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ACUPUNCTURE AND NSAIDS REDUCE NEUROGENIC-PAIN AND MATRIX DEGRADATION BIOMARKERS IN A RAT MODEL OF OSTEOARTHRITIS

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ABSTRACT
Osteoarthritis (OA) is a degenerative joint disease characterized by neurogenic pain and cartilage degradation, with serum biomarkers (SP, NGF, COMP, and MMP-13) serving as indicators of pain signaling, tissue damage, and treatment effects. This study aimed to compare the effects of acupuncture and a nonsteroidal anti-inflammatory drug (NSAID) on neurogenic pain and cartilage degradation biomarkers in a rat OA model. A randomized post-test-only experimental study was conducted using 32 male Wistar rats selected by purposive sampling and randomly allocated into four groups (n=8/group): healthy control, OA control, OA+acupuncture, and OA+NSAID. OA was induced by intra-articular monosodium iodoacetate. Acupuncture was administered at ST35, SP9, and GB34 for 10 sessions, while the NSAID group received oral meloxicam. Serum biomarkers were measured by ELISA and analyzed using one-way ANOVA with Tukey's HSD ($p<0.05$). Results: Significant differences were observed among all groups for each biomarker ($p<0.001$) with large effect sizes. Biomarker levels followed the pattern A < M ≈ S < K. Both treatment groups showed significant reductions compared to OA controls, with no significant difference between acupuncture and NSAID. Acupuncture and NSAID treatments produced comparable improvements in OA-related biomarkers, supporting multimodal therapeutic approaches for OA.

Keywords: acupuncture; biomarkers; NSAID; osteoartritis

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INTRODUCTION

Osteoarthritis (OA) is a leading cause of musculoskeletal pain and disability in older adults, with substantial impacts on function, quality of life, and healthcare costs. Its socioeconomic burden is amplified by high prevalence, chronic disease course, and the need for long-term therapy, whereas the effectiveness of available symptomatic treatments is often insufficient to control pain or halt structural progression (Leifer et al., 2022; Moulin et al., 2025). This gap between clinical need and therapeutic achievement underscores the requirement for safer, more sustainable strategies that both reduce pain and slow joint damage.

Biologically, OA is not merely "mechanical wear" but reflects an interaction between biomechanical stress, low-grade immune-inflammatory responses, oxidative stress, and activation of neurogenic pain pathways. These axes form a feedback loop that accelerates structural degradation and maintains hyperalgesia, explaining persistent symptoms even when systemic inflammatory markers may appear modest at clinical assessment (Khristich, 2023; Moulin et al., 2025). This integrative pathophysiological perspective highlights the need to evaluate disease-relevant biological targets rather than relying on symptoms alone. Within this framework, OA characterization becomes more informative when it links two key dimensions structure and pain through a biomarker panel. Structurally, MMP-13 is a key protease that degrades type II collagen, while circulating COMP reflects cartilage damage activity and progression; on the pain axis, NGF

mediates peripheral sensitization via TrkA activation and substance P (SP) facilitates nociceptive transmission and neurogenic inflammation (Bao et al., 2022; Li et al., 2021). Combined structure pain markers align assessments more closely with disease mechanisms than do nonspecific inflammatory indices (Bao et al., 2022; Moulin et al., 2025).

Therapeutically, NSAIDs are commonly used to control pain and inflammation, but long-term use is constrained by gastrointestinal, cardiovascular, and renal risks, limiting treatment continuity in vulnerable groups (Tjenggal et al., 2021). Conversely, acupuncture shows neuro-immune modulatory potential relevant to OA pain, including reductions in neuromediators and pro-inflammatory cytokines, although heterogeneity of endpoints and biomarkers across studies hampers strongly mechanistic synthesis (Li et al., 2021; Kim et al., 2022). Preclinical OA models also support chemokine and nociceptive pathways as targets for modulation (Li et al., 2020; Li et al., 2021). Standardized OA models such as monosodium iodoacetate (MIA) demonstrate inflammatory degenerative trajectories in cartilage and subchondral bone that can be monitored through tissue and serum biomarkers, providing methodological foundations for intervention evaluation (Bao et al., 2022; Yu et al., 2024). Accordingly, comparing NGF, SP, COMP, and MMP-13 across healthy, OA, OA+acupuncture, and OA+NSAID groups can enrich the biological rationale for safer, sustainable multimodal approaches (Bao et al., 2022; Li et al., 2020).

