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Immunohistochemical changes in the mammary gland following experimental local mycobacterial exposure

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ABSTRACT: Mammary tuberculosis and other mycobacterial forms of granulomatous mastitis are uncommon but clinically important lesions that closely mimic carcinoma, and the receptor and proliferative reorganisation they induce in the gland is poorly characterised. This study quantified the proliferation marker Ki-67 and the estrogen (ER) and progesterone (PR) receptors in the mammary gland of outbred female rats after local mycobacterial exposure, and tested whether oral curcumin corrects the resulting changes. One hundred rats were assigned to an intact control group, a group receiving a complete Freund adjuvant–killed mycobacterial emulsion adjacent to the mammary gland, and a group receiving the same exposure followed by oral curcumin, and were studied at 4 and 9 months of age. Paraffin sections were immunostained for Ki-67, ER and PR and quantified by positive-cell detection in QuPath 0.5.1; positivity indices were compared by chi-square or Fisher exact tests with Benjamini–Hochberg control of the false-discovery rate. Mycobacterial exposure lowered the Ki-67 index by 47% at 4 months and 36% at 9 months and the PR index by about 50% and 42% (all adjusted $p < 0.01$), and reduced the ER index by roughly one-half, although the ER comparison did not survive correction owing to few detected nuclei. Curcumin restored about 61% of the lost proliferative activity at 4 months and produced smaller, non-significant gains in receptor expression. Local mycobacterial exposure therefore suppresses epithelial proliferation and hormone-receptor expression in the mammary gland, and curcumin partially reverses the proliferative component, supporting its evaluation as an adjunct natural biocorrector.

1. INTRODUCTION

Tuberculosis remains one of the leading infectious causes of death worldwide, and extrapulmonary forms continue to pose disproportionate diagnostic difficulty (World Health Organization, 2024). Mammary involvement is among the rarest of these forms: the breast is comparatively resistant to mycobacterial colonisation, and mammary tuberculosis accounts for well under 0.1% of breast disease in low-incidence settings while remaining appreciably more frequent in endemic regions (Mihai et al., 2024). Its importance is out of proportion to its frequency because it reproduces, both clinically and radiologically, the presentation of carcinoma, so that a granulomatous infection is repeatedly mistaken for malignancy and managed with unnecessary surgery (Mihai et al., 2024; Li et al., 2024).

Mycobacterial mastitis belongs to the wider family of granulomatous mastitis, in which epithelioid macrophages, multinucleated giant cells and lymphocytes assemble into granulomas that compress and replace the secretory parenchyma

(Khanal et al., 2023). The organising principle of this lesion is the mycobacterial granuloma itself, a structure maintained by the crosstalk between antigen-specific CD4+ T cells and infected macrophages and critically dependent on tumour necrosis factor-α (Flynn et al., 2011). Complete Freund adjuvant, an emulsion of mineral oil and killed mycobacteria, reproduces this cell-mediated, granulomatous response with high fidelity and is therefore an established tool for modelling mycobacterial inflammation in laboratory animals (Hunter et al., 2023).

How this granulomatous microenvironment reshapes the epithelial compartment of the gland has received far less attention than the granuloma itself. The mammary epithelium is governed by the balance between proliferation and steroid-hormone signalling, and this balance is read most directly through three nuclear markers used in routine breast pathology: the proliferation antigen Ki-67 and the estrogen (ER) and progesterone (PR) receptors (Tuominen et al., 2010). Chronic inflammation is not neutral toward these markers. Activation of nuclear factor-κB, the central transcriptional hub of the mycobacterial response, is closely associated with downregulation of the estrogen receptor in the breast (Van Laere et al., 2007), and inflammatory signalling antagonises progesterone-receptor function as well, so that a sustained infective stimulus would be expected to depress both receptors together with the proliferative index they support.

