ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug237

DNA Methylation as a Mediator of Acupuncture Analgesia: A Systematic Review of Preclinical and Clinical Evidence

Rahul R. K.[1]; Aswathy M.[2]

[1]Lecturer, Department of Acupuncture and Energy Medicine,
[2]Professor, Department of Acupuncture and Energy Medicine,
Sree Ramakrishna Medical College of Naturopathy and Yogic Sciences, Kulasekharam, Tamil Nadu, India.

Publication Date: 2026/08/17

Abstract:

- ***Background:***
  DNA methylation is a plausible mechanism through which acupuncture might produce persistent analgesic effects, but association, pathway involvement, and causal mediation are often conflated.

- ***Objective:***
  To systematically review preclinical and clinical evidence on whether DNA methylation mediates acupuncture analgesia.

- ***Methods:***
  PubMed/MEDLINE and Europe PMC were searched from inception to May 2026. Eligible original studies evaluated acupuncture or electroacupuncture, reported pain or nociceptive outcomes, and directly measured DNA methylation or experimentally investigated methylation-related machinery. Two reviewers independently conducted study selection, data extraction, and risk-of-bias assessment, with disagreements resolved by consensus. Owing to methodological heterogeneity, the findings were synthesized narratively.

- ***Results:***
  The searches retrieved 132 database records; 62 duplicates were removed, 70 unique records were screened, 13 reports underwent eligibility assessment, and four studies were included. All four were animal studies; no eligible clinical analgesia study was identified. In neuropathic-pain mice, manual acupuncture altered region-specific global methylation and prefrontal-cortex methylome patterns while reducing allodynia. In a tibial-nerve-injury model, electroacupuncture reduced contralateral S1 5mC alongside improved mechanical thresholds. A TET1/Prox1 demethylation pathway supported durable antidepressant effects in pain-comorbid mice but was explicitly unrelated to nociception. A rat study functionally implicated a DNMT3a/MOR pathway, yet did not directly measure CpG methylation. No study performed formal mediation analysis or a methylation-specific rescue experiment that established necessity and sufficiency for acupuncture analgesia.

- ***Conclusions:***
  Current evidence is consistent with acupuncture-associated, tissue-specific methylation remodeling during neuropathic pain, but is insufficient to conclude that DNA methylation mediates analgesia. The Overall confidence in a causal mediation effect remains very low., and the clinical evidence base is absent.

Keywords: *Acupuncture; Electroacupuncture; Analgesia; Neuropathic Pain; DNA Methylation; DNMT3a; TET1; Epigenetics.*

How to Cite: Rahul R. K.; Aswathy M. (2026) DNA Methylation as a Mediator of Acupuncture Analgesia: A Systematic Review of Preclinical and Clinical Evidence. *International Journal of Innovative Science and Research Technology*, 11(8), 597-603. https://doi.org/10.38124/ijisrt/26aug237

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug237

I. INTRODUCTION

Chronic pain reflects durable plasticity across peripheral, spinal, and supraspinal systems. Beyond pain modulation, acupuncture has also been investigated as a neuromodulatory intervention that may influence cortical activity, synaptic remodeling, neurogenesis, neurotrophic signaling, and inflammatory regulation in neurological disorders (Rahul R. K, Aswathy M., 2026). Epigenetic mechanisms—including DNA methylation—can stabilize transcriptional states without changing nucleotide sequence and are therefore plausible contributors to pain persistence and treatment-induced recovery (Denk & McMahon, 2012; Descalzi et al., 2015). In principle, acupuncture could influence pain through neural activity, neuroimmune signaling, stress regulation, and downstream chromatin remodeling. Whether methylation is merely a correlate of these changes or an intervening causal mechanism is a more demanding question.

Several narrative reviews have linked acupuncture, epigenetic regulation, and neuropathic pain (Gao et al., 2025; Hong et al., 2020; Jang et al., 2024). Their mechanistic language, however, sometimes combines direct methylome measurements, global 5mC changes, expression of DNA methyltransferases or TET enzymes, and non-pain clinical epigenomic studies under a single heading. These evidence types do not carry the same inferential weight. A true mediator should lie on the causal pathway from acupuncture to analgesia: acupuncture should alter the methylation state; that alteration should predict the pain outcome; and targeted disruption or restoration of the methylation process should attenuate or reproduce analgesia.