This study aimed to compare NGF, SP, COMP, and MMP-13 concentrations across four groups: healthy (A), OA (K), OA+acupuncture (M), and OA+NSAID (S). We hypothesized that the OA group would exhibit the highest levels for all markers; that both intervention groups (M and S) would show significant reductions versus OA; and that the healthy group would have the lowest levels. The study is expected to strengthen the biological basis for evaluating non-pharmacological and pharmacological interventions within a safer, sustainable multimodal OA strategy.

METHOD

This pure experimental study employed a post test only control group design in male Wistar rats aged 8 - 10 weeks and weighing 180 - 220 g. Animals were housed in a biomedical facility in standard cages with absorbent bedding and environmental enrichment (e.g., nesting material/tunnels), at a density of 2 - 4 rats per cage, under controlled temperature (22 ± 2 °C), humidity (50–60%), and a 12/12-h light/dark cycle. Standard chow and water were provided ad libitum. All animals underwent 7 day acclimatization prior to intervention, with daily monitoring by trained technicians. The unit of analysis was the individual animal. The a priori sample size was determined for a four-group one-way ANOVA assuming a medium large effect (Cohen's f = 0.5), α = 0.05, and power = 0.80, yielding a minimum of 7 rats per group; to allow for potential drop-out, 8 rats per group were used (total n = 32). Allocation to four groups healthy control (A), osteoarthritis (K), osteoarthritis + acupuncture (M), and osteoarthritis + NSAID (S) was performed by block randomization stratified by body weight using a computer-generated sequence. To minimize bias, sample collectors, ELISA operators, and statisticians were blinded to group codes until all analyses were completed.

OA induction was performed on day 8 by intra-articular injection of monosodium iodoacetate (MIA) 2 mg/50 µL saline into the right knee under injectable anesthesia (e.g., ketamine 80 - 100 mg/kg + xylazine 5 - 10 mg/kg intraperitoneal), with skin asepsis. Post-procedural analgesia was provided with buprenorphine 0.05 mg/kg subcutaneously. The healthy control group received saline (sham) in an equivalent volume. Interventions were delivered on days 15 - 25. The acupuncture group received 10 daily sessions at ST35 (Dubi), SP9 (Yinlingquan), and GB34 (Yanglingquan) using 0.18 × 13 mm stainless needles, inserted 2 - 3 mm per anatomical landmarks; retention 20 min with light manual stimulation every 5 min. The pharmacological comparator received meloxicam 1 mg/kg per os once daily (gavage volume ≈ 10 mL/kg) over the same period. Body weight, activity scores, protocol adherence, and adverse events were monitored daily; humane endpoints were predefined as > 20% weight loss, > 24 h anorexia, or severe distress.

On day 26, sampling was performed following humane euthanasia under isoflurane to loss of reflexes, then cardiac exsanguination. Cardiac blood was collected into plain tubes, allowed to clot 30–60 min, and centrifuged at 1,500 - 2,000 g for 10 - 15 min at 4 °C. Serum was aliquoted into labeled cryovials and stored at -80 °C until analysis. To mitigate batch effects, the order of processing and ELISA plate loading was randomized across groups, with inter-plate controls included. Serum NGF, substance P (SP), COMP, and MMP-13 were quantified using species-validated sandwich ELISAs per manufacturer datasheets. Each sample was run in duplicate; 4 parameter logistic (4 - PL) models were fitted to standard curves. Quality criteria were: $R^2 \geq 0.99$, back-calculated standards within ±20% of nominal (±25% near the LLOQ), and duplicate CV ≤ 15%; assays were repeated if CV exceeded the threshold. LLOQ/ULOQ followed kit validation; out-of-range samples were re-run or diluted per SOP. Low/high controls were included on each plate to support calibration and drift monitoring. Co-primary outcomes were serum NGF and MMP-13; secondary outcomes were COMP and SP. Statistical analyses were two-sided ($\alpha = 0.05$). Assumptions were assessed using Shapiro Wilk (normality per group) and Levene's test (homogeneity of variances). If assumptions were met, data were analyzed by one-way ANOVA per biomarker followed by Tukey's HSD post-hoc testing.