Curcumin, the principal polyphenol of Curcuma longa, is a plausible counter-measure to precisely this cascade. It is a potent antioxidant and anti-inflammatory agent that suppresses NF-κB, MAPK and JAK/STAT signalling and the downstream production of TNF-α, IL-1β and IL-6 (Hewlings and Kalman, 2017; Weng and Goel, 2022; Kah et al., 2023). In the mammary gland specifically, curcumin attenuates lipopolysaccharide- and toxicant-induced injury of epithelial cells through the NFE2L2 antioxidant axis and by restraining NF-κB (Li et al., 2021; He et al., 2026), which makes it a rational candidate for correcting inflammation-driven receptor loss, notwithstanding its well-known limitation of low oral bioavailability (Bučević Popović et al., 2024; Ayub et al., 2024).

Against this background, the present study had three aims: to quantify Ki-67, ER and PR in the rat mammary gland after local mycobacterial exposure using reproducible digital image analysis; to establish how these changes differ between two ages; and to test whether oral curcumin corrects them. We hypothesised that mycobacterial exposure suppresses epithelial proliferation and hormone-receptor expression and that curcumin partially restores this profile.

2. MATERIALS AND METHODS

2.1. Ethics statement

All procedures involving laboratory animals were approved by the Ethics Committee of the Ministry of Health of the Republic of Uzbekistan (protocol No. 4 of 26 August 2020; approval letter No. 4/1439 of 21 September) and were carried out in accordance with the Directive 2010/63/EU principles for the protection of animals used for scientific purposes. The study is reported in accordance with the ARRIVE 2.0 guidelines (Percie du Sert et al., 2020). Animals that died during the experiment were disposed of under the institutional act on the disposal of laboratory animals after decontamination with 20% chlorine solution.

2.2. Animals and experimental design

The experiment was performed at the research laboratory of Bukhara State Medical Institute. One hundred healthy outbred female rats were used, entering the study at two ages: 3 months (mean body weight 220 g, range 200–240 g) and 8 months (mean 350 g, range 320–380 g). Animals were housed in a common vivarium under standard temperature and humidity with free access to water and a balanced diet, and were acclimatised for 7–10 days before any intervention. Rats were allocated to three groups (Table 1): an intact control group (n = 20); a mycobacterial-exposure group (n = 40) receiving a complete Freund adjuvant–killed mycobacterial emulsion adjacent to the mammary gland; and a biocorrection group (n = 40) receiving the same exposure followed by oral curcumin. Each group was balanced across the two ages, and outcomes were assessed at 4 and 9 months of age, giving the study a 3 (group) × 2 (age) factorial structure.

Table 1. Distribution of animals by experimental group and age.

Group	Treatment	3 mo (220 g)	8 mo (350 g)	Total
I – Control	Intact, no exposure	10	10	20

II – Mycobacterial	Complete Freund adjuvant + killed mycobacteria near mammary gland (0.1–0.2 ml)	20	20	40
III – Biocorrection	Mycobacterial exposure + oral curcumin	20	20	40
Total		50	50	100

2.3. Mycobacterial exposure and curcumin biocorrection

Complete Freund adjuvant, containing mineral oil, an emulsifier and killed mycobacteria, was mixed with a mycobacterial suspension to a uniform emulsion and injected with a sterile syringe into the tissue adjacent to the mammary gland under aseptic conditions, at 0.1 ml in the 220 g (3-month) rats and 0.2 ml in the 350 g (8-month) rats, so as to induce a local granulomatous inflammatory focus. Injection volume and technique were held constant across animals. In the biocorrection group, curcumin was suspended fresh each day in 0.5% carboxymethyl-cellulose and administered once daily by oral gavage through a ball-tipped stainless-steel cannula, at a volume not exceeding 10 ml/kg body weight, with care taken to avoid tracheal misplacement and regurgitation.

2.4. Tissue processing and immunohistochemistry

Mammary tissue was fixed in 10% neutral buffered formalin, dehydrated through graded ethanols, cleared in chloroform and embedded in paraffin; sections of 4–6 μm were mounted on poly-L-lysine–coated slides. Immunohistochemistry for Ki-67, ER and PR was performed by the avidin–biotin immunoperoxidase method. After dewaxing and rehydration, endogenous peroxidase was blocked with 3% hydrogen peroxide for 10 min; sections were washed in Tris-NaCl buffer (pH 7.6) and incubated with the respective primary monoclonal antibody against Ki-67, ER or PR. The antigen–antibody complex was visualised with 3,3'-diaminobenzidine (DAB) chromogen, and sections were counterstained with haematoxylin. Positive nuclei appeared brown against the blue haematoxylin background.

2.5. Digital image analysis

Immunostained slides were scanned and analysed in QuPath 0.5.1 (Bankhead et al., 2017). For each specimen, five fields of view were captured at ×200–×400. Nuclei were segmented and classified as positive or negative by the built-in positive-cell detection command (Figure 1), and the positivity index was expressed as the number of DAB-positive nuclei divided by the total number of detected nuclei, in per cent (Tuominen et al., 2010; Usman and Zainal Abidin, 2021). Ki-67 was graded as low (< 20%), moderate (20–60%) or high (> 60%) expression; ER and PR were graded as negative (< 1%), low (1–10%), moderate (11–50%) or high (> 50%), following the thresholds pre-specified in the study protocol.

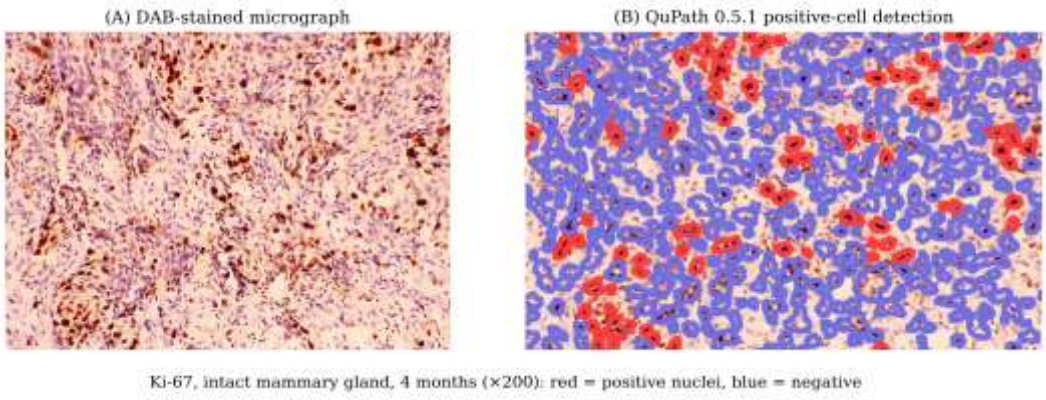

Figure 1. Representative QuPath 0.5.1 workflow. (A) DAB-stained micrograph of Ki-67 in the intact mammary gland at 4 months (×200); (B) the same field after positive-cell detection, in which positive nuclei are outlined in red and negative nuclei in blue. The positivity index is the number of red nuclei divided by the total number of detected nuclei.

2.6. Statistical analysis

Because QuPath classifies each detected nucleus dichotomously, the positivity index is a binomial proportion, and analysis was performed at the level of the classified nuclei. For each marker, age and group the index is reported with a Wilson 95% confidence interval (CI). Between-group differences in the proportion of positive nuclei were tested with the Pearson chi-square test, or the Fisher exact test where any expected count was below five, applied to the three planned contrasts within each marker–age stratum: control versus mycobacterial exposure, mycobacterial exposure versus curcumin, and control versus curcumin. To control for the resulting eighteen comparisons, p-values were adjusted by the Benjamini–Hochberg false-discovery-rate procedure, and adjusted values below 0.05 were considered significant. Effect sizes are given as odds ratios (with the Haldane–Anscombe correction where a zero cell occurred) and as relative changes in the index. Analyses were performed in Python 3 (SciPy and statsmodels). A limitation of this design is that nuclei from the same specimen are not fully independent; the nuclei-level test may therefore underestimate variance, and the indices are consequently interpreted primarily as descriptive effect sizes (see Section 3.5).

3. RESULTS AND DISCUSSION

The immunohistochemical profile of the three groups is summarised in Table 2 and the planned contrasts in Table 3, with the marker-specific micrographs shown in Figures 2–4 and the overall pattern in Figure 5. Across all three markers the direction of change was the same: local mycobacterial exposure lowered the positivity index, and curcumin moved it back toward the control value to a marker-dependent degree.

Table 2. Immunohistochemical positivity indices (positive nuclei / total detected nuclei) with Wilson 95% confidence intervals.

Marker	Age	Group	Positive / total	Index (%)	95% CI
Ki-67	4 mo	Control	77 / 375	20.5	16.8–24.9
Ki-67	4 mo	Mycobacterial	31 / 283	10.9	7.8–15.1
Ki-67	4 mo	Curcumin	66 / 392	16.8	13.5–20.9
Ki-67	9 mo	Control	98 / 361	27.1	22.8–32.0
Ki-67	9 mo	Mycobacterial	46 / 266	17.3	13.2–22.3
Ki-67	9 mo	Curcumin	97 / 477	20.3	17.0–24.2
PR	4 mo	Control	82 / 170	48.2	40.9–55.7
PR	4 mo	Mycobacterial	58 / 240	24.2	19.2–30.0
PR	4 mo	Curcumin	53 / 192	27.6	21.8–34.3
PR	9 mo	Control	50 / 131	38.2	30.3–46.7
PR	9 mo	Mycobacterial	100 / 448	22.3	18.7–26.4
PR	9 mo	Curcumin	24 / 114	21.1	14.6–29.4
ER	4 mo	Control	93 / 233	39.9	33.8–46.3
ER	4 mo	Mycobacterial	5 / 27	18.5	8.2–36.7
ER	4 mo	Curcumin	70 / 343	20.4	16.5–25.0

ER	9 mo	Control	120 / 354	33.9	29.2–39.0
ER	9 mo	Mycobacterial	7 / 33	21.2	10.7–37.8
ER	9 mo	Curcumin	21 / 100	21.0	14.2–30.0

Groups: Control = intact; Mycobacterial = complete Freund adjuvant–killed mycobacterial exposure; Curcumin = exposure followed by oral curcumin. Indices computed by QuPath 0.5.1 positive-cell detection.

Table 3. Planned between-group contrasts within each marker–age stratum: relative change, odds ratio and Benjamini–Hochberg–adjusted significance.

Marker · Age	Contrast	Δ index	Odds ratio	p (adj.)	Sig.
Ki-67 · 4 mo	Control vs Mycobacterial	−46.7%	2.10	0.004	**
	Mycobacterial vs Curcumin	+53.7%	0.61	0.052	ns
	Control vs Curcumin	−17.9%	1.28	0.262	ns
Ki-67 · 9 mo	Control vs Mycobacterial	−36.3%	1.78	0.010	**
	Mycobacterial vs Curcumin	+17.6%	0.82	0.403	ns
	Control vs Curcumin	−25.1%	1.46	0.042	*
PR · 4 mo	Control vs Mycobacterial	−49.9%	2.92	3.7×10^{-6}	***
	Mycobacterial vs Curcumin	+14.2%	0.84	0.500	ns
	Control vs Curcumin	−42.8%	2.44	3.1×10^{-4}	***
PR · 9 mo	Control vs Mycobacterial	−41.5%	2.15	0.001	**
	Mycobacterial vs Curcumin	−5.7%	1.08	0.862	ns
	Control vs Curcumin	−44.8%	2.31	0.010	**
ER · 4 mo	Control vs Mycobacterial	−53.6%	2.92	0.052	ns
	Mycobacterial vs Curcumin	+10.2%	0.89	0.862	ns
	Control vs Curcumin	−48.9%	2.59	3.7×10^{-6}	***
ER · 9 mo	Control vs Mycobacterial	−37.4%	1.90	0.207	ns
	Mycobacterial vs Curcumin	−1.0%	1.01	0.979	ns
	Control vs Curcumin	−38.0%	1.93	0.031	*

*⊿ index = relative change in the positivity index; positive values for the mycobacterial-versus-curcumin contrast denote recovery toward control. Significance after Benjamini–Hochberg control of the false-discovery rate: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, ns = not significant.*

3.1. Mycobacterial exposure suppresses epithelial proliferation (Ki-67)

In the intact gland the Ki-67 index rose with age, from 20.5% (95% CI 16.8–24.9) at 4 months to 27.1% (22.8–32.0) at 9

months, consistent with continuing physiological turnover of the maturing epithelium. Mycobacterial exposure reduced proliferation at both ages: the index fell to 11.0% (7.8–15.1) at 4 months and 17.3% (13.2–22.3) at 9 months, corresponding to relative reductions of 47% and 36% (control versus exposure, adjusted p = 0.004 and p = 0.010; odds ratio 2.10 and 1.78; Table 3). The change is evident on the detection images (Figure 2), where the density of red, Ki-67–positive nuclei is visibly lower in the exposed panels (B, E) than in the controls (A, D). A granulomatous, TNF-α–driven microenvironment thus restrains rather than stimulates epithelial cycling, in keeping with the diversion of the tissue toward a defensive, macrophage-dominated programme (Flynn et al., 2011; Hunter et al., 2023). The suppression was proportionally greater in the younger animals, whose epithelium normally carries the higher proliferative load, indicating that the actively developing gland has more proliferative activity to lose.

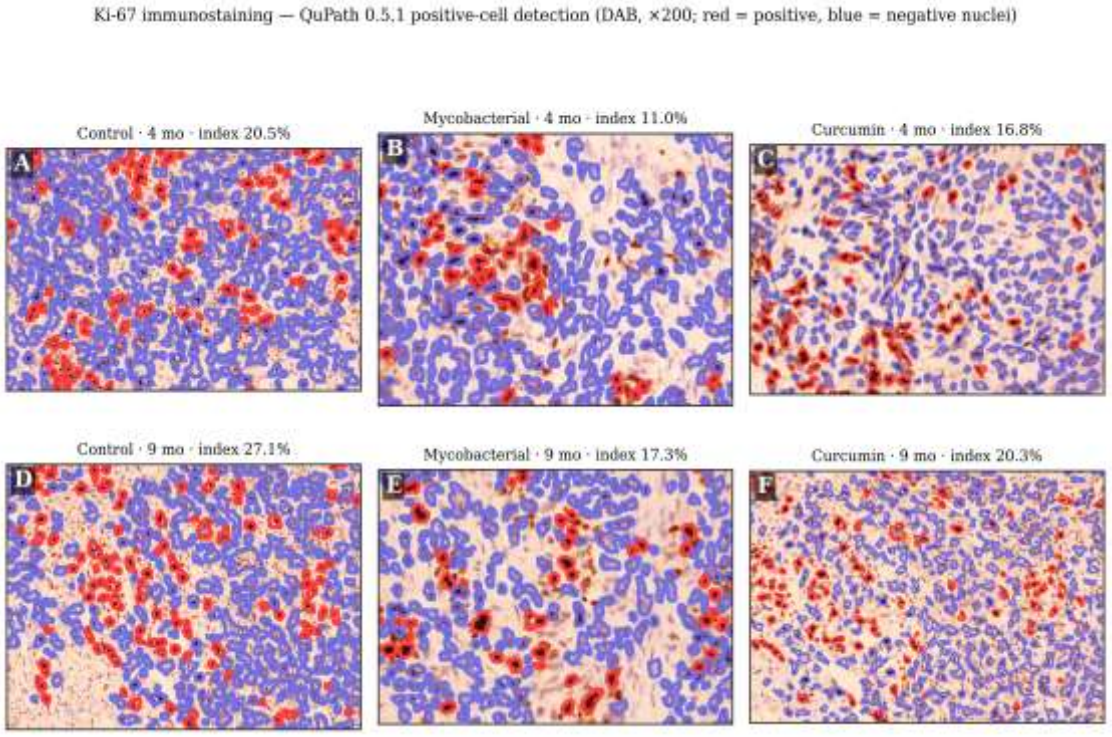

Figure 2. Ki-67 immunostaining across groups and ages (QuPath 0.5.1 positive-cell detection; DAB, ×200; red = positive, blue = negative nuclei). (A–C) 4 months and (D–F) 9 months; columns show the control, mycobacterial-exposure and curcumin-biocorrection groups. The proportion of red nuclei falls after exposure and recovers partially with curcumin.

3.2. Mycobacterial exposure depresses progesterone-receptor expression (PR)

PR was the most strongly affected receptor. In controls the index was 48.2% (40.9–55.7) at 4 months and 38.2% (30.3–46.7) at 9 months, the modest age-related decline being the expected physiological trend. After mycobacterial exposure PR fell to 24.2% (19.2–30.0) and 22.3% (18.7–26.4), reductions of about 50% and 42% (adjusted $p = 3.7 \times 10^{-6}$ and p = 0.001; odds ratio 2.92 and 2.15; Figure 3). This is the change most readily explained by the inflammatory microenvironment: sustained NF-ϰB activation, the signature of the mycobacterial response, antagonises steroid-receptor signalling and is associated with loss of receptor expression in mammary tissue (Van Laere et al., 2007). The fall in PR therefore reads as a molecular correlate of the functional "progesterone withdrawal" that inflammation imposes on the gland, over and above any age effect.

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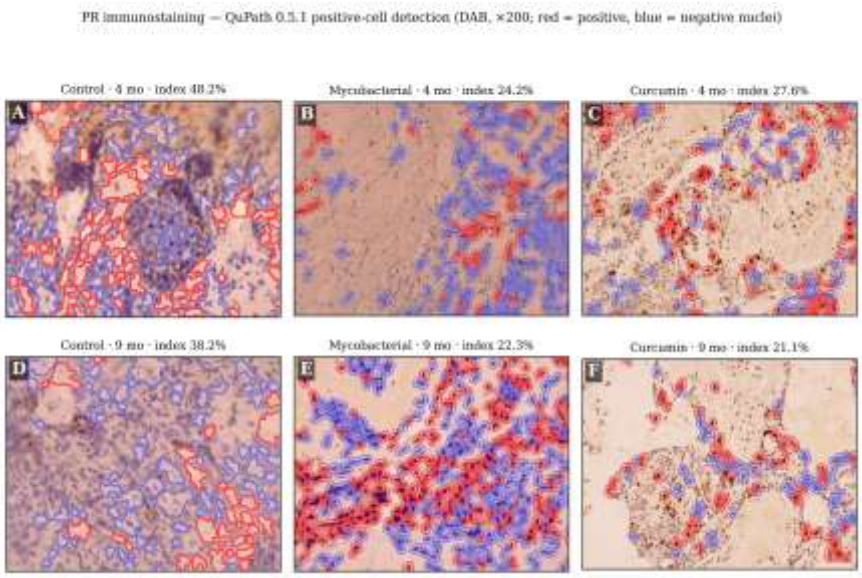

Figure 3. Progesterone-receptor (PR) immunostaining across groups and ages (QuPath 0.5.1 positive-cell detection; DAB, ×200; red = positive, blue = negative nuclei). Layout as in Figure 2. PR positivity is markedly reduced after mycobacterial exposure and is only partly restored by curcumin.

3.3. Mycobacterial exposure lowers estrogen-receptor expression (ER)

ER followed the same direction. The control index was 39.9% (33.8–46.3) at 4 months and 33.9% (29.2–39.0) at 9 months; after exposure the point estimates fell to 18.5% and 21.2%, relative reductions of roughly 54% and 37% with odds ratios of 2.92 and 1.90. Unlike Ki-67 and PR, however, the ER control-versus-exposure contrast did not survive false-discovery correction (adjusted p = 0.052 at 4 months and 0.21 at 9 months). The reason is methodological rather than biological: very few nuclei were detected in the exposed ER fields (27 and 33), so that despite a large effect size the confidence intervals are wide (Table 2), and this paucicellularity is directly visible in the exposed panels of Figure 4. Such paucicellularity is itself characteristic of mycobacterial mastitis, in which the epithelium is replaced by granulomatous and fibrotic tissue. The direction and magnitude of the ER change agree with the established link between NF-κB activation and estrogen-receptor downregulation (Van Laere et al., 2007), but the ER result is reported here as a strong trend that requires confirmation in larger samples rather than as a statistically secure effect.

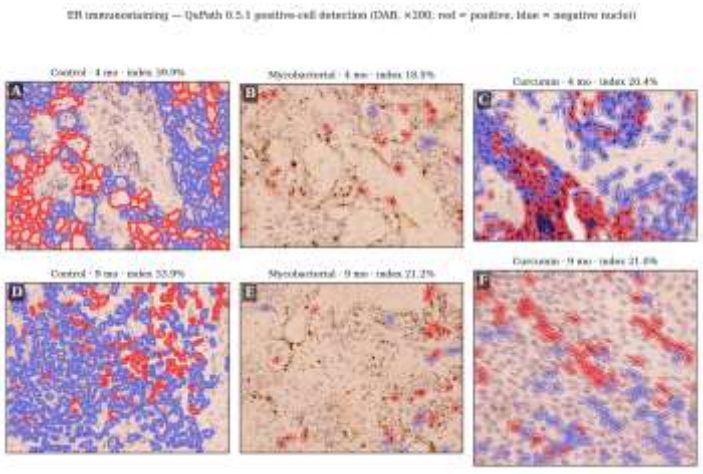

Figure 4. Estrogen-receptor (ER) immunostaining across groups and ages (QuPath 0.5.1 positive-cell detection; DAB, ×200; red = positive, blue = negative nuclei). Layout as in Figure 2. Note the small number of detected nuclei in the exposed panels (B, E), reflecting paucicellular, granulomatous replacement of the epithelium.

3.4. Curcumin partially restores the proliferative index

Oral curcumin had its clearest effect on proliferation. At 4 months the Ki-67 index rose from 11.0% in the exposed group to 16.8% (13.5–20.9), recovering about 61% of the difference from control and no longer differing significantly from the intact gland (control versus curcumin adjusted p = 0.26). At 9 months the gain was smaller (17.3% to 20.3%; about 31% recovery). For the hormone receptors the correction was weaker and did not reach significance against the exposed group: PR rose modestly at 4 months (24.2% to 27.6%, ~14% recovery) but not at 9 months, and ER was essentially unchanged at either age. The pattern is summarised in Figure 5. This graded response—substantial for proliferation, partial for PR, minimal for ER—is consistent with curcumin acting chiefly by damping the NF-κB–driven inflammatory brake on epithelial cycling (Li et al., 2021; Weng and Goel, 2022; He et al., 2026), while full restoration of nuclear-receptor expression, which depends on slower transcriptional and differentiation programmes, is not achieved within the treatment window. The limited and age-dependent receptor rescue is also compatible with the low systemic bioavailability of orally administered curcumin (Bučević Popović et al., 2024; Ayub et al., 2024), and argues that bioavailability-enhanced formulations deserve testing in this model.

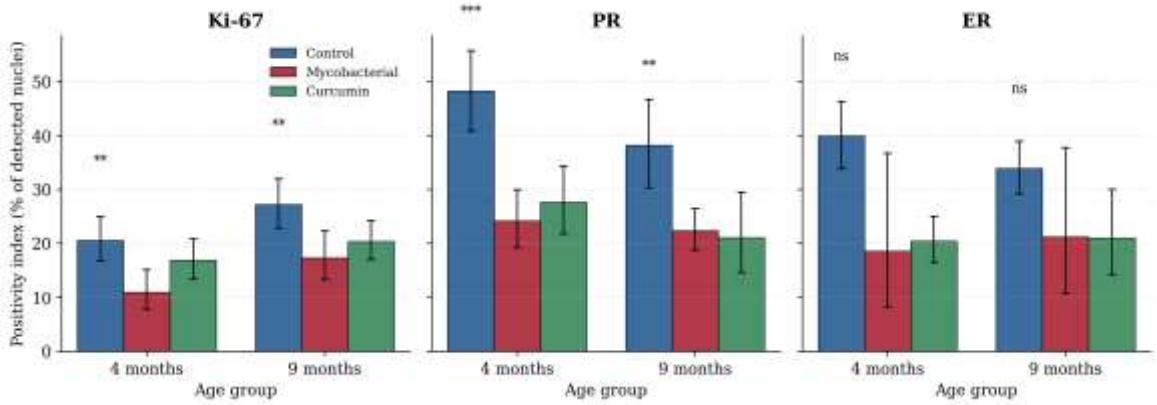

Figure 5. Immunohistochemical positivity indices (% of detected nuclei) for Ki-67, PR and ER by group and age. Bars show the index; whiskers show Wilson 95% confidence intervals. Symbols above the control bars denote the adjusted significance of the control-versus-exposure contrast (** $p < 0.01$, *** $p < 0.001$, ns = not significant after Benjamini–Hochberg correction).

3.5. Integration, strengths and limitations

Taken together, the three markers describe a coherent lesion. Local mycobacterial exposure shifts the mammary epithelium from a proliferative, hormone-responsive state to a quiescent, receptor-poor one, with proliferation and progesterone-receptor loss the most robust changes and estrogen-receptor loss a strong but statistically less secure accompaniment; curcumin reverses the proliferative component most effectively and the receptor components only partly. The main strength of the study is its fully reproducible, operator-independent quantification: every index derives from QuPath positive-cell detection and every inference from the underlying nuclei counts, so the analysis can be reproduced exactly from Table 2. The principal limitation is that inference was performed at the level of classified nuclei pooled from five fields per group; because nuclei from one specimen are not independent, the nuclei-level tests may understate biological variance, and the p-values should be read alongside the effect sizes rather than in isolation. A confirmatory study with animal-level replication and mixed-effects (or beta-binomial) modelling of per-animal indices, ideally combined with dual staining for macrophage and lymphocyte markers and with a bioavailability-enhanced curcumin arm, is the natural next step. The low detected-cell counts in the exposed ER fields specifically limit the ER conclusion and should be addressed by larger sampled areas in future work.

4. CONCLUSION

Local mycobacterial exposure produces a consistent immunohistochemical reorganisation of the rat mammary gland, marked by a significant fall in the proliferation index (Ki-67) and in progesterone-receptor expression at both ages studied, and by a parallel, large but statistically less secure reduction in estrogen-receptor expression. Oral curcumin partially corrects this profile, restoring the majority of the lost proliferative activity in younger animals while producing only modest, non-significant gains in receptor expression. These findings identify Ki-67, ER and PR as informative readouts of the epithelial

response to mycobacterial mastitis and support the further evaluation of curcumin—preferably in a bioavailability-enhanced form and with animal-level statistical replication—as an adjunct natural biocorrector for inflammation-driven remodelling of the mammary gland.

Author contributions

S.Kh.A. designed the study, performed the animal experiments, immunohistochemistry and digital image analysis, interpreted the data and drafted the manuscript. L.J.S. supervised the project, contributed to the design and interpretation and critically revised the manuscript. Both authors read and approved the final version.

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Conflict of interest

The authors declare no conflict of interest.

Ethics statement

All animal procedures were approved by the Ethics Committee of the Ministry of Health of the Republic of Uzbekistan (protocol No. 4 of 26 August 2020; approval letter No. 4/1439 of 21 September) and conducted in accordance with EU Directive 2010/63/EU and the ARRIVE 2.0 guidelines.

Data availability

The nuclei-level counts underlying all indices and statistics are provided in full in Table 2 and Table 3; the QuPath project files are available from the corresponding author on reasonable request.

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