This review therefore asked a focused question: in animal models or people with pain, what evidence shows that DNA methylation mediates the analgesic effect of acupuncture or electroacupuncture? Direct methylation evidence was distinguished from indirect evidence involving methylation machinery, and analgesic mechanisms were separated from mechanisms affecting comorbid mood or other non-pain outcomes.

II. METHODS

➢ *Review Design and Reporting*

This systematic review was prepared using the PRISMA 2020 framework (Page et al., 2021). The protocol was not prospectively registered. Two reviewers independently performed study selection, data extraction, and risk-of-bias assessment. Disagreements were resolved through discussion and consensus.

➢ *Eligibility Criteria*

Table 1 Eligibility Criteria and Operational Definitions

Domain	Included	Excluded
Population/model	Animals with experimentally induced pain or humans with a pain condition	No pain model/condition
Intervention	Needle acupuncture or electroacupuncture	Non-acupuncture intervention or isolated molecular treatment
Outcome	Nociceptive behavior or patient-reported/clinical pain	Only inflammation, cartilage, mood, or other non-pain outcomes
Methylation evidence	Direct 5mC/5hmC, bisulfite/methylome/locus demethylation; or functional DNMT/TET pathway evidence	Histone marks, miRNA, or expression data without a DNA-methylation link
Study design	Original controlled preclinical or clinical research	Reviews, editorials, protocols, conference compendia, or conceptual articles
Language/status	Any language represented in the indexed databases; full report or sufficiently detailed publisher/indexed record	Record insufficient to establish eligibility

➢ *Information Sources and Search Strategy*

PubMed/MEDLINE and Europe PMC were searched from database inception to May 2026. Terms covered acupuncture/electroacupuncture and DNA methylation, methylome, DNMT, epigenetic, 5mC, 5hmC, or TET1 concepts. Queries were intentionally sensitive and therefore retrieved many non-pain epigenetic acupuncture records.

➢ *Study Selection and Data Collection*

Records were deduplicated using PMID, DOI, and normalized titles. Two reviewers independently screened the titles and abstracts and subsequently assessed potentially eligible full-text reports. Data were independently extracted using a prespecified form. Disagreements concerning eligibility or extracted information were resolved through discussion and consensus. Extracted fields included species and pain model, group sizes, acupuncture parameters, comparators, pain outcomes, tissue, methylation assay, principal findings, and the strength of mediation inference.

➢ *Evidence Tiers and Mediation Framework*

Tier 1 comprised direct DNA-methylation measurements (global 5mC/5hmC, bisulfite sequencing, methylome profiling, or locus-specific demethylation). Tier 2 comprised methylation machinery or pathway experiments without direct DNA-methylation measurement. Evidence was considered causal only if methylation-specific perturbation established its necessity or sufficiency for the analgesic response, or if a valid formal mediation analysis supported an indirect effect. Parallel change in pain and methylation was classified as association, not mediation.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug237

➢ *Risk of Bias and Synthesis*

Risk of bias was assessed with domains adapted from the SYRCLE tool for animal intervention studies (Hooijmans et al., 2014). Judgments were low, high, or unclear with supporting text. Meta-analysis was not attempted because the four studies used different species, injury models, acupuncture schedules, pain measures, tissues, and methylation endpoints, and did not report a common effect estimate. Findings were synthesized without meta-analysis in line with SWiM principles (Campbell et al., 2020).

III. RESULTS

➢ *Study Selection*

The searches retrieved 132 records (PubMed/MEDLINE, 68; Europe PMC, 64). After removal of 62 duplicates, 70 unique records were screened. Fifty-seven were excluded at title/abstract level. Thirteen reports were assessed for eligibility; nine were excluded (eight reviews/conceptual reports and one osteoarthritis methylation study without a pain outcome). Four studies were included. All were preclinical; no eligible human analgesia study was found (Figure 1).