RESULT

The means and standard deviations of the four biomarkers followed the a priori hypothesis: the osteoarthritis group (K) showed the highest levels, the healthy group (A) the lowest, with the acupuncture (M) and NSAID (S) intervention groups falling in between. For the pain neurogenic dimension, SP and NGF in M/S were lower than in K; for the matrix-degradation dimension, COMP and MMP-13 in M/S were also reduced relative to K. This trend is visualized in Figure 1 (panels A - D) bar charts of mean ± SD demonstrating a uniform pattern of A < M ~ S < K across all markers. Assumption checks indicated that the data met normality (Shapiro Wilk, all $p > 0.05$) and homogeneity of variance (Levene's test, all $p > 0.05$) for all biomarkers; therefore, one-way ANOVA with Tukey's HSD was applied. The ANOVA results (Table 2) confirmed significant between-group differences for all biomarkers with large effect sizes: SP $F(3,28) \approx 234.82$, $p < 0.001$, $\eta^2 \approx 0.88$; NGF $F(3,28) \approx 137.24$, $p < 0.001$, $\eta^2 \approx 0.82$; COMP $F(3,28) \approx 255.41$, $p < 0.001$, $\eta^2 \approx 0.90$; and MMP-13 $F(3,28) \approx 139.16$, $p < 0.001$, $\eta^2 \approx 0.83$. Consistent with these findings, Figure 1A - B (SP, NGF) and Figure 1C - D (COMP, MMP-13) show the tallest bars for K, with clear reductions in M and S. Post-hoc Tukey's HSD tests (Table 3) indicated that K vs M and K vs S differed significantly for all biomarkers (p-adjusted < 0.001), reflecting consistent decreases in the intervention groups relative to OA. Differences between M and S were generally non-significant, and both remained higher than A for most markers (p-adjusted < 0.05), while M vs S was generally non-significant. Figure 1 (panels A - D) depicts mean ± SD per group; Figure 2 presents a z-score heatmap per sample, reinforcing the intermediate positioning of M and S relative to A and K.

Table 1.
Descriptive statistics per group (mean ± SD, n)

group	SP pg mL mean	SP pg mL std	SP pg mL count	NGF pg mL mean	NGF pg mL std	NGF pg mL count	COMP ng mL mean	COMP ng mL std	COMP ng mL count	MMP13 ng mL mean	MMP13 ng mL std	MMP13 ng mL count
A	122.03	12.56	8	1353.66	64.92	8	59.7	1.36	8	6.54	0.48	8
K	201.05	6.79	8	1914.24	70.74	8	97.35	1.88	8	10.87	0.47	8
M	169	8.31	8	1773.31	72.98	8	82.34	3.04	8	9.21	0.38	8
S	187.41	9.64	8	1888.22	97.19	8	90.23	3.24	8	10.16	0.34	8

Table 2.
One-way ANOVA per biomarker (F, p, η^2; Levene p).

Biomarker	F(3,28)	P	eta_squared	Levene_p
SP_pg_mL	104.11	0	0.918	0.4277
NGF_pg_mL	90.02	0	0.906	0.1847
COMP_ng_mL	340.37	0	0.973	0.3036
MMP13_ng_mL	160.72	0	0.945	0.7755

Table 3.
Tukey HSD pairwise comparisons (Δmean, 95% CI, p-adjusted).

