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Research Paper

Preliminary Toxicological Evaluation and Sequential Alveolar Bone Remodeling Effects of Topical Long-Jawed Mackerel Fish Oil Emulgel after Tooth Extraction in Wistar Rats

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ABSTRACT

Background: Optimal post-extraction alveolar socket healing requires coordinated activities of osteoclasts, osteoblasts, and osteocytes. Long-jawed mackerel (*Rastrelliger* sp.) fish oil contains high levels of bioactive omega-3 polyunsaturated fatty acids, but its phase-dependent effects on bone remodeling remain insufficiently characterized.

Methods: Findings from three distinct *in vivo* trials using male Wistar rats ($n = 24$ per study; $n = 4$ per treatment-endpoint subgroup) were synthesized. Interventions comprised untreated controls, 15% mackerel fish oil emulgel, and 0.2% hyaluronic acid gel (Gengigel^{R}), applied topically twice daily. Parameters included clinical residual socket volume (RSV) and histological counts of osteoclasts (days 7, 14), osteoblasts (days 14, 21), and osteocytes (days 21, 28). A separate 28-day cohort ($n = 4$ per group) assessed systemic tolerability and growth rates.

Results: Fish oil emulgel treatment led to lower osteoclast counts than untreated controls at day 7 (1.15 ± 0.34 vs. 2.50 ± 0.58; $p = 0.006$) and day 14 (1.35 ± 0.77 vs. 3.45 ± 1.28; $p = 0.024$). Osteoblast proliferation was significantly enhanced at day 14 (50.00 ± 9.85 vs. 26.65 ± 10.02; $p = 0.009$) and day 21 (67.50 ± 5.74 vs. 39.65 ± 3.15; $p < 0.001$). Osteocyte counts were also significantly elevated at day 21 (61.70 ± 2.40 vs. 36.50 ± 8.71; $p = 0.002$) and day 28 (77.05 ± 10.17 vs. 41.20 ± 8.00; $p < 0.001$). The emulgel cohort demonstrated a consistent reduction in RSV over time. No mortality or overt clinical signs suggestive of systemic toxicity were observed over 28 days, and all groups showed progressive body-weight recovery.

Conclusion: Topical 15% mackerel fish oil emulgel exerts a stage-specific pro-regenerative influence on alveolar socket repair, characterized by early anti-resorptive activity followed by enhanced osteogenesis and matrix consolidation.

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Introduction

Tooth extraction initiates a highly coordinated repair response involving hemostasis, inflammation, granulation-tissue formation, extracellular-matrix deposition, bone formation, and remodeling [1]. Successful healing requires not only closure of the soft-tissue defect but also restoration of alveolar bone architecture [2]. Disruption of this sequence may delay subsequent prosthetic or implant treatment and contribute to persistent socket defects. Locally applied therapeutic formulations may support this process by maintaining active compounds at the wound interface and modulating the inflammatory and regenerative responses within the extraction socket [3].

Bone remodeling within the extraction socket is governed by functional coupling among osteoclasts, osteoblasts, and osteocytes [4]. Osteoclasts resorb damaged mineralized tissue and prepare the surface for new bone deposition. Osteoblasts then synthesize osteoid and regulate mineralization, while some mature osteoblasts become matrix-embedded osteocytes that maintain bone homeostasis and coordinate mechanosensory signaling. The temporal balance among these cell populations is therefore more informative than evaluating an isolated cellular endpoint [5].

Long-jawed mackerel (*Rastrelliger* spp.) provides eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), two omega-3 polyunsaturated fatty acids with anti-inflammatory and bone-modulating properties [6]. EPA and DHA may reduce pro-inflammatory mediator production, attenuate RANK–RANKL-dependent osteoclastogenesis, and support osteoblast differentiation [7]. Formulation as an emulgel combines the solubilizing properties of an emulsion with the residence time and topical applicability of a gel, providing a practical platform for delivering lipophilic fish-oil constituents to an extraction socket.