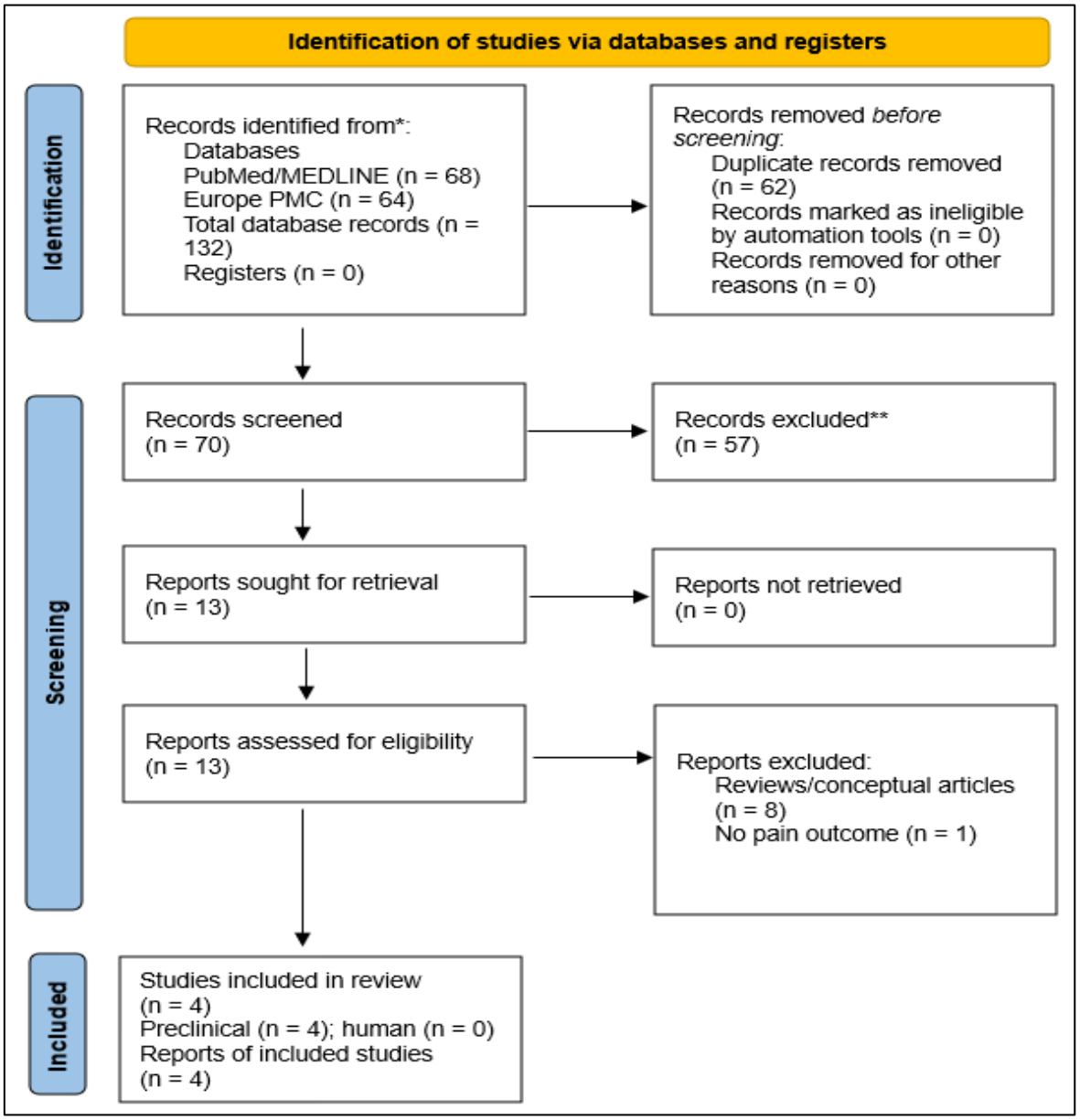

Fig 1 PRISMA 2020-Style Study Selection.

➢ *Characteristics of Included Studies*

The four studies were published from 2021 to 2025 and used male mice or rats with partial sciatic nerve ligation, tibial nerve injury, spared nerve injury with depression-like comorbidity, or chronic constriction injury (Jang et al., 2021; Li et al., 2023; Ping et al., 2023; Wang et al., 2025). Three used electroacupuncture and one manual acupuncture. Treatment ranged from seven daily sessions to three sessions weekly for six months. Pain outcomes were evoked mechanical, thermal, or cold responses; no study assessed spontaneous pain, affective pain interference, or a patient-reported outcome.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug237

Table 2 Included Study Characteristics and Mediation Interpretation

Study and model	Acupuncture exposure	Methylation evidence	Pain result and mediation judgment
Jang et al., 2021 Male C57BL/6J mice; PSNL	Manual acupuncture at bilateral GB30/GB34; 30-s rotation; 3 days/week for 6 months; non-acupoint and amitriptyline comparators	Global 5mC in five brain regions; PFC whole-genome bisulfite sequencing; MeCP2/DNMT expression; selected loci	Mechanical and cold allodynia improved. Region-specific and PFC methylation shifted toward sham patterns. Association only; no methylation perturbation or formal mediation.
Ping et al., 2023 49 male C57BL/6 mice; tibial nerve injury	EA at bilateral GB34; 2/100 Hz, 0.1 mA, 15 min daily on days 7–14; sham and sham-EA controls	Global 5mC/5hmC immunofluorescence in bilateral S1 and ACC; RNA sequencing	Mechanical threshold improved. EA reduced elevated 5mC only in contralateral S1; ACC global 5mC was unchanged. Parallel association.
Li et al., 2023 Mice; spared nerve injury with depression-like comorbidity	EA plus neural-stem-cell ablation and TET1/Prox1 experiments;	TET1 binding and demethylation at Prox1 promoter in ventral dentate gyrus neural stem cells	The pathway supported durable antidepressant/neurogenic effects but was reported not to be associated with nociception. Negative specificity evidence for analgesic mediation.
Wang et al., 2025 48 male Sprague–Dawley rats; CCI and AAV-DNMT3a	EA at ST36/GB34; 20/100 Hz, 1.5 mA, 30 min daily for 7 days under isoflurane; n=8/group	DRG/spinal DNMT3a and MOR expression plus AAV-DNMT3a overexpression; no direct CpG/5mC assay	Mechanical and thermal hypersensitivity improved; DNMT3a decreased and MOR increased. Functional pathway support, but indirect for DNA methylation.

➢ *Direct Methylation Findings*

Sustained behavioral benefits were observed during a six-month intervention in partial sciatic nerve ligation mice(Jang et al., 2021). Global methylation changed in a region-dependent manner, and prefrontal-cortex whole-genome bisulfite sequencing identified acupuncture-associated differentially methylated regions. Selected loci including Nr4a1, Chkb, Rasgrp1, and Rassf1 shifted toward sham-like patterns. The use of non-acupoint needling and a pharmacological comparator strengthened treatment specificity. Nevertheless, methylation was measured as a downstream endpoint. Because no DNMT/TET manipulation was used to block or reproduce analgesia, the study supports association and biological plausibility, not causal mediation.

Electroacupuncture improved mechanical withdrawal thresholds and modified cortical epigenetic signals, including global 5mC and 5hmC levels in the cortex, in tibial nerve–injured mice (Ping et al., 2023). Injury increased global 5mC bilaterally in primary somatosensory cortex; electroacupuncture reduced 5mC in contralateral S1 but not ipsilateral S1. The anterior cingulate cortex did not show a significant global 5mC change. The regional asymmetry argues against a nonspecific global effect and is consistent with circuit-level specificity. However, small molecular samples and multiple regional comparisons increase imprecision, and the study did not test whether preventing the S1 methylation change abolished analgesia.

Electroacupuncture was investigated in a mouse model of neuropathic pain with depression-like comorbidity(Li et al., 2023). TET1-dependent Prox1 promoter demethylation restored ventral dentate-gyrus neurogenesis and contributed to persistent antidepressant benefit. Crucially, neural-stem-cell ablation and the reported mechanistic analyses indicated that this pathway was not associated with nociception. The study is therefore informative precisely because it separates an epigenetic acupuncture mechanism for a pain-comorbid mood phenotype from the mechanism of analgesia.

➢ *Indirect Methylation-Machinery Evidence*

Wang et al. found that electroacupuncture reduced dorsal-root-ganglion DNMT3a expression, increased μ-opioid receptor expression, and improved mechanical and thermal hypersensitivity in chronic-constriction-injury rats (Wang et al., 2025). AAV-mediated DNMT3a overexpression provided a functional perturbation of the proposed pathway. Yet the study did not measure methylation of the MOR promoter or another CpG target. DNMT3a also has molecular effects not captured by a single promoter model, so altered enzyme abundance cannot be treated as proof of altered DNA methylation. This study offers the strongest pathway-level functional evidence but remains Tier 2 for the review question.

➢ *Clinical Evidence*

No human study simultaneously evaluated acupuncture analgesia and DNA methylation. Human acupuncture studies have shown blood epigenomic change in burnout and tissue-specific methylation or transcriptional responses in polycystic ovary syndrome (Benrick et al., 2020; Kokosar et al., 2018; Petitpierre et al., 2022), demonstrating clinical feasibility of methylation profiling but not addressing pain mediation. These studies were excluded from the focused review because they did not report an eligible pain or nociceptive outcome. Thus, the 'clinical evidence' component of the review is a documented evidence gap rather than an evidence stream.

➢ *Risk of Bias*

Random allocation was reported in three studies and outcome-assessor blinding in one, but allocation concealment, random housing, random outcome order, and caregiver blinding were generally unclear. Molecular sample

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug237

sizes were small, prospective analysis plans were not located, and one study excluded animals with motor impairment or death without group-wise accounting. Other-bias judgments were high in all four studies because of absent mediation testing, incomplete direct methylation measurement, long treatment exposure without a priori sample-size justification, or outcome-specific mechanistic mismatch.

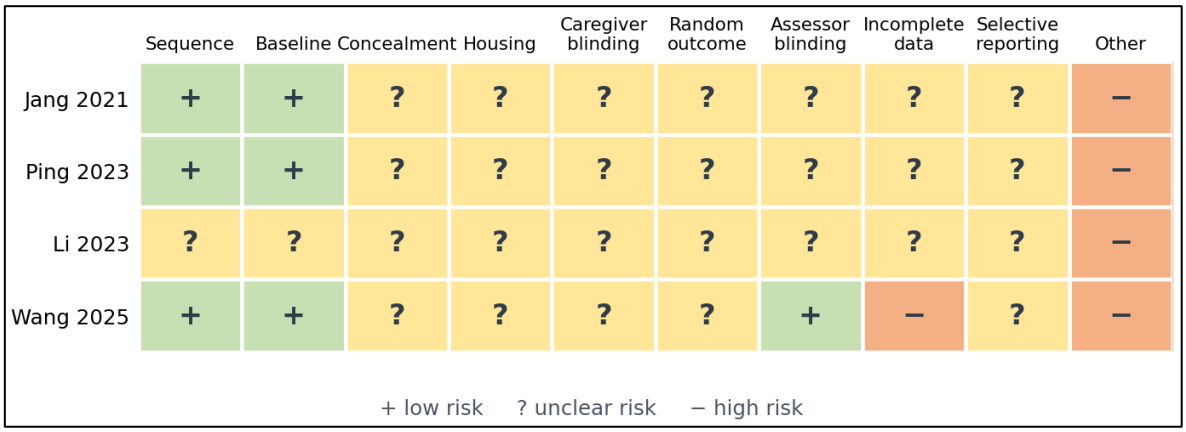

Fig 2 SYRCLE-Adapted risk-of-Bias Judgments. Green (+), Low Risk; Amber (?), Unclear Risk; Orange-Red (−), High Risk.

Table 3 Study-Level Risk-of-Bias Summary

Study	Low	Unclear	High	Principal limitation
Jang et al., 2021	2	7	1	No causal methylation test; very long intervention; no a priori sample-size calculation
Ping et al., 2023	2	7	1	Small molecular samples and multiple regional comparisons; no mediation perturbation
Li et al., 2023	0	9	1	Incomplete reporting of methodological details; Epigenetic pathway specific to antidepressant, not nociceptive, outcome
Wang et al., 2025	3	5	2	Attrition/exclusion accounting; no direct methylation assay; no sham-EA comparator

➢ *Overall, Strength of Evidence*

The evidence that acupuncture changes methylation-related measures during neuropathic-pain treatment is consistent but sparse. The evidence that these changes cause analgesia is very uncertain. There was no compatible effect measure for pooling, no replicated locus across independent laboratories, no female-animal evidence, no human pain evidence, and no formal indirect-effect estimate. Overall confidence that DNA methylation causally mediates acupuncture analgesia was considered very low because of the small evidence base, methodological limitations, mechanistic indirectness, absence of replication, and lack of clinical evidence.

IV. DISCUSSION

➢ *Principal Interpretation*

This review identifies a narrow but coherent preclinical signal: acupuncture and electroacupuncture can accompany region-specific DNA-methylation changes in neuropathic-pain models (Jang et al., 2021; Ping et al., 2023), and methylation machinery may intersect with opioid-receptor signaling (Wang et al., 2025). The signal is not yet a causal chain. In the strongest direct studies, analgesia and methylation changed together, but methylation was not selectively blocked. In the strongest mechanistic demethylation study, the demonstrated TET1/Prox1 mechanism explained persistent antidepressant effects rather than nociception (Li et al., 2023). Accordingly, the most defensible conclusion is 'candidate mechanism' rather than 'established mediator.'

This distinction matters for translation. Global 5mC fluorescence or bulk-tissue methylomes integrate many cell types and can change because of altered cell composition, neural activity, inflammation, stress hormones, or treatment exposure. A signal in prefrontal cortex, S1, dentate gyrus, or dorsal-root ganglion does not identify the responsible cell class. Likewise, DNMT3a abundance is an upstream mechanistic clue but does not identify which CpGs change or whether the change is required for analgesia.

➢ *Relationship to Prior Reviews*

Prior reviews describe DNA methylation as a promising component of acupuncture analgesia (Gao et al., 2025; Hong et al., 2020; Jang et al., 2024). The present synthesis narrows that proposition by applying a pain-outcome requirement and an explicit mediation hierarchy. The osteoarthritis study by Ding et al. demonstrated electroacupuncture-associated DNA-methylation regulation of miR-146a and miR-140-5p, but it was excluded because it did not report a nociceptive or patient-reported pain outcome (Ding et al., 2023). Similarly, clinical epigenomic studies in burnout and polycystic ovary syndrome support feasibility but do not constitute clinical analgesia evidence (Benrick et al., 2020; Kokosar et al., 2018; Petitpierre et al., 2022). These distinctions explain why the final evidence base is smaller than the broader acupuncture-epigenetics literature.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/26aug237

➢ *What would Establish Mediation?*

- *Temporal and Cellular Specificity*

Future studies should obtain baseline, early, peak-analgesia, and post-treatment samples and use cell-type-resolved methylome methods in dorsal-root ganglion, spinal cord, and defined pain-processing circuits. Sex-inclusive designs are essential. A priori primary tissues, CpGs, and behavioral outcomes would reduce selective interpretation.

- *Necessity and Rescue*

The critical experiment is a methylation-specific perturbation during acupuncture. Region- and cell-specific DNMT/TET editing, locus-targeted dCas9 methylation or demethylation, or conditional genetic manipulation should test whether blocking the acupuncture-induced methylation change diminishes analgesia. A rescue experiment should then restore the methylation state and the behavioral phenotype. Enzyme-expression changes alone are insufficient.

