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Narrative Review

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Wet-Cupping Therapy (Hijama), Systemic Homeostasis, and Evidence for Inflammatory and Neuroimmune Modulation: A Narrative Review

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ABSTRACT

Wet-cupping therapy (Hijama) is a traditional therapeutic intervention that has gained increasing scientific interest because of its potential immunomodulatory, anti-inflammatory, and physiological effects. Emerging evidence suggests that wet-cupping therapy may influence inflammatory pathways, oxidative stress, microcirculation, and neuroimmune interactions, although the underlying biological mechanisms remain incompletely understood. This narrative review summarizes the current evidence on the physiological mechanisms and clinical implications of wet-cupping therapy by evaluating studies published between January 2015 and March 2025 identified through searches of PubMed, PubMed Central (PMC), and Scopus. Eligible publications included clinical trials, observational studies, systematic reviews, meta-analyses, and mechanistic investigations, and the available evidence was qualitatively synthesized. Current findings indicate that wet-cupping therapy may modulate immune responses through regulation of pro-inflammatory cytokines, reduce oxidative stress by improving antioxidant status, enhance local microcirculation, and influence neuroimmune pathways through autonomic nervous system modulation. Clinical studies have also reported improvements in pain, inflammatory markers, metabolic parameters, and patient-reported quality of life across several chronic conditions. However, the available evidence remains heterogeneous because of variations in study design, sample size, treatment protocols, and outcome measures. Overall, wet-cupping therapy appears to exert complementary physiological effects through interconnected immune, vascular, oxidative, and neuroimmune mechanisms. Nevertheless, robust randomized controlled trials and mechanistic studies are required to establish standardized treatment protocols and confirm its long-term clinical efficacy and safety.

Key-words: Heliothis armigera, Argemone mexicana, Ethanol, acetone, Epithelial lining, Epithelial cells, vacuoles, Gut lining, Gut wall

INTRODUCTION

Wet-cupping therapy, commonly known as Hijama, is an ancient therapeutic practice that has been used for centuries in traditional medical systems across the Middle East, Asia, and parts of Europe.

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The procedure involves the application of negative pressure using suction cups, followed by superficial skin scarification to facilitate the removal of a small quantity of blood from the superficial circulation. [1]

Traditionally, wet-cupping therapy has been employed for pain relief and the management of various chronic conditions, including musculoskeletal disorders, inflammatory diseases, and metabolic disturbances. [2] In recent years, growing scientific interest has shifted toward understanding its underlying biological mechanisms. Emerging evidence suggests that wet-cupping therapy may modulate inflammatory pathways, reduce oxidative stress, regulate immune responses, and

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influence autonomic nervous system activity, thereby contributing to systemic physiological homeostasis. [3,4]

Experimental and clinical studies have proposed that the mechanical stimulation generated during cupping enhances local microcirculation, promotes neurovascular responses, and facilitates the clearance of inflammatory mediators. [5] In addition, biochemical investigations have demonstrated alterations in inflammatory cytokines, oxidative stress markers, and immune mediators following wet-cupping therapy, supporting its potential immunomodulatory and antioxidant effects. [6,7]

More recently, attention has focused on the role of wet-cupping therapy in neuroimmune regulation. Mechanical stimulation of the skin and underlying tissues may activate cutaneous sensory nerve fibers, triggering autonomic and neuroendocrine responses that interact with immune signaling pathways. [8] These interconnected mechanisms may contribute to the therapeutic benefits reported in chronic inflammatory and pain-related conditions.

The aim of this narrative review is to summarize the current evidence on the physiological mechanisms, clinical implications, and existing research gaps related to wet-cupping therapy, with particular emphasis on its immunological, oxidative, vascular, and neuroimmune effects.

A narrative literature review was conducted to evaluate the current evidence regarding the physiological mechanisms and clinical implications of wet-cupping therapy (Hijama). A comprehensive search of the published literature was performed using PubMed, PubMed Central (PMC), and Scopus to identify relevant studies published between January 2015 and March 2025. The search strategy incorporated combinations of the following keywords and Medical Subject Headings (MeSH), where applicable: *"wet cupping therapy," "Hijama," "cupping therapy," "immune modulation," "inflammation," "oxidative stress," "neuroimmune interaction," and "autonomic nervous system"*. [3,9]

The review included randomized controlled trials, observational clinical studies, systematic reviews, meta-analyses, and experimental or mechanistic investigations that evaluated the physiological effects or clinical outcomes associated with wet-cupping therapy. Studies focusing on immunological, inflammatory, oxidative stress, vascular, neurophysiological, and neuroimmune mechanisms were given particular emphasis. Publications published before 2015, non-English articles without accessible abstracts, conference abstracts, editorials, and studies lacking relevant physiological or clinical outcome data were excluded.

To ensure comprehensive coverage of the available evidence, the reference lists of eligible articles were manually screened to identify additional relevant publications not retrieved during the initial database search. [3,10] The selected literature was qualitatively synthesized to summarize the proposed biological mechanisms, therapeutic applications, and current research gaps related to wet-cupping therapy.

The literature search identified experimental studies, randomized controlled trials, observational studies, systematic reviews, and meta-analyses evaluating the physiological and clinical effects of wet-cupping therapy (Hijama). Collectively, the available evidence suggests that wet-cupping therapy may influence multiple interconnected physiological pathways, including immune modulation, inflammatory regulation, oxidative stress reduction, enhancement of microcirculation, and neuroimmune signaling. Several studies also reported improvements in clinical outcomes such as pain severity, inflammatory biomarkers, metabolic parameters, and patient-reported quality of life, although the magnitude of these effects varied across studies.

Physiological Mechanisms of Wet-Cupping Therapy

The therapeutic effects of wet-cupping therapy (Hijama) have been attributed to multiple interconnected physiological mechanisms involving immune modulation, inflammatory regulation, oxidative stress reduction, microcirculatory enhancement, and neuroimmune interactions. Current evidence from experimental and clinical studies suggests that these biological pathways may collectively contribute to its reported therapeutic benefits. A summary of the selected clinical and observational studies published between 2015 and 2025 is presented **in** Table 1, while the proposed physiological mechanisms are illustrated in Fig. 1**.** The major biological mechanisms are further summarized in Table 2**,** and the proposed neuroimmune pathways activated by wet-cupping therapy are depicted in Fig. 2. The following sections discuss each of these mechanisms in detail.

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Table 1: Summary of clinical studies investigating the physiological effects of wet-cupping therapy (2015–2025)

Year	Study Focus	Population	Key Findings
2015	Hijama in autoimmune diseases	Autoimmune patients	Reduction in inflammatory mediators
2016	Systematic review of cupping therapy	Multiple populations	Evidence of benefits but limited RCTs
2018	Heavy metal removal	Healthy volunteers	Reduction in selected heavy metals
2019	Oxidative stress markers	Adult subjects	Improved antioxidant status
2022	Chronic disease outcomes	Chronic disease patients	Improved symptoms and quality of life
2024	Hematological parameters	Clinical cohort	Changes in immune and blood parameters

Legend: *This table summarizes selected clinical and observational studies published between 2015 and 2025 that investigated the physiological and clinical effects of wet-cupping therapy (Hijama). The studies include diverse populations and evaluated outcomes such as inflammatory markers, oxidative stress parameters, hematological indices, and patient-reported clinical improvements. Although many studies reported beneficial outcomes, the heterogeneity in study design, sample size, and treatment protocols highlights the need for larger and more rigorously designed randomized controlled trials to establish definitive clinical efficacy.*

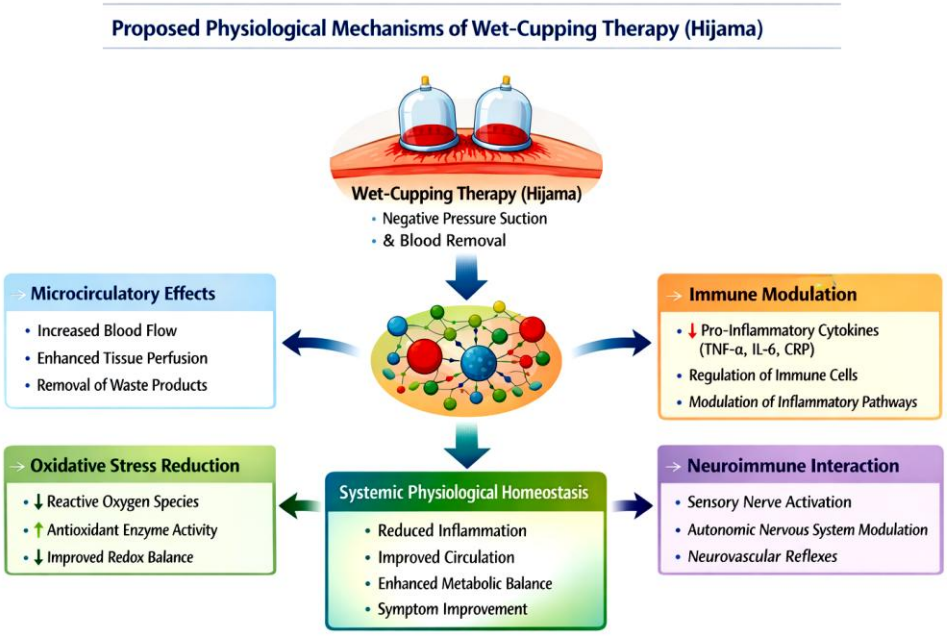

Fig. 1: Proposed physiological mechanisms underlying wet-cupping therapy (Hijama).

Legends- *Wet-cupping therapy involves the application of negative pressure through suction cups followed by superficial scarification and removal of a small quantity of blood from the superficial circulation. The mechanical stimulation produced during cupping may enhance local microcirculation and activate cutaneous sensory receptors. These processes may subsequently influence inflammatory signaling pathways, oxidative stress balance, and immune cell activity. Additionally, stimulation of sensory nerves may trigger autonomic nervous system responses and neuroimmune interactions. Collectively, these physiological effects may contribute to systemic homeostasis through reduction of inflammation, improvement of circulation, and regulation of metabolic and immune processes.*

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Table 2: Proposed biological mechanisms underlying the therapeutic effects of wet-cupping therapy

Mechanism	Physiological Effect
Immune modulation	Regulation of cytokines and immune cell activity
Anti-inflammatory effect	Reduction of pro-inflammatory mediators
Oxidative stress regulation	Increased antioxidant capacity
Microcirculatory effects	Improved local blood flow
Neuroimmune interaction	Activation of sensory nerves and autonomic responses

Legend: *This table outlines the major physiological mechanisms that have been proposed to explain the therapeutic effects of wet-cupping therapy based on findings from experimental and clinical studies. These mechanisms include immune modulation, anti-inflammatory effects, regulation of oxidative stress pathways, improvements in microcirculation, and neuroimmune interactions mediated through autonomic nervous system activity. The integration of these pathways may contribute to systemic physiological homeostasis and symptom improvement in certain clinical conditions.*

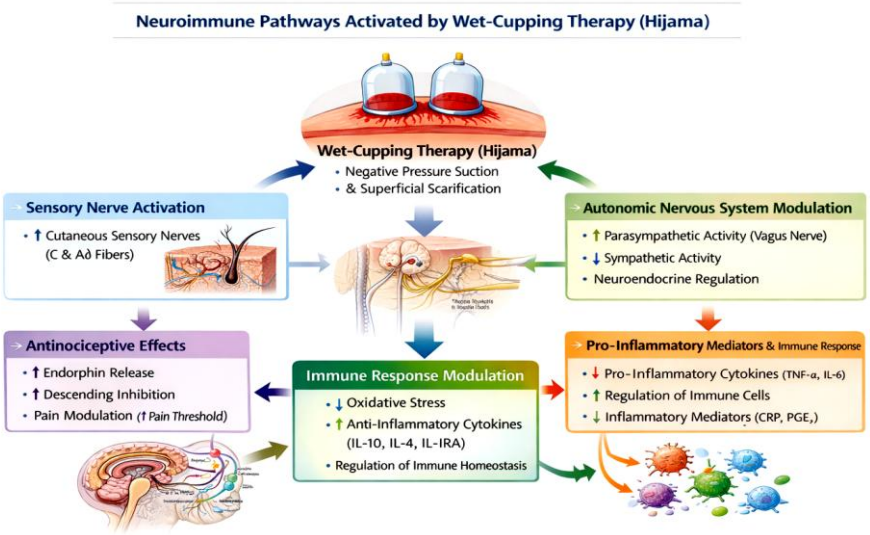

Fig. 2: Neuroimmune pathways activated by wet-cupping therapy.

Legends- *Mechanical stimulation of the skin during wet-cupping therapy may activate cutaneous sensory nerve fibers, including C-fibers and A-delta fibers. Activation of these neural pathways can transmit signals to the spinal cord and higher central nervous system centers, leading to modulation of autonomic nervous system activity. Increased parasympathetic activity and reduced sympathetic tone may influence neuroendocrine responses and inflammatory signaling pathways. These neuroimmune interactions may result in modulation of cytokine production, reduction of oxidative stress, and enhancement of anti-inflammatory mechanisms, contributing to pain modulation and systemic physiological regulation.*

Immune Modulation

Immune modulation is considered one of the principal mechanisms underlying the therapeutic effects of wet-cupping therapy (Hijama). Experimental and clinical studies suggest that Hijama may influence both innate and adaptive immune responses by regulating immune cell activity and cytokine production, thereby promoting immunological homeostasis. Reductions in pro-inflammatory mediators and improvements in immune function have been reported following treatment, supporting its potential role as an adjunctive therapy for chronic inflammatory and autoimmune disorders. [3,6,11–13]

Anti-inflammatory Effects

Chronic inflammation contributes to the pathogenesis and progression of numerous diseases, including musculoskeletal, metabolic, rheumatic, and autoimmune disorders. Emerging evidence indicates that wet-cupping therapy may attenuate inflammatory responses through modulation of inflammatory signaling pathways, suppression of pro-inflammatory mediators, and enhancement of local tissue perfusion. These anti-inflammatory effects may help alleviate disease activity, reduce symptom severity, and improve overall clinical outcomes. [3,6,11-14]

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Oxidative Stress Regulation

Oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) generation and antioxidant defense mechanisms, plays a critical role in cellular injury and chronic disease progression. Several studies have demonstrated that wet-cupping therapy may enhance endogenous antioxidant capacity while reducing oxidative damage, thereby restoring redox homeostasis. These effects may contribute to cellular protection, attenuation of oxidative injury, and improvement of physiological function. [7,9,14,15]

Microcirculatory and Hemodynamic Effects

The application of negative pressure during wet-cupping therapy may improve local microcirculation by increasing blood flow and enhancing tissue perfusion. Improved microvascular function facilitates oxygen and nutrient delivery while promoting the clearance of inflammatory mediators and metabolic waste products from affected tissues. Collectively, these hemodynamic changes may support tissue repair, accelerate recovery, and contribute to the therapeutic benefits observed in various chronic conditions. [4,5,15–17]

Neurovascular Reflex Mechanisms

Mechanical stimulation of the skin and underlying tissues during wet-cupping therapy activates cutaneous sensory receptors, initiating neurovascular reflexes that influence both local and systemic physiological responses. These neural reflex pathways may modulate vascular tone, autonomic nervous system activity, and regional blood flow, thereby contributing to pain relief and regulation of inflammatory processes. Such neurovascular mechanisms provide a biologically plausible explanation for several of the systemic effects attributed to Hijama.[4,5,16,17]

Cytokine Regulation and Inflammatory Pathways

Cytokines are key mediators of immune and inflammatory responses and play a pivotal role in the development of chronic inflammatory diseases. Wet-cupping therapy has been associated with reductions in circulating levels of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP), suggesting modulation of inflammatory signaling pathways. Regulation of these biomarkers may represent an important mechanism through which Hijama exerts its immunomodulatory and anti-inflammatory effects.[3,6,11,12,18]

Neuroimmune Interactions

The nervous and immune systems interact through complex bidirectional pathways that regulate inflammation and maintain physiological homeostasis. Wet-cupping therapy may stimulate cutaneous sensory nerve fibers, leading to activation of autonomic and neuroendocrine pathways that influence immune function and inflammatory signaling. These neuroimmune interactions may contribute to pain modulation, suppression of systemic inflammation, enhancement of tissue repair, and restoration of physiological balance, thereby supporting the broader therapeutic effects of Hijama. [5,16–20]

Integration of Current Evidence

The evidence reviewed in this narrative synthesis suggests that wet-cupping therapy (Hijama) exerts its therapeutic effects through multiple interconnected physiological pathways rather than a single isolated mechanism. Experimental and clinical studies consistently indicate that Hijama may modulate inflammatory responses, attenuate oxidative stress, enhance microcirculatory function, and regulate neuroimmune interactions. Collectively, these mechanisms provide a biologically plausible explanation for the clinical improvements reported in chronic musculoskeletal pain, rheumatic disorders, metabolic diseases, and other chronic inflammatory conditions. [3,11–20]

Biological Mechanisms and Clinical Implications

Among the proposed mechanisms, immune modulation appears to be one of the most consistently reported findings. Several studies have demonstrated reductions in pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP), suggesting that wet-cupping therapy may suppress inflammatory signaling pathways involved in the pathogenesis of chronic diseases. [3,6,11,12] Concurrent improvements in oxidative stress biomarkers indicate enhanced antioxidant defenses and reduced reactive oxygen species, supporting restoration of cellular redox homeostasis. [7,9,14,15]

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Another important aspect is the interaction between neurovascular and neuroimmune pathways. Mechanical stimulation of the skin during cupping therapy may activate cutaneous sensory receptors, initiating neural reflexes that influence autonomic nervous system activity. Enhanced parasympathetic activity, together with improved local microcirculation, may facilitate tissue perfusion, promote clearance of inflammatory metabolites, and contribute to pain modulation and tissue repair. [4,5,16,17] Although these mechanisