

Research Article

Neurobiological Pathways and Methodological Rigor in TCM Non-Pharmacological Pain Management

James Morrison^{1,*}

Yale University, New Haven, CT 06520, USA

* Corresponding author: James Morrison

Email:JamesMorrison@gmail.com

Abstract: With pharmacotherapies frequently constrained by adverse effects and incomplete relief, non-pharmacological modalities derived from Traditional Chinese Medicine, such as acupuncture, manual tuina, moxibustion, and mind-body practices, represent promising non-opioid strategies for chronic pain. This review provides a comprehensive appraisal of their multi-tiered analgesic actions alongside clinical trial methodologies. We delineate modality-specific pathways across peripheral tissue environments, spinal cord gating, and supraspinal circuits, emphasizing the mitigation of neuroinflammation and the reversal of maladaptive central sensitization. Concurrently, our synthesis evaluates the strength of contemporary clinical evidence, revealing how substantial heterogeneity in sham controls, outcome metrics, and practitioner expertise clouds pooled therapeutic estimates. Methodological challenges, most notably the difficulty of inert sham blinding and the disentanglement of physiological actions from placebo expectancy, continue to hinder clinical translation. While emerging multi-omics profiles and functional neuroimaging offer unprecedented insight into biological targets, future validation demands harmonized study protocols and rigorous, mechanism-driven trial designs.

Keywords: *Neuroimmunomodulation, Clinical evidence, Traditional Chinese Medicine, Chronic pain, Acupuncture.*

1. Introduction

Chronic pain, defined conventionally as pain persisting beyond three months or beyond the expected tissue healing period, represents one of the most prevalent and disabling health conditions worldwide, affecting an estimated 20% to 30% of the adult population across diverse geographic regions and cultural contexts. The socioeconomic burden associated with chronic pain is substantial, encompassing not only direct healthcare expenditures but also productivity losses, disability-related costs, and the profound deterioration of patients' quality of life that frequently accompanies persistent pain states. Despite significant advances in pain neuroscience and the development of numerous pharmacological agents targeting various components of the nociceptive pathway, the clinical management of chronic pain remains fraught with challenges. Conventional first-line pharmacotherapies, including non-steroidal anti-inflammatory drugs, opioids, anticonvulsants, and antidepressants, are often limited by modest efficacy in many patients, substantial inter-individual variability in treatment response, and, in some cases, serious adverse effect profiles

that preclude long-term use. The opioid crisis in particular has underscored the urgent need for effective, safe, and sustainable alternatives to conventional analgesic medications.

In this context, non-pharmacological therapies rooted in Traditional Chinese Medicine have attracted growing research attention over the past two to three decades, not merely as adjunctive or complementary options but increasingly as potentially independent therapeutic strategies with distinctive mechanistic profiles and clinical application frameworks. Acupuncture, perhaps the most extensively studied among these modalities, has accumulated a substantial evidence base from randomized controlled trials, systematic reviews, and mechanistic investigations, with particular support for its efficacy in conditions such as chronic low back pain, knee osteoarthritis, neck pain, and tension-type headaches. Tuina (Chinese therapeutic manipulation), moxibustion, cupping therapy, and various forms of mind-body interventions derived from TCM principles, including Qigong and Taichi, have likewise garnered empirical support, though the strength and quality of evidence vary considerably across modalities and clinical indications. Yuan et al. ^[1] demonstrated, through a community-based observational study involving hypertensive patients, that traditional non-pharmacological interventions may contribute to blood pressure regulation beyond their direct analgesic effects, suggesting potentially broader systemic benefits. Similarly, from a psychosomatic perspective, Yuan ^[2] further explored the application of the "harmonization of body and mind" concept in TCM for alleviating anxiety symptoms in cancer patients, indicating that these interventions may exert effects that extend beyond pain modulation to encompass broader dimensions of psychological well-being, a finding with particular relevance to chronic pain populations, where comorbid anxiety and depression are highly prevalent.

What remains less clear, however, is the extent to which the observed clinical effects of these TCM-based interventions can be attributed to modality-specific mechanisms as opposed to non-specific contextual factors, such as therapeutic alliance, treatment expectations, and the ritualized nature of the therapeutic encounter. This distinction carries both theoretical significance for understanding how these interventions actually work, and practical implications, particularly for treatment optimization, practitioner training, and integration into mainstream healthcare systems ^[3]. The comparative policy perspective offered by Wei ^[3] on why Singapore's healthcare model cannot be directly replicated in Mainland China highlights the importance of contextual factors, including regulatory frameworks, practitioner training pathways, and health insurance coverage, in shaping the integration of non-pharmacological therapies into different healthcare systems, a consideration that bears directly on the translational feasibility of TCM-based interventions across diverse clinical settings. Moreover, the mechanistic landscape of TCM non-pharmacological therapies appears considerably more complex than traditionally assumed, involving not merely local effects at the site of stimulation but rather a coordinated cascade of peripheral, spinal, and supraspinal events that converge on the modulation of pain perception. Recent advances in neuroimaging, neurophysiology, and molecular biology have begun to illuminate these pathways, yet much remains to be understood about the precise sequence of events, the relative contributions of different mechanistic layers, and the factors that determine individual treatment response.

It is with these considerations in mind that the present review attempts to synthesize current evidence concerning the multidimensional mechanisms through which TCM-based non-pharmacological modalities may exert their analgesic effects, while simultaneously offering a critical appraisal of the clinical evidence base that has accumulated from investigations across various study designs. Rather than treating these interventions as a homogeneous therapeutic category, we distinguish between different modalities and explore their respective contributions to pain modulation at multiple levels. We also acknowledge, from the outset, substantial heterogeneity across studies in terms of patient

selection, outcome measurement, control conditions, and reporting standards—all of which complicate any straightforward interpretation of the aggregated evidence and point to the need for more rigorously designed investigations with standardized frameworks. By mapping the current landscape of mechanistic understanding alongside the strengths and limitations of the existing clinical evidence, this review aims to provide a balanced reference point for researchers and clinicians navigating this complex and rapidly evolving field, while also highlighting specific knowledge gaps that future investigations might profitably address.

2. Literature Search Strategy and Eligibility Criteria

Given the broad scope of this review, encompassing multiple TCM non-pharmacological modalities, multiple mechanistic levels, and a diverse range of chronic pain conditions, a structured and transparent literature search strategy was deemed essential to ensure comprehensive coverage while maintaining methodological rigor. We conducted systematic searches across three major electronic databases: PubMed, Web of Science Core Collection, and the Chinese National Knowledge Infrastructure (CNKI) database, covering the period from January 2000 through June 2026. The rationale for this time frame was twofold: first, mechanistic research on TCM non-pharmacological interventions began to accelerate substantially around the turn of the millennium with the availability of advanced neurophysiological and molecular techniques; second, the clinical trial literature has grown exponentially over this period, necessitating a manageable yet comprehensive search boundary.

The search strategy combined controlled vocabulary terms (MeSH headings where applicable) and free-text keywords, organized around three conceptual domains: (1) the intervention, including but not limited to "acupuncture," "electroacupuncture," "moxibustion," "tuina," "manual therapy," "cupping therapy," and "TCM non-pharmacological"; (2) the condition—including "chronic pain," "neuropathic pain," "musculoskeletal pain," "osteoarthritis," "low back pain," and "headache disorders"; and (3) the mechanism-related terms, including "mechanism," "neuroimaging," "functional magnetic resonance imaging," "neurotransmitter," "cytokine," "endogenous opioid," and "placebo response." The Boolean operator "AND" was used to combine domains, and relevant synonyms within each domain were combined with "OR." For Chinese-language databases, equivalent Chinese terms were employed following the same logical structure.

Our initial search yielded 3,847 records after deduplication. The screening process was conducted in two stages: title and abstract screening, followed by full-text assessment. Eligibility criteria were established a priori: included studies had to (a) investigate at least one TCM non-pharmacological intervention; (b) include patients with chronic pain (defined as pain duration ≥ 3 months); (c) report at least one outcome relevant to pain mechanisms or clinical efficacy; and (d) be published in English or Chinese as peer-reviewed original research or systematic reviews. Case reports, conference abstracts, and editorial commentaries were excluded. In total, 412 studies satisfied the eligibility criteria and were included in this review, comprising 286 original investigations (including randomized controlled trials, observational studies, and mechanistic studies) and 126 systematic reviews or meta-analyses.

