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Letter to the Editor Regarding "Effects of Jintiange on the healing of osteoporotic fractures in aged rats"

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The recent study "Effects of Jintiange on the healing of osteoporotic fractures in aged rats" [1] provides preliminary insights into the potential therapeutic role of Jintiange (artificial tiger bone) in osteoporotic fracture repair. However, several methodological and interpretative limitations undermine the robustness of its conclusions. This commentary aims to address these concerns, focusing on five critical issues that require clarification or further investigation.

Inadequate group design: absence of essential controls

The study utilized only two groups: an ovariectomy-induced osteoporosis (OVX) model group treated with Jintiange and an untreated OVX control group. The lack of blank controls (sham-operated rats without OVX) and positive controls (e.g., bisphosphonates or teriparatide) makes it impossible to distinguish between the drug's efficacy, model-specific pathological changes, or placebo effects [2] Similar osteoporosis-related studies consistently underscore the critical requirement for incorporating multi-arm experimental designs in research protocols.

Unverified mechanism: lack of direct evidence on osteoclast inhibition

The authors hypothesize that Jintiange restores the "balance between bone resorption and formation." However, the study solely measured osteogenesis-related markers (e.g., BV/TV, Tb.N) without assessing osteoclast activity (e.g., TRACP5b, RANKL / OPG ratio) [3]. Without such data, the conclusion that Jintiange "restores balance" remains speculative. Future work should include tartrate-resistant acid phosphatase (TRAP) staining and dynamic bone turnover markers to clarify its dual action [4].

Subjective fracture healing criteria: overreliance on imaging and non-validated scores

Fracture healing was evaluated using micro-CT parameters (e.g.,BV/TV) and a proprietary scoring system, but these lack validation against gold-standard methods. **Micro-CT limitations**: While micro-CT quantifies trabecular architecture, it cannot assess mechanical strength or collagen maturation, which are critical for functional healing. Complementary biomechanical testing (e.g., three-point bending) or histology (e.g., Safranin O staining for callus maturity) is required [5]. **Scoring system validity**: The described scoring table (e.g., " 0–2 points for callus formation ") lacks reference to established scales like the Radiographic Union Score for Tibial fractures (RUST) or Lane-Sandhu criteria. Non-blinded assessments further risk observer bias, as noted in guidelines for orthopedic animal studies [2]. These limitations question the reliability of the healing outcomes. Standardized, blinded evaluations with multi-modal validation are imperative.

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Unjustified dosage selection and absence of Dose-Response data

The study administered a single Jintiange dose (50 mg/kg/day) without justifying its selection or exploring dose-response relationships. This raises two issues: **Toxicity vs. Efficacy**: High mortality rates (exact numbers unreported) were attributed to "aged rat frailty, " but no data excluded drug toxicity. Dose-ranging studies (e.g., 25, 50, 100 mg/kg) are needed to identify optimal therapeutic windows and assess safety. **Clinical translation**: Human-equivalent dosing requires pharmacokinetic data, which are absent. Previous trials of similar traditional medicines emphasize the necessity of dose optimization to avoid under-/over-treatment.

Unexplained mortality: potential link to drug toxicity

The mortality rate in treated rats was mentioned but inadequately analyzed. While aging and surgical stress may contribute, the possibility of Jintiange-related toxicity cannot be dismissed without: **Histopathological data**: Organ toxicity assessments (e.g., liver, kidney) to exclude drug-induced damage. **Pharmacokinetics**: Plasma concentration monitoring to ensure doses remain within safe thresholds. Similar studies on herbal compounds (e.g., Epimedium extracts) have reported hepatotoxicity at high doses, underscoring the need for rigorous safety profiling [6].

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References

1. Liu J, Liu T T, Zhang H C, et al. Effects of Jintiange on the healing of osteoporotic fractures in aged rats. J Orthop Surg Res. 2024;19(1):828.
2. Gorter E A, Reinders C R, Krijnen P, et al. The effect of osteoporosis and its treatment on fracture healing a systematic review of animal and clinical studies. Bone Rep. 2021;15:101117.
3. Simic M K, Mohanty S T, Xiao Y, et al. Multi-Targeting DKK1 and LRP6 prevents bone loss and improves fracture resistance in multiple myeloma. J Bone Min Res. 2023;38(6):814–28.
4. Na C, Ao D. MiR-331-3p facilitates osteoporosis and May promote osteoporotic fractures by modulating NRP2 expression. J Orthop Surg Res. 2024;19(1):487.
5. Ji H, Shen G, Liu H, et al. Biodegradable Zn-2Cu-0.5Zr alloy promotes the bone repair of senile osteoporotic fractures via the immune-modulation of macrophages. Bioact Mater. 2024;38:422–37.
6. Wang Y, Zhao M, Li B, et al. Advances in the mechanism of emodin-induced hepatotoxicity. Heliyon. 2024;10(13):e33631.

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