	Biomarker	group1	group2	meandiff	lower	upper	p-adj	reject
3	COMP_ng_mL	K	M	-15.0019	-18.4191	-11.5847	0	TRUE
4	COMP_ng_mL	K	S	-7.1191	-10.5363	-3.7019	0	TRUE
5	COMP_ng_mL	M	S	7.8828	4.4656	11.3001	0	TRUE
0	COMP_ng_mL	A	K	37.6423	34.2251	41.0596	0	TRUE
1	COMP_ng_mL	A	M	22.6404	19.2232	26.0576	0	TRUE
2	COMP_ng_mL	A	S	30.5233	27.106	33.9405	0	TRUE
3	MMP13_ng_mL	K	M	-1.6637	-2.2418	-1.0856	0	TRUE
4	MMP13_ng_mL	K	S	-0.7119	-1.29	-0.1338	0.0114	TRUE
5	MMP13_ng_mL	M	S	0.9518	0.3737	1.5299	0.0006	TRUE
0	MMP13_ng_mL	A	K	4.3345	3.7565	4.9126	0	TRUE
1	MMP13_ng_mL	A	M	2.6708	2.0928	3.2489	0	TRUE
2	MMP13_ng_mL	A	S	3.6226	3.0446	4.2007	0	TRUE
3	NGF_pg_mL	K	M	-140.927	-246.649	-35.2036	0.0057	TRUE
4	NGF_pg_mL	K	S	-26.0167	-131.74	79.7061	0.9068	FALSE
5	NGF_pg_mL	M	S	114.9098	9.1869	220.6326	0.0293	TRUE
0	NGF_pg_mL	A	K	560.5763	454.8534	666.2992	0	TRUE
1	NGF_pg_mL	A	M	419.6498	313.9269	525.3727	0	TRUE
2	NGF_pg_mL	A	S	534.5595	428.8366	640.2824	0	TRUE
3	SP_pg_mL	K	M	-32.0543	-45.1076	-19.001	0	TRUE
4	SP_pg_mL	K	S	-13.6423	-26.6956	-0.589	0.038	TRUE
5	SP_pg_mL	M	S	18.412	5.3587	31.4653	0.0033	TRUE
0	SP_pg_mL	A	K	79.0206	65.9673	92.0739	0	TRUE
1	SP_pg_mL	A	M	46.9663	33.913	60.0196	0	TRUE
2	SP_pg_mL	A	S	65.3783	52.325	78.4316	0	TRUE

Figure 1. Serum biomarker profiles per group (mean ± SD). Panels: (A) SP; (B) NGF; (C) COMP; (D) MMP-13. Groups: A = healthy; K = OA; M = OA+acupuncture; S = OA+NSAID; n = 8/group.

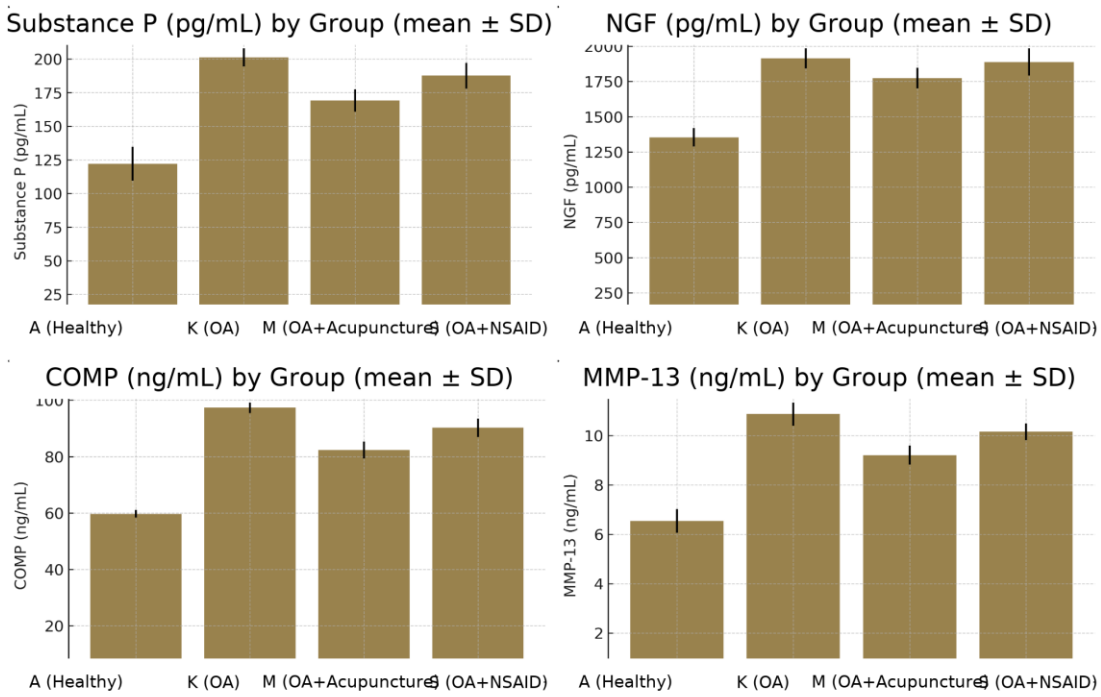
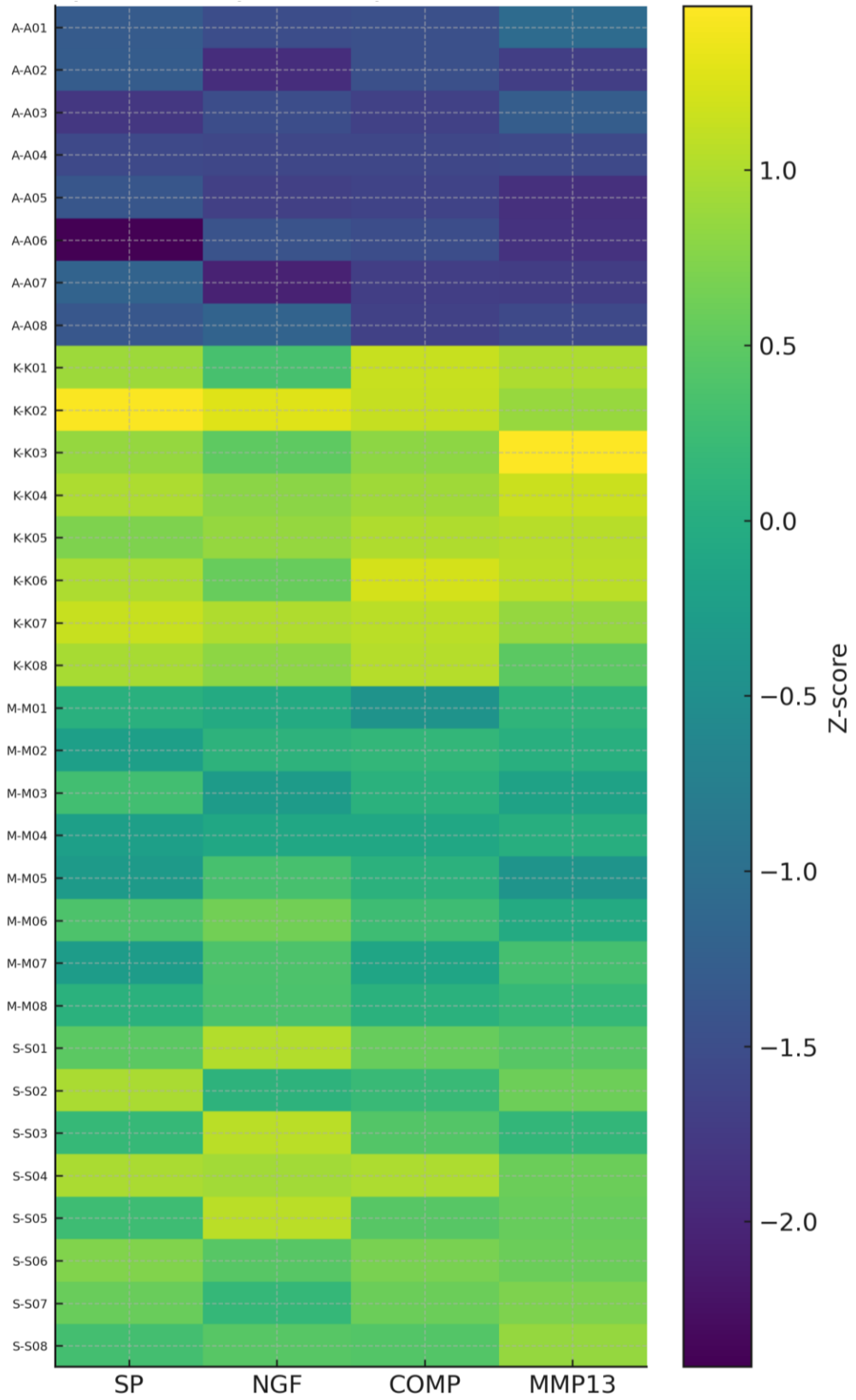