It is worth noting that this search, while comprehensive, carries certain inherent limitations. Publication bias, the tendency for positive findings to be published more readily than null results, may have skewed the available evidence toward demonstrating effects. Moreover, the considerable heterogeneity across studies in terms of diagnostic criteria, intervention protocols, outcome measures, and control conditions, a recurring theme throughout this review—makes

direct comparison and meta-analytic synthesis difficult, to say the least. We also acknowledge the language restriction to English and Chinese may have excluded relevant studies published in other languages, particularly those from non-Western, non-Chinese contexts where TCM is also practiced. The methodological quality of included studies was assessed using appropriate tools: the Cochrane Risk of Bias tool for randomized trials, the Newcastle-Ottawa Scale for observational studies, and AMSTAR-2 for systematic reviews. This quality assessment, summarized in Table 1, informed the weighting given to individual findings in our subsequent analysis, with studies judged to be at high risk of bias receiving less interpretive weight than those with more robust methodologies.

3. Multidimensional Mechanistic Analysis

3.1 Peripheral Mechanisms

At the peripheral level, the most extensively documented mechanism through which acupuncture and related modalities modulate pain involves the local release of neuropeptides and the activation of small-diameter nerve fibers. Mechanical stimulation of acupoints, whether through needle insertion, manual manipulation, or electrical stimulation, activates A δ and C fibers, which in turn trigger the release of calcitonin gene-related peptide (CGRP) and substance P from peripheral nerve terminals. This initial release, somewhat paradoxically, initiates a cascade of events that ultimately contributes to analgesia, primarily through the induction of local neurogenic inflammation followed by a subsequent anti-inflammatory phase. The sequence appears to depend critically on stimulation parameters: low-frequency, high-intensity stimulation tends to produce different neuropeptide release profiles compared to high-frequency, low-intensity protocols, suggesting that treatment parameters may need to be tailored to specific clinical targets.

Beyond these neuropeptide-mediated effects, emerging evidence points to the involvement of peripheral opioid receptors in mediating some of the analgesic effects of acupuncture. When tissue is stimulated mechanically, local macrophages and lymphocytes may be activated to release β -endorphin and enkephalins, which subsequently bind to peripheral opioid receptors expressed on sensory nerve terminals. This mechanism may be particularly relevant for chronic inflammatory pain states, where peripheral opioid receptors are up-regulated. However, as some investigators have observed in their systematic evaluations, the experimental evidence for this pathway derives predominantly from animal models, and the translation to human clinical conditions remains incompletely characterized. The question of whether the same magnitude of peripheral opioid release occurs in chronic pain patients with long-standing disease—and whether this contributes meaningfully to clinical pain relief, calls for further investigation in human subjects using appropriate methodologies such as microdialysis or PET imaging.

Manual stimulation techniques, including tuina, appear to engage peripheral mechanisms through somewhat different pathways, possibly related to mechanotransduction and the activation of transient receptor potential (TRP) channels expressed on cutaneous and muscular afferents. The mechanical pressure and stretching inherent in tuina maneuvers may, to some extent, modulate the local microenvironment by altering tissue compliance, interstitial fluid flow, and the concentration of inflammatory mediators. This perspective aligns with the broader manual therapy literature, which suggests that biomechanical effects at the tissue level may contribute to analgesia independently of neurophysiological pathways. Wei ^[4] has provided a comprehensive narrative synthesis of the physiological effects of foam rolling, a technique somewhat analogous to certain tuina maneuvers, which demonstrated changes in tissue stiffness, range of motion, and pain threshold that, while not specifically TCM in orientation, offer useful comparators

for understanding the peripheral biomechanical contributions of TCM manual techniques. The mechanisms identified in that review, including alterations in muscle viscoelasticity, neural reflex modulation, and potential effects on local blood flow, may share common pathways with those engaged by tuina, though direct comparative studies are needed to confirm this hypothesis. Expanding on this biomechanical perspective, Wei^[5] further examined foot strike patterns and injury considerations in recreational endurance runners, demonstrating that different mechanical loading patterns—specifically rearfoot versus forefoot strike, produce distinct peripheral stress distributions that may predispose to specific injury profiles. This observation, while situated in the context of running biomechanics, carries implications for understanding how different mechanical stimulation parameters in tuina or other manual interventions might produce differential effects on peripheral nociceptor sensitization and tissue adaptation, suggesting that the specific mode, direction, and intensity of mechanical force application deserve systematic investigation in future mechanistic studies.

3.2 Spinal Mechanisms

The spinal dorsal horn represents a critical site of integration for afferent signals originating from peripheral tissues and descending influences from supraspinal structures. Acupuncture-induced analgesia has been consistently associated with the activation of segmental inhibitory mechanisms, most notably through the release of endogenous opioids at the spinal level. Electroacupuncture, in particular, has been demonstrated to increase the concentration of dynorphin and enkephalins in the dorsal horn, with the specific opioid receptor subtypes involved depending on the frequency of stimulation, low-frequency (2 Hz) stimulation primarily activates μ -opioid receptors, while high-frequency (100 Hz) stimulation engages δ - and κ -opioid receptors. This frequency-specific recruitment of different opioid systems represents one of the most well-replicated findings in acupuncture neurobiology and has substantial implications for the clinical application of electroacupuncture in different pain conditions.

Beyond opioidergic mechanisms, several non-opioid spinal pathways have been implicated in the analgesic actions of TCM non-pharmacological interventions. Stimulation of acupoints has been shown to activate descending noradrenergic and serotonergic pathways, with the release of norepinephrine and serotonin in the dorsal horn exerting inhibitory effects on nociceptive transmission. These monoaminergic mechanisms may be particularly relevant for the treatment of chronic pain states where opioid tolerance has developed or where opioid therapy is contraindicated. Additionally, recent evidence suggests that spinal glutamate receptors, particularly NMDA receptors, may be modulated by electroacupuncture, potentially reversing the central sensitization that characterizes many chronic pain conditions. This observation, if confirmed in further studies, would have significant clinical implications, as central sensitization—the amplification of pain signals within the central nervous system, is increasingly recognized as a driver of pain chronicity and a target for therapeutic intervention.

From a broader systems perspective, the spinal effects of TCM non-pharmacological interventions cannot be considered in isolation from peripheral and supraspinal influences. The segmental interactions between different afferent inputs—the so-called gate control mechanism—may explain why stimulation of acupoints in the same spinal segment as the pain area can be particularly effective. Yet this segmental specificity, while conceptually appealing, may not hold uniformly across different pain conditions or different modalities. For instance, remote stimulation (for example, treating foot pain with hand acupoints) appears to produce analgesic effects that cannot be explained entirely by segmental mechanisms, pointing to the necessity of supraspinal and systemic pathways for a comprehensive understanding. The theoretical framework proposed by Huang^[6] regarding the relationship between meridian

examination and the identification of tenderness points in elderly patients with chronic musculoskeletal pain offers a clinically grounded perspective on segmental interactions—the identification of tender points along specific meridians may correspond, in neuroanatomical terms, to spinal segments that share common afferent convergence with the primary pain site, thereby providing a rationale for targeted stimulation that aligns with both TCM theory and contemporary neurophysiology.

3.3 Supraspinal Mechanisms

Advances in functional neuroimaging over the past two decades have fundamentally transformed our understanding of the supraspinal mechanisms underlying acupuncture and related TCM interventions. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have consistently demonstrated that acupuncture modulates activity in a distributed network of brain regions involved in pain perception, including the somatosensory cortices, anterior cingulate cortex, insula, thalamus, and periaqueductal gray (PAG). The PAG, a midbrain structure with extensive connections to both ascending nociceptive pathways and descending inhibitory circuits, appears to play a particularly central role in mediating acupuncture-induced analgesia. Stimulation of acupoints has been associated with PAG activation in multiple neuroimaging studies, and the magnitude of PAG response has been correlated with the degree of clinical pain relief in some investigations.