- *Within-Subject Mediation and Replication*

When repeated sampling is feasible, individual-level methylation change should be related to individual-level analgesic response using a prespecified mediation model with uncertainty intervals. Candidate loci should be replicated in an independent cohort and validated by targeted bisulfite sequencing. Multiple-testing correction, batch control, cell-composition adjustment, and blinded analysis should be explicit.

- *Clinical Translation*

A clinical trial should randomize people with a defined chronic-pain condition to standardized acupuncture, credible sham acupuncture, and usual-care or active control groups. Clinical pain intensity and interference should be primary outcomes, with blood collected at prespecified time points and, where ethically feasible, cerebrospinal fluid or imaging-linked biomarkers. Peripheral methylation should not be assumed to represent brain tissue; its role may instead be predictive, pharmacodynamic, or immune-mediated. Replication and external validation are necessary before proposing a clinical biomarker.

➢ *Strengths and Limitations of this Review*

Strengths include a reproducible record-level audit trail, explicit separation of direct methylation assays from methylation-machinery evidence, inclusion of negative specificity evidence, and conservative treatment of causality. The main limitations are the use of two overlapping bibliographic sources, absence of Embase, Scopus, Web of Science, and dedicated trial-registry searches, no prospective protocol registration. Language representation depended on indexed metadata.

V. CONCLUSIONS

Preclinical studies indicate that acupuncture analgesia can co-occur with region-specific DNA-methylation remodeling and altered methylation machinery. They do not yet demonstrate that DNA methylation is the causal mediator of analgesia. The only direct TET1/Prox1 mechanistic chain in a pain-comorbidity model was specific to antidepressant persistence rather than nociception, and the DNMT3a/MOR perturbation study lacked direct methylation measurement. With four animal studies, no eligible human study, and substantial risk-of-bias uncertainty, Overall confidence in a causal mediation effect remains very low. The field now needs preregistered, sex-inclusive, sham-controlled experiments combining cell-specific methylome measurement with targeted perturbation, rescue, and formal mediation analysis, followed by carefully designed clinical trials.

REFERENCES

[1]. Benrick, A., Pillon, N. J., Nilsson, E., Lindgren, E., Krook, A., Ling, C., & Stener-Victorin, E. (2020). Electroacupuncture Mimics Exercise-Induced Changes in Skeletal Muscle Gene Expression in Women With Polycystic Ovary Syndrome. The Journal of Clinical Endocrinology and Metabolism, 105(6), 2027–2041. https://doi.org/10.1210/CLINEM/DGAA165

[2]. Campbell, M., McKenzie, J. E., Sowden, A., Katikireddi, S. V., Brennan, S. E., Ellis, S., Hartmann-Boyce, J., Ryan, R., Shepperd, S., Thomas, J., Welch, V., & Thomson, H. (2020). Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. BMJ, 368. https://doi.org/10.1136/BMJ.L6890

[3]. Denk, F., & McMahon, S. B. (2012). Chronic pain: Emerging evidence for the involvement of epigenetics. Neuron, 73(3), 435–444. https://doi.org/10.1016/j.neuron.2012.01.012

[4]. Descalzi, G., Ikegami, D., Ushijima, T., Nestler, E. J., Zachariou, V., & Narita, M. (2015). Epigenetic mechanisms of chronic pain. Trends in Neurosciences, 38(4), 237–246. https://doi.org/10.1016/j.tins.2015.02.001

[5]. Ding, L., Wang, H., Li, Y., Li, J., Li, L., Gao, Y., Guan, J., & Geng, W. (2023). Electroacupuncture stimulating Neixiyan (EX-LE5) and Dubi (ST35) alleviates osteoarthritis in rats induced by anterior cruciate ligament transaction affecting DNA methylation regulated transcription of miR-146a and miR-140-5p. Journal of Traditional Chinese Medicine = Chung i Tsa Chih Ying Wen Pan, 43(5), 983–990. https://doi.org/10.19852/J.CNKI.JTCM.2023.05.004

[6]. Gao, S., Pan, X., Liu, B., Luo, L., Xiong, X., & Yu, S. (2025). [Research Progress in the Mechanisms of Acupuncture in Regulating DNA Methylation]. Sichuan Da Xue Xue Bao. Yi Xue Ban = Journal of Sichuan University. Medical Science Edition, 56(1), 19–25. https://doi.org/10.12182/20250160101

[7]. Hong, H., Jing, X. yue, Liu, S. bao, Peng, Y. jun, & Zhu, B. mei. (2020). Epigenetic Landscape Changes Due to Acupuncture Treatment: From Clinical to Basic Research. Chinese Journal of Integrative Medicine, 26(8), 633–640. https://doi.org/10.1007/S11655-020-2852-X

[8]. Hooijmans, C. R., Rovers, M. M., De Vries, R. B. M., Leenaars, M., Ritskes-Hoitinga, M., & Langendam, M. W. (2014). SYRCLE's risk of bias tool for animal studies. BMC Medical Research Methodology, 14(1). https://doi.org/10.1186/1471-2288-14-43

[9]. Jang, J. H., Lee, Y. J., Ha, I. H., & Park, H. J. (2024). The analgesic effect of acupuncture in neuropathic pain: regulatory mechanisms of DNA methylation in the brain. Pain Reports, 9(6), e1200. https://doi.org/10.1097/PR9.0000000000001200

[10]. Jang, J. H., Song, E. M., Do, Y. H., Ahn, S., Oh, J. Y., Hwang, T. Y., Ryu, Y., Jeon, S., Song, M. Y., & Park, H. J. (2021). Acupuncture alleviates chronic pain and comorbid conditions in a mouse model of neuropathic pain: the involvement of DNA methylation in the prefrontal cortex. Pain, 162(2), 514–530. https://doi.org/10.1097/J.PAIN.0000000000002031

[11]. Kokosar, M., Benrick, A., Perfilyev, A., Nilsson, E., Källman, T., Ohlsson, C., Ling, C., & Stener-Victorin, E. (2018). A Single Bout of Electroacupuncture Remodels Epigenetic and Transcriptional Changes in Adipose Tissue in Polycystic Ovary Syndrome. Scientific Reports, 8(1). https://doi.org/10.1038/S41598-017-17919-5

[12]. Li, Y., Liu, X., Fu, Q., Fan, W., Shao, X., Fang, J., Liu, J. G., & Xu, C. (2023). Electroacupuncture Ameliorates Depression-Like Behaviors Comorbid to Chronic Neuropathic Pain via Tet1-Mediated Restoration of Adult Neurogenesis. Stem Cells, 41(4), 384–399. https://doi.org/10.1093/STMCLS/SXAD007

[13]. Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ, 372. https://doi.org/10.1136/BMJ.N71

[14]. Petitpierre, M., Stenz, L., & Paoloni-Giacobino, A. (2022). Epigenomic Changes after Acupuncture Treatment in Patients Suffering from Burnout. Complementary Medicine Research, 29(2), 109–119. https://doi.org/10.1159/000521347

[15]. Ping, X., Xie, J., Yuan, C., & Jin, X. (2023). Electroacupuncture Induces Bilateral S1 and ACC Epigenetic Regulation of Genes in a Mouse Model of Neuropathic Pain. Biomedicines, 11(4), 1030. https://doi.org/10.3390/BIOMEDICINES11041030/S1

[16]. Rahul R. K.; Aswathy M. "Neuroplastic Effects of Acupuncture in Stroke and Parkinson's Disease: A Narrative Review." Volume. 11 Issue.5, May 2026 International Journal of Innovative Science and Research Technology (IJISRT) 2495-2499 https://doi.org/10.38124/ijisrt/26May1017

[17]. Wang, F., Zhou, C., Xie, C., Wang, H., Li, X., & Zhao, G. (2025). Electroacupuncture alleviates pain-like behaviors through modulating DNMT3a/MOR signaling pathway in CCI rats. PLOS ONE, 20(10), e0334695. https://doi.org/10.1371/JOURNAL.PONE.0334695