Figure 2. Heatmap of z-scored biomarkers (SP, NGF, COMP, MMP-13) across samples ordered by group



DISCUSSION

This study demonstrates that all evaluated biomarkers MMP-13, COMP, NGF, and substance P differed significantly across groups, with very large effect sizes and a consistent pattern. These findings reinforce the hypothesis that acupuncture is associated not only with analgesia but also with potential suppression of cartilage matrix degradation pathways. In the context of a chronic degenerative disease such as osteoarthritis (OA), this is relevant given the high disability burden and the limitations of long-term symptomatic therapy (Leifer et al., 2022; Moulin et al., 2025).

Biologically, MMP-13 is a central protease that degrades type II cartilage collagen; its reduction aligns with diminished tissue-destructive activity. Circulating COMP, a marker of cartilage damage, rises with OA progression; its modulation suggests possible structural protection. On the pain axis, NGF drives peripheral sensitization via TrkA, while substance P contributes to pain transmission and neurogenic inflammation; changes in both are consistent with reduced sensitization and hyperesthesia (Li et al., 2021; Moulin et al., 2025; Sun et al., 2025). Accordingly, the combined "structure pain" panel employed here captures two pathophysiologic axes of OA simultaneously, offering greater informativeness than general inflammatory markers alone (Bao et al., 2022; Moulin et al., 2025; Sun et al., 2025).

The consistency of these results accords with literature indicating that acupuncture can reduce pro-inflammatory mediators and modulate the neuro-immune axis. Preclinical OA studies have shown that acupuncture suppresses the MCP-2/CCR2 pathway implicated in hyperalgesia, while mechanistic reviews position acupuncture as a neuromodulator acting from acupoints to target organs via neural and immune networks (Li et al., 2020; Li et al., 2021). Caution is warranted, however, regarding potential bias from sham controls that are not fully inert in acupuncture trials, which may obscure or underestimate true effects (Birch et al., 2022a; Birch et al., 2022b; Kim et al., 2022). Although prior studies have primarily focused on IL-1β, IL-6, and TNF-α, the present findings broaden the spectrum by demonstrating concomitant effects on matrix degradation markers (MMP-13/COMP) and neurogenic pain markers (NGF/substance P), a combination that remains infrequently reported (Li et al., 2020; Li et al., 2021; Kim et al., 2022).

The MIA-induced OA model used in this study is recognized for recapitulating key histopathologic and molecular features of human OA, including subchondral bone microstructural changes and early inflammation (Bao et al., 2022). Thus, reductions in structure–pain biomarkers in this model provide biologically plausible and translationally relevant signals. The selection of ST35, SP9, and GB34 acupoints has an anatomic rationale for the knee; clinical and preclinical reports indicate potential pain reduction in knee OA when periarticular or functionally overlapping points are stimulated (Huang et al., 2022; Yoon et al., 2022). From a clinical-trial methods standpoint, the literature also highlights conceptual and operational issues concerning the definition of acupuncture and the use of sham controls, which can introduce bias into effect estimation; interpretation should therefore account for these limitations (Birch et al., 2022a; Birch et al., 2022b). The combination of model validity, point relevance, and methodological caution strengthens the plausibility of the mechanisms underlying these findings (Bao et al., 2022; Huang et al., 2022; Birch et al., 2022b).

From a service delivery perspective, these results should be viewed alongside the widespread use of NSAIDs, whose long-term adverse effects, including gastrointestinal, cardiovascular, and renal complications, constrain chronic management (Tjenggal et al., 2021). With a comparatively favorable safety profile, acupuncture could serve as a multimodal component to reduce pain burden and potentially slow tissue degeneration in selected patients, particularly when needle manipulation and stimulation intensity are optimized to elicit physiologically relevant de qi responses (Rosa et al., 2023; Sun et al., 2025). This aligns with the need for approaches that target not only symptoms but also the complex disease processes underlying OA (Khristich, 2023; Moulin et al., 2025).

The strengths of this study include a complementary biomarker panel linking structure and pain, a balanced group design, and rigorous laboratory quality control, including duplicate measurements, plate controls, and blinded outcome assessment. Several limitations merit consideration. First, although sufficient for detecting medium-to-large effects, the animal sample size limits subgroup analyses and causal inference regarding specific molecular pathways. Second, behavioral pain assessments, such as weight-bearing or von Frey testing, were not included, which may have strengthened linkage between biomarker changes and functional outcomes. Third, the post-intervention observation window was singular, precluding evaluation of longer-term biomarker trajectories and potential washout effects (Bao et al., 2022; Yu et al., 2024). These constraints motivate future studies incorporating longitudinal designs, behavioral endpoints, and more granular

mapping of molecular networks, including regional NGF/TrkA and substance P/NK1 signaling pathways (Li et al., 2021; Sun et al., 2025).

The principal scientific implication is the need for translational studies linking modulation of MMP-13/COMP and NGF/substance P to clinically meaningful improvements in function and quality of life. Methodologically, future work may benefit from multivariate approaches such as MANOVA for combined biomarker endpoints, exploration of dose response relationships in acupuncture stimulation parameters, and inclusion of active clinical comparators. Along the clinical trajectory, randomized controlled trials evaluating acupuncture as an adjunct to conventional therapy, with mechanistic biomarkers as secondary outcomes, will be critical for determining its added value (Li et al., 2020; Huang et al., 2022).

In sum, this study demonstrates robust and consistent biomarker differences across structural (MMP-13/COMP) and pain-related (NGF/substance P) dimensions, consistent with contemporary models of OA involving tissue neurogenic interactions. Given the substantial burden of OA and the limitations of purely symptomatic therapies, these findings strengthen the rationale for acupuncture as a mechanism-informed complementary intervention that warrants further investigation within translational research frameworks and rigorously designed clinical trials (Leifer et al., 2022; Moulin et al., 2025).

CONCLUSION

This experimental study shows a consistent A < M ~ S < K pattern across all four biomarkers. SP and NGF (pain–neurogenic) and COMP and MMP-13 (matrix degradation) followed the same directionality. Assumption checks were satisfied; one-way ANOVA with Tukey post-hoc tests confirmed significant reductions in the intervention groups M (acupuncture) and S (NSAID) relative to OA (K), with large effect sizes, although biomarker levels did not fully reach those of the healthy group (A). Visualizations (bar charts and a z-score heatmap) corroborate cross-marker consistency and indicate that M and S occupy a similar intermediate range.

Limitations include a short observation window, serum-only outcomes without tissue/functional confirmation, use of male Wistar rats, and the absence of a sham control, which constrains mechanistic inference. Future work should extend follow-up duration, incorporate behavioral pain outcomes and/or tissue imaging, standardize the acupuncture protocol (including de qi parameters), explore NSAID dose response relationships, and employ multivariate/computational approaches to map response signatures. Overall, these findings support the role of multimodal pharmacologic and neuromodulatory interventions in reducing the biological burden of OA.

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