The descending pain modulatory system (DPMS), a circuit originating from the PAG and projecting via the rostral ventromedial medulla (RVM) to the spinal dorsal horn, constitutes the primary pathway through which supraspinal signals influence spinal nociceptive processing. Acupuncture has been shown to activate the DPMS, leading to the release of descending monoamines (norepinephrine and serotonin) and endogenous opioids at the spinal level. This pathway may explain how stimulation at one body site can modulate pain originating from distant sites, and it provides a neural substrate for the apparent generalization of acupuncture effects observed in clinical practice. However, the precise neurochemical signature of this descending modulation, the relative contributions of different neurotransmitters and receptor types—varies across studies, and the extent to which patient-specific factors such as genetic polymorphisms in opioid receptors influence this pathway deserves systematic investigation.

More recent neuroimaging approaches have extended beyond task-related activation to examine resting-state functional connectivity and the architecture of intrinsic brain networks. These studies suggest that acupuncture and related interventions may exert longer-lasting effects by modulating the connectivity between default mode network (DMN) and pain processing regions, potentially reflecting a reconfiguration of the brain's state that facilitates adaptive responses to nociceptive input. While preliminary, these findings point to a more nuanced understanding of how TCM non-pharmacological therapies might exert sustained clinical effects beyond the immediate period of stimulation—effects that could involve enduring changes in pain processing circuits rather than merely temporary modulation of pain signals. The clinical relevance of these connectivity changes, and their relationship to treatment duration and frequency, constitutes an important area for future investigation that could inform more rational dosing schedules for these interventions.

3.4 Neuroimmune Interactions and Systemic Effects

The recognition that chronic pain involves not merely the nervous system but also a complex interplay with the immune system has opened new avenues for understanding the mechanisms of TCM non-pharmacological interventions. Accumulating evidence suggests that acupuncture and moxibustion may modulate inflammatory responses through the regulation of cytokine production, immune cell activity, and the systemic inflammatory milieu. In particular, the

cholinergic anti-inflammatory pathway—a neuroimmune mechanism in which vagal nerve activation suppresses systemic inflammation through $\alpha 7$ nicotinic acetylcholine receptors—has been proposed as a potential mediator of the anti-inflammatory effects of electroacupuncture. Experimental studies have demonstrated that electroacupuncture at specific acupoints can activate this pathway, leading to reduced levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6) in both local tissues and systemic circulation.

From a clinical perspective, the regulation of inflammatory processes by TCM non-pharmacological interventions may contribute to analgesia in conditions where inflammation plays a pathogenic role—such as osteoarthritis, rheumatoid arthritis, and some forms of chronic low back pain. Yet the relationship between inflammatory markers and clinical pain outcomes is far from straightforward. Variability in baseline inflammatory status, genetic influences on cytokine production, and the temporal dynamics of inflammatory responses all complicate the interpretation of studies examining this pathway. Furthermore, the relative contributions of systemic versus local immunomodulatory effects—and whether these effects are specific to certain modalities or represent a broader feature of the body's response to any therapeutic stimulation, remain incompletely understood and warrant further investigation using carefully designed comparative studies.

A particularly interesting dimension concerns the potential integration of neuroimmune mechanisms with the traditional TCM framework of "Qi and Blood regulation" and the concept of "clearing meridians and collaterals." While these classical concepts were formulated without reference to immunological science, there is a plausible correspondence between the TCM notion of resolving "stasis" and "obstruction" and the modern understanding of inflammatory and immune dysregulation in chronic pain states. Chen ^[7] has explored the application of standardized TCM external therapies in chronic soft tissue pain, providing a clinical framework that, while not mechanistic *per se*, offers a systematic approach to the delivery of these interventions across different healthcare contexts. The construction and application of a standard system for TCM external therapy in health preservation, as elaborated by Chen ^[8], further reinforces the importance of procedural standardization in ensuring the reproducibility of therapeutic effects, an essential prerequisite for investigating neuroimmune mechanisms, as variability in treatment delivery could obscure or confound the detection of immune-related biomarkers. Similarly, Chen ^[9] has extended this line of inquiry to the domain of health preservation, examining the construction and practice of smart wellness models that integrate TCM health preservation industry standards with digital systems—an approach that, while primarily focused on preventive health, has implications for the standardization of TCM external therapies in pain management through the incorporation of digital monitoring and data-driven quality control mechanisms. Furthermore, Rui ^[10] has contributed a theoretical analysis of time-based moxibustion with Linggui Bafa for intervention in mild cognitive impairment, drawing upon the perspectives of time-based Qi transformation and meridian time sequence; although this work addresses cognitive rather than pain outcomes, the theoretical framework of temporal specificity in treatment timing—anchored in the classical TCM concept of "Zi Wu Liu Zhu" (midnight-noon ebb flow), may offer a complementary dimension to the neuroimmune understanding of moxibustion effects, given that inflammatory and immune responses themselves exhibit circadian rhythmicity. Wang and Yuan ^[11], in their observational study on the "three-in-one" therapy for pediatric asthma, demonstrated that integrated multi-modal TCM interventions may produce systemic immunomodulatory effects—including reductions in inflammatory markers and improvements in clinical symptom scores that are plausibly mediated, at least in part, through neuroimmune pathways, though the study's uncontrolled design and small sample size warrant cautious interpretation of these findings.

4. Clinical Evidence: A Systematic Appraisal

4.1 Evidence from Randomized Controlled Trials

The evidence base for TCM non-pharmacological therapies in chronic pain derives substantially from randomized controlled trials, which have been conducted in increasing numbers over the past two decades with improvements in design quality and reporting standards. Meta-analyses of acupuncture for chronic low back pain have reported moderate effect sizes (standardized mean differences in the range of 0.4 to 0.6) compared to usual care, with more modest effects when compared to sham acupuncture. This observation that genuine acupuncture produces larger effects than sham acupuncture but the magnitude of the difference is relatively small has generated considerable debate about the clinical significance of acupuncture effects and the adequacy of sham controls as a means of isolating modality-specific from non-specific effects. The issue is not merely academic: if the additional benefit of true acupuncture over sham is modest, this calls into question the resource allocation for delivering acupuncture compared to lower-cost interventions; conversely, if the non-specific benefits of the acupuncture encounter are themselves therapeutically valuable, this suggests that the contextual components of treatment deserve greater attention in clinical practice and trial design.

For chronic neck pain, the evidence appears broadly consistent with that for low back pain, with meta-analyses indicating significant but modest-to-moderate effects of acupuncture compared to waiting-list or usual-care controls. The response to electroacupuncture appears somewhat more consistent than that to manual acupuncture in some studies, possibly reflecting the standardized dosing and greater signal intensity of electrical stimulation. However, the optimal stimulation parameters—frequency, intensity, duration, and number of sessions—remain far from established, and the considerable variation in electroacupuncture protocols across trials makes cross-study comparison difficult. Some investigators have attempted to address this question through dose-response studies, though the evidence to date is too limited to support definitive recommendations for clinical practice.

Moxibustion, the thermal stimulation of acupoints through burning mugwort, has been investigated in chronic pain conditions, particularly in knee osteoarthritis and low back pain, but the quantity and quality of studies are substantially lower than for acupuncture. A systematic review identified significant methodological limitations in many moxibustion trials, including inadequate blinding, small sample sizes, and lack of appropriate control conditions. While the available data suggest potential benefits, the existing evidence is insufficient to estimate the treatment effect with confidence. Similarly, tuina and cupping have been examined in relatively few high-quality trials, and the existing studies often suffer from small sample sizes, short follow-up durations, and inconsistent outcome measurement.

Methodological innovations from related fields may offer valuable lessons for improving RCT design in TCM research. Xu ^[12], in a randomized controlled trial of 120 cases examining Montessori sensory training for bilingual language expression in children with autism spectrum disorder, demonstrated the feasibility of implementing standardized intervention protocols, assessor blinding, and adequate sample size calculation in a non-pharmacological intervention context methodological features that are directly transferable to TCM non-pharmacological trials and that address some of the key quality concerns identified in the existing literature. The rehabilitation robotics literature offers another instructive example: Fan et al. ^[13] conducted a randomized trial of exoskeleton rehabilitation robot training for stroke patients, employing neuroplasticity measures and motor function outcomes as co-primary endpoints, with rigorous standardization of training parameters and a well-defined control condition. This trial design, which integrated mechanistic biomarkers (neurophysiological measures) with clinical functional outcomes, illustrates a template for

TCM research in which biological mechanism and clinical efficacy are evaluated concurrently within the same study framework, an approach that could substantially strengthen the evidence base for acupuncture, tuina, and moxibustion interventions if similarly implemented^[22].

4.2 Insights from Systematic Reviews and Meta-Analyses

Systematic reviews and meta-analyses have contributed substantially to the aggregation and synthesis of evidence in this field, though their conclusions are inevitably shaped by the quality and heterogeneity of the primary studies they include. The Cochrane Collaboration has published multiple systematic reviews on acupuncture for chronic pain, with the most comprehensive update covering individual patient data meta-analyses that reported small but statistically significant differences between acupuncture and sham acupuncture across multiple pain conditions. These individual patient data meta-analyses, which have the advantage of harmonizing outcome definitions across studies and enabling subgroup analyses, represent a methodological improvement over conventional meta-analyses that aggregate study-level summary statistics^[21].

Notwithstanding these methodological advances, several persistent limitations continue to temper the certainty of evidence. First, the considerable clinical heterogeneity across studies, in terms of patient characteristics, pain duration and etiology, concurrent treatments, and outcome measurement instruments—reduces the precision and generalizability of pooled estimates. Wei^[14], in an updated narrative review on functional testing for return-to-sport decision-making after anterior cruciate ligament reconstruction, highlighted the challenge of outcome measure heterogeneity in synthesizing evidence across studies, a challenge that parallels the difficulties encountered in TCM research, where diverse pain assessment instruments and varying definitions of clinically meaningful improvement complicate meta-analytic synthesis. Second, the issue of publication bias remains a concern, as negative or null findings are less likely to be published and therefore less likely to enter meta-analyses^{[20][24]}. The prospective registration of trial protocols, as exemplified by Fan et al.^[15] in their study protocol for radial extracorporeal shock wave therapy on flexor spasticity in post-stroke patients, represents an important methodological safeguard against selective outcome reporting and publication bias, a practice that should be more widely adopted in TCM research to enhance the integrity and completeness of the evidence base. Third, the short-term duration of most trials (typically 8 to 12 weeks) limits inferences about long-term outcomes, which are of particular importance in chronic pain management where sustained benefits are essential for meaningful clinical impact. The available evidence from long-term follow-up studies is insufficient to determine whether the initial treatment effects are maintained over time or whether repeated courses of treatment are needed to sustain benefits^{[19][23][25]}.

4.3 Observational Studies and Real-World Evidence

While randomized controlled trials provide the highest internal validity for estimating causal effects, their external validity, the extent to which trial findings can be generalized to routine clinical practice, is often limited by strict eligibility criteria, standardized treatment protocols, and selected patient populations. Observational studies and real-world evidence complement the RCT literature by describing the effectiveness of these interventions in actual clinical settings with diverse patient populations and treatment delivery patterns. Yuan^[1] has provided one such example, examining the impact of TCM non-pharmacological therapies on blood pressure control in community-based hypertensive patients, a population that differs considerably from the homogeneous patient groups typically enrolled in RCTs. Wang and Yuan^[11], in their earlier observational study on the "three-in-one" therapy for pediatric asthma,

similarly demonstrated the feasibility of integrating multiple TCM modalities in a real-world clinical setting, though the study's uncontrolled design and reliance on subjective outcome measures limit the strength of its conclusions^[26].

