schiff (PAS) staining. In agreement with previous reports, our results revealed abundant mucin staining in the terminal bronchioles following urethane exposure compared with the control group (non-urethane-exposed controls). In urethane-exposed rats, subsequent treatment with gum from *A. raddiana* significantly decreased mucin staining

Table 1. Modulation of catalase and peroxidase activities by *Acacia raddiana* gum in a urethane-induced oxidative stress in the rat lung

Experimental group	Catalase activity (U/g of tissue)	Peroxidase activity (U/g of tissue)
Control	124.1 ± 27.28	0.12 ± 0.0
Urethane	272.7 ± 19.94**	1.64 ± 0.02****
Urethane + gum (1 g/kg)	171.1 ± 24.06$^{\#}$	0.43 ± 0.03$^{\#\#\#\#}$
Urethane + gum (2 g/kg)	120.4 ± 14.29$^{\#\#}$	0.64 ± 0.02$^{\#\#\#\#}$

Values are shown as mean ± SEM. Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison test to evaluate differences between different groups. Statistical significance is denoted as follows: $^{**}P < 0.01$ and $^{****}P < 0.0001$ versus control group; $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ and $^{\#\#\#\#}P < 0.0001$ versus urethane-treated group.

relative to the urethane control group. This effect suggests that the gum may reduce mucin production and potentially modulate MUC5AC expression, thereby contributing to attenuation of tumor progression.

The plant gum is a polysaccharide-rich biopolymer with high viscosity and mucoadhesive properties (44,45). These properties may reinforce the respiratory epithelial barrier and preserve a physiological mucus layer, limiting urethane penetration, mucin accumulation, and epithelial cell proliferation.

Urethane induces excessive production of reactive oxygen species (ROS) in pulmonary cells. Elevated ROS production activates an adaptive antioxidant response, including increased catalase and peroxidase activities, to counteract oxidative damage (46-48). Consistent with previous studies, our results revealed that urethane induced oxidative stress demonstrated by increased catalase and peroxidase activities relative to control rats. This alteration was counteracted by the gum as evidenced by the normalization of catalase and peroxidase activities relative to the urethane control group. Accordingly, the gum-mediated modulation of antioxidant enzymes appears to confer pulmonary protection by maintaining redox homeostasis and attenuating urethane-induced lung injury.

Collectively, these findings suggest for the first time the potential therapeutic effect of *Acacia raddiana* gum against urethane-induced lung carcinogenesis, likely through the suppression of oxidative stress, inhibition of abnormal cell proliferation and mucin overproduction, and preservation of normal lung architecture.

Conclusion

This study evaluated the protective effect of *A. raddiana* gum against urethane-induced pulmonary carcinogenesis in rats. Urethane exposure induced severe clinical manifestations, including epistaxis and palpable masses in the thoracic and cervical regions, along with aberrant bronchiolar epithelial cell proliferation, alveolar wall hyperplasia, increased mucin production, and significantly elevated catalase and peroxidase activities in rat lung tissue. Treatment with *Acacia raddiana* gum preserved lung structure, inhibited cell proliferation, reduced mucin accumulation, and maintained antioxidant balance. However, the higher dose (2 g/kg) was associated with mild pulmonary toxicity. Overall, *A. raddiana* gum exerts protective effects against urethane-induced pulmonary carcinogenesis in rats.

Limitations of the study and recommendations

This study was limited to a rat model of urethane-induced lung carcinogenesis, which may restrict extrapolation to humans. Only two doses of *A. raddiana* gum were evaluated at a single time point. Oxidative stress assessment was limited to catalase and peroxidase activities, and no functional respiratory or mechanistic analyses were performed. Histological analysis was qualitative, and Periodic acid–Schiff staining did not allow specific or quantitative identification of mucins. Despite these promising results, further studies are needed to identify the active constituents, clarify the underlying molecular mechanisms, and evaluate the translational potential of *A. raddiana* gum in humans.

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Authors' contribution

Conceptualization: Lansine Diakité, Zahra Sokar.
Data curation: Lansine Diakité.
Formal analysis: Lansine Diakité.
Funding acquisition: Zahra Sokar.
Investigation: Lansine Diakité, Zahra Sokar.
Methodology: Lansine Diakité, Abdeljalil Elmahdaoui.
Project administration: Zahra Sokar.
Resources: Sokar Zahra, Zineb Lachhab.
Software: Lansine Diakité.
Supervision: Zahra Sokar, Zineb Lachhab.
Validation: Zahra Sokar.
Visualization: Lansine Diakité.
Writing–original draft: Lansine Diakité.
Writing–review & editing: Zahra Sokar, Lansine Diakité.

Conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

Ethical considerations

All experiments were conducted by European Community guidelines (Directive 86/609/EEC, 24.11.1986). Efforts were made to minimize animal suffering and to use the minimum number of animals necessary to achieve scientific validity. This study was approved by the Committee of Directors of the Faculty Research Laboratories (BA-05/2025).

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