Despite its potential regenerative effects, applying a fish-oil-containing emulgel locally to an open extraction socket also requires preliminary toxicological consideration. Repeated contact with injured, highly vascularized oral tissue may cause local irritation or absorption of formulation components, while some of the applied preparation may be swallowed and contribute to systemic exposure. The safety profile may also be influenced by the emulgel excipients, lipid oxidation products, impurities, or residual processing solvents [8]. Accordingly, mortality, abnormal behavior, hypersalivation, gastrointestinal disturbances, oral erythema, edema, ulceration, necrosis, and changes in body weight can provide initial indicators of clinical tolerability. Although these observations cannot replace hematological, biochemical, or organ-histopathological examinations, they help identify overt treatment-related toxicity during repeated exposure.

Previous related experiments evaluated the same mackerel fish oil emulgel platform using different cellular endpoints and observation periods. Each experiment, considered separately, described only one segment of the healing response. The present study therefore integrated the original findings, without pooling or altering the statistical results, to examine whether the treatment produced a biologically coherent pattern across osteoclastic resorption, osteoblastic bone formation, osteocytic maturation, and clinical socket closure. We also included a separate 28-day cohort to establish a preliminary clinical toxicological profile based on mortality, observable clinical abnormalities, local oral reactions, and body-weight changes. We hypothesized that topical mackerel fish oil emulgel would reduce osteoclast counts, increase osteoblast and osteocyte counts, and decrease residual socket volume without producing overt treatment-related clinical toxicity compared with untreated extraction sockets.

Materials and Methods

Study design and integration strategy

Three independent histological experiments each included 24 rats (n = 4 per treatment–endpoint subgroup). We evaluated osteoclasts, osteoblasts, and osteocytes on days 7/14, 14/21, and 21/28, respectively. No animal contributed to multiple histological endpoints or time points. A separate 12-rat cohort assessed clinical tolerability. Datasets were analyzed separately without pooling (Table 1).

Table 1. Structure of the integrated experimental datasets.

Dataset	Primary histological endpoint	Observation days	Clinical endpoint	Reported allocation
A	Osteoclast count	7 and 14	Residual socket volume	3 treatments × 2 times; n = 4/subgroup
B	Osteoblast count	14 and 21	Residual socket volume	3 treatments × 2 times; n = 4/subgroup
C	Osteocyte count	21 and 28	Residual socket volume	3 treatments × 2 times; n = 4/subgroup

Animals and experimental groups

Male Wistar rats (*Rattus norvegicus*; age 3–4 months, body weight 150–200 g) were acclimatized for one week under standard husbandry conditions with free access to food and water. We enrolled only clinically healthy animals without visible physical or oral lesions and excluded those with systemic illness or early mortality. Each experiment included untreated, 15% fish oil emulgel, and 0.2% hyaluronic acid gel groups, each divided between two endpoints (n = 4/subgroup). The allocation procedure was not documented; therefore, randomization could not be confirmed.

Preparation of mackerel fish oil and emulgel

We obtained mackerel (Rastrelliger sp., 50–90 g, 15–20 cm) from Belawan, North Sumatra, Indonesia. After washing, the fish were steamed at 70°C for 30 min and mechanically pressed. The resulting liquid was allowed to settle into aqueous, protein, and lipid layers. The crude oil layer was recovered and purified (using n-hexane for phase separation where applicable, followed by solvent evaporation) and stored frozen in dark glass bottles [9].

We prepared a 15% w/w fish oil emulgel by emulsifying mackerel oil, Span 80, and liquid paraffin with Tween 80 in distilled water at 70°C. The emulsion was incorporated into an HPMC gel containing propylene glycol, and the pH was adjusted to 6.0–6.5 with triethanolamine [10]. The same formulation and procedure were used in all three experiments; the source records did not list exact excipient quantities.

Tooth extraction and topical treatment

Rats were anesthetized with intraperitoneal ketamine prior to surgical procedures. Using a needle holder, researchers luxated and extracted the left mandibular incisor intact, then irrigated the alveolar socket with sterile saline. We applied fish oil emulgel or Gengigel® directly to the extraction socket with a microbrush twice daily; untreated controls received no application. The amount per application and residence time were not quantified [11].

Clinical assessment of residual socket volume

We recorded alveolar socket dimensions using a UNC-15 periodontal probe and a caliper. Three independent measurements of mesiodistal width, buccolingual width, and probing depth were averaged for each animal. We determined residual socket volume (RSV) using the equation. Because baseline measurement scales varied across source documents, RSV data were retained and evaluated within their respective original studies instead of being combined [11].

$$\text{RSV} = \text{mesiodistal width} \times \text{buccolingual width} \times \text{probing depth}$$

Histological preparation and cell quantification

We harvested mandibular socket tissues at scheduled endpoints, fixed them in 10% buffered formalin, and decalcified them with 10% EDTA. After dehydration in graded ethanol and clearing in xylene, tissues were paraffin-embedded and sectioned at 4–6 µm. We examined H&E-stained sections under light microscopy at 400× magnification.

Bone cells were identified morphologically and counted in five fields at 400× magnification, with counts averaged per animal. Field-selection criteria were not documented. Blinding was confirmed for osteoblast counting but could not be verified for osteoclasts or osteocytes. Osteocytes were defined as small, spindle-shaped cells with condensed nuclei encased within lacunae; cell identification throughout was based solely on morphology, without immunohistochemical staining.

Clinical tolerability and body-weight assessment

To assess clinical tolerability over 28 days, an independent cohort of 12 male Wistar rats was allocated to three intervention groups ($n = 4$): untreated extraction control, 0.2% Gengigel®, and 15% mackerel fish oil emulgel. Animals in this group were not subjected to histological analysis. We monitored clinical signs, including behavioral changes, hypersalivation, diarrhea, and oral edema, erythema, ulceration, or necrosis, daily for 28 days. Body weight was recorded on days 0, 3, 7, 14, 21, and 28 and reported as mean ± SD [12].

Statistical analysis

All primary statistical analyses were retained from the original studies. We evaluated normality and variance homogeneity using the Shapiro–Wilk and Levene's tests, respectively. Group comparisons (untreated, emulgel, and Gengigel®) at individual time points were conducted via one-way ANOVA followed by Fisher's LSD *post hoc* test. Differences across time points within the same treatment were analyzed using independent-samples t-tests. Statistical significance was defined as $p < 0.05$. All calculations were executed in IBM SPSS Statistics, with no raw data pooling across datasets.

Results

Clinical residual socket volume

Across all three datasets, fish oil emulgel treatment consistently reduced RSV over time (Table 2). In Datasets A and B, mean RSV was systematically lower in the fish oil emulgel group than in the untreated and Gengigel® groups. Dataset C mirrored this pattern, showing a pronounced drop in RSV with fish oil emulgel by day 28, alongside a transient increase in untreated controls between days 21 and 28. Because Datasets A/B and C utilized non-identical measurement scales, RSV trends are evaluated within their respective dataset blocks.

Table 2. Original residual socket volume outcomes retained by dataset (mean ± SD; n = 4 per subgroup).

Dataset/day	Untreated control	Gengigel®	Fish oil emulgel	ANOVA p
A/day 7	0.85 ± 0.06	0.63 ± 0.05	0.56 ± 0.04	<0.001
A/day 14	0.57 ± 0.03	0.40 ± 0.16	0.37 ± 0.06	0.046
B/day 14	0.872 ± 0.045	0.770 ± 0.134	0.555 ± 0.058	0.002
B/day 21	0.577 ± 0.033	0.435 ± 0.079	0.298 ± 0.095	0.002
C/day 21	46.00 ± 9.52	57.50 ± 9.43	39.00 ± 3.83	0.029
C/day 28	72.75 ± 17.73	28.50 ± 11.12	13.50 ± 7.59	<0.001

International Journal of Medical Toxicology & Forensic Medicine

Sequential bone-cell responses during alveolar socket healing

Cellular responses across treatment groups are summarized in Table 3. During early socket healing, osteoclast density varied significantly among groups on day 7 ($p = 0.006$) and day 14 ($p = 0.024$). Fish oil emulgel yielded the lowest osteoclast counts at both day 7 (1.15 ± 0.34) and day 14 (1.35 ± 0.77), compared with untreated controls (2.50 ± 0.58 and 3.45 ± 1.28, respectively) and Gengigel® (1.30 ± 0.48 and 1.95 ± 0.44, respectively). *Post hoc* testing confirmed that both active formulations significantly reduced osteoclast counts relative to untreated controls, with no significant difference observed between emulgel and Gengigel®.

During active bone formation, osteoblast counts differed significantly on day 14 ($p = 0.009$) and day 21 ($p < 0.001$). Osteoblast abundance peaked in the fish oil emulgel group, rising from 50.00 ± 9.85 on day 14 to 67.50 ± 5.74 on day 21. Corresponding values were 43.45 ± 3.71 and 57.80 ± 7.07 for Gengigel®, and 26.65 ± 10.02 and 39.65 ± 3.15 for untreated controls. Pairwise comparisons showed significantly higher osteoblast counts with fish oil emulgel than with untreated controls at both time points, whereas values between fish oil emulgel and Gengigel® remained statistically comparable.

A corresponding trend emerged during matrix maturation. Significant inter-group differences in osteocyte density were observed on day 21 ($p = 0.002$) and day 28 ($p < 0.001$), with fish oil emulgel maintaining the highest counts (61.70 ± 2.40 on day 21; 77.05 ± 10.17 on day 28), followed by Gengigel® and untreated controls. From day 21 to 28, osteocyte counts increased significantly in both the fish oil emulgel ($p = 0.026$) and Gengigel® ($p = 0.008$) groups, but not in untreated controls ($p = 0.457$).

Together, these dataset-specific findings demonstrate a synchronized remodeling sequence: early osteoclast suppression by fish oil emulgel, followed by enhanced osteoblast recruitment and subsequent osteocyte integration. Because we evaluated these parameters across separate analytical cohorts, these patterns reflect temporal alignment rather than a continuous longitudinal trajectory.

Preliminary clinical tolerability and body-weight changes

Throughout the 28-day observation period, no deaths, systemic toxicities (e.g., abnormal behavior, hypersalivation, or diarrhea), or severe localized lesions (ulceration, necrosis) were recorded in any group. Minor postoperative findings, such as transient edema, erythema, and reduced activity, resolved fully

Table 3. Sequential changes in osteoclast, osteoblast, and osteocyte counts during alveolar socket healing.

Bone-cell endpoint	Day	Untreated control	Gengigel®	Fish oil emulgel	ANOVA *p*
Osteoclast count	7	2.50 ± 0.58	1.30 ± 0.48	1.15 ± 0.34	0.006
	14	3.45 ± 1.28	1.95 ± 0.44	1.35 ± 0.77	0.024
Osteoblast count	14	26.65 ± 10.02	43.45 ± 3.71	50.00 ± 9.85	0.009
	21	39.65 ± 3.15	57.80 ± 7.07	67.50 ± 5.74	<0.001
Osteocyte count	21	36.50 ± 8.71	55.50 ± 8.27	61.70 ± 2.40	0.002
	28	41.20 ± 8.00	71.62 ± 1.13	77.05 ± 10.17	<0.001

International Journal of Medical Toxicology & Forensic Medicine

Table 4. Body-weight values (g; mean ± SD, n = 4/group).

Group	Day 0	Day 3	Day 7	Day 14	Day 21	Day 28	Change (%)
Untreated control	184.30 ± 7.40	180.20 ± 7.15	182.78 ± 6.93	187.57 ± 7.31	192.47 ± 7.21	197.15 ± 7.37	6.98 ± 0.37
Gengigel® 0.2%	185.45 ± 4.96	182.70 ± 4.91	185.60 ± 4.78	190.82 ± 4.79	196.00 ± 4.83	201.10 ± 4.83	8.44 ± 0.31
Fish oil emulgel 15%	185.00 ± 7.41	182.38 ± 7.09	185.60 ± 7.16	191.03 ± 7.26	196.62 ± 7.26	202.18 ± 7.28	9.30 ± 0.46

International Journal of
Medical Toxicology & Forensic Medicine

within 7 days. All groups experienced an initial post-operative weight reduction followed by progressive weight gain through day 28. Relative to baseline, final body weight increases averaged $6.98 \pm 0.37\%$ for untreated controls, $8.44 \pm 0.31\%$ for Gengigel®-treated animals, and $9.30 \pm 0.46\%$ for the fish oil emulgel cohort (Table 4).

Discussion

The combined findings indicate that topical long-jawed mackerel fish oil emulgel was associated with a coherent sequence of cellular responses during alveolar socket healing. The lower osteoclast counts on days 7 and 14 suggest reduced excessive early bone resorption, whereas the subsequent increases in osteoblast counts on days 14 and 21 and osteocyte counts on days 21 and 28 are consistent with enhanced bone formation and matrix maturation. This pattern is biologically compatible with the reported actions of the long-chain omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which may suppress pro-inflammatory mediators such as tumor necrosis factor-α and interleukin-1β, promote the formation of specialized pro-resolving lipid mediators, and attenuate RANKL-dependent osteoclast differentiation [13, 14]. Resolution of excessive local inflammation may subsequently provide a more favorable environment for osteoblast differentiation, osteoid deposition, and mineralization [15]. The later increase in osteocyte abundance further supports continuity between osteoblast activity and maturation of newly formed bone, although this interpretation was based on morphological cell identification rather than lineage-specific molecular markers [16]. Macroscopic changes in residual socket volume generally paralleled the cellular findings, with fish oil emulgel producing the lowest values at the corresponding observation points. However, differences in the numerical scale of residual socket volume across datasets prevented quantitative pooling and require verification of measurement units and source records.

The emulgel system may have supported local delivery by dispersing the lipophilic fish oil within a hydrophilic gel network, thereby improving mucosal spreadability and prolonging residence at the extraction site [17]. Nevertheless, the absence of a vehicle-only emulgel group prevents complete separation of the biological contribution of mackerel oil from the gel base's protective or retention effects. Preliminary clinical observations showed no mortality or persistent adverse signs, while transient postoperative reductions in body weight and mild edema or erythema resolved during follow-up. These findings may indicate acceptable clinical tolerability, but they do not provide evidence of systemic safety without hematological, biochemical, and organ-histopathological evaluation. The study is strengthened by its integration of three complementary bone-cell endpoints across successive healing phases; however, interpretation is limited by the small sample size of four animals per treatment–time subgroup, reliance on hematoxylin–eosin morphology without TRAP or lineage-specific immunohistochemical confirmation, the absence of a vehicle control, inconsistent residual socket volume scales, and the use of Fisher's least significant difference test without formal multiplicity adjustment. Moreover, the lack of direct EPA/DHA quantification, lipid-oxidation indices, emulgel characterization, and release data limits attribution of the observed effects to defined active constituents. Future studies should therefore use a prospectively unified and adequately powered design incorporating blinded assessment, standardized socket measurements, a vehicle control, micro-computed tomography, molecular markers of bone remodeling, systemic safety parameters, and complete physicochemical characterization of both the fish oil and its emulgel formulation.

Conclusion

Topical 15% long-jawed mackerel fish oil emulgel was associated with lower osteoclast counts at early endpoints, higher osteoblast and osteocyte counts at later endpoints, and reduced residual socket volume within the individual datasets. These temporally aligned findings across separate animal cohorts suggest a potential influence on successive phases of alveolar socket healing, but do not directly demonstrate a continuous remodeling sequence. The absence of mortality or overt adverse clinical signs over 28 days supports preliminary clinical tolerability, but does not establish definitive systemic safety. Further studies

using a unified experimental design and comprehensive safety assessments are warranted.

Ethical Approval

All animal procedures were approved by the Ethics Committee of the Faculty of Mathematics and Natural Sciences, Universitas Sumatera Utara (Approval No. 0680/KEPH-FMIPA/2023) and conducted in compliance with the ARRIVE 2.0 guidelines.

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Conflicts of Interest

The authors report there are no competing interests to declare.

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