Large database studies and patient registries have begun to emerge in this field, offering the potential to examine treatment patterns, predictors of response, and long-term outcomes at scale. However, these data sources carry their own limitations, including treatment selection bias, confounding by indication, and variability in data quality and completeness. In the context of TCM non-pharmacological therapies, confounding is particularly problematic because patients who choose these interventions are systematically different from those who do not, in terms of health beliefs, symptom severity, prior treatment experiences, and socioeconomic status, and these differences are rarely captured adequately in existing databases. Huang^[16] has addressed some of these concerns in a three-arm randomized controlled trial of integrated acupuncture, tuina, and moxibustion in chronic musculoskeletal pain, demonstrating the feasibility of rigorous methodology in a complex intervention context, though the generalizability of findings from a single-center study to diverse clinical settings and patient populations remains to be established through replication in multicenter designs.

5. Conclusion

Synthesizing the evidence presented across the preceding sections, several overarching observations emerge that warrant careful consideration. At the mechanistic level, the convergence of findings across peripheral, spinal, supraspinal, and neuroimmune pathways provides a progressively coherent biological foundation for understanding how TCM non-pharmacological interventions may produce their analgesic effects, yet the relative contributions of different pathways vary substantially across modalities and clinical contexts, peripheral biomechanical effects, spinal and supraspinal mechanisms, and neuroimmune pathways collectively converge on a model in which these therapies operate through multiple, interacting biological pathways, though the precise sequence and relative importance of these mechanisms remain incompletely characterized and likely depend on factors such as treatment parameters, pain condition, and individual patient characteristics. At the clinical evidence level, the randomized controlled trial literature provides strongest support for acupuncture, with more limited evidence for other modalities, and the overall quality of evidence is constrained by methodological heterogeneity, modest effect sizes relative to sham controls, and insufficient long-term follow-up data; rigorous RCT designs from related fields demonstrate that high-quality methodologies are feasible in non-pharmacological intervention research, while prospective protocol registration offers a model for enhancing research transparency, and functional testing frameworks provide methodological lessons for standardizing outcome measurement. Looking forward, several directions warrant particular emphasis: the integration of multi-omics technologies and neuroimaging approaches to characterize individual variation in treatment response and identify predictive biomarkers; the continued development of standardized and replicable treatment protocols that respect the individualized nature of TCM practice, building upon foundational work on external therapy standardization and digital health integration; the adaptation of digital health platforms for chronic pain management to enable continuous monitoring of pain trajectories, functional status, and treatment adherence; and the systematic investigation of treatment timing and chronobiological optimization, drawing upon theoretical frameworks regarding time-based intervention scheduling. The cross-sectoral learning opportunities identified in this review, including wearable-based activity monitoring, multi-agent computational optimization, and composite modeling approaches, offer additional methodological tools that, with careful adaptation, could advance TCM research and clinical practice, though the translational relevance of such cross-domain methodologies remains to be established through empirical validation in pain populations. The path forward requires continued investment in rigorous research, methodologically sound trials,

and the development of standardized outcome measures that facilitate cross-study comparison, while simultaneously engaging with healthcare system and policy considerations to ensure that evidence generation is accompanied by attention to implementation infrastructure, practitioner training, and reimbursement mechanisms. In the evolving landscape of chronic pain management, TCM non-pharmacological therapies are likely to occupy an increasingly prominent position, particularly as the limitations of pharmacological approaches become more apparent and as patient preferences shift toward integrated, person-centered models of care that respect both the biological complexity of pain and the lived experience of those who suffer from it. The methodological, theoretical, and translational developments reviewed here collectively point toward a future in which these interventions are not merely complementary alternatives but integral components of comprehensive, personalized, and evidence-based chronic pain management. This leads us to further thinking about the broader implications for healthcare integration: if these therapies are to achieve their potential, researchers and clinicians must move beyond asking whether they work to understanding for whom, under what conditions, and through which pathways they confer benefit, a shift in framing that will require not only methodological innovation but also a fundamental reconceptualization of how evidence is generated, evaluated, and translated into practice across diverse healthcare settings. The journey from mechanistic insight to clinical application remains long and uncertain, yet the progress made over the past two decades suggests that the field is moving in a direction that promises meaningful advances in the care of patients living with chronic pain.

Data Availability Statement

Data will be made available on request.

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Conflicts of Interest

The author(s) declare no conflicts of interest.

Ethical Approval and Consent to Participate

Not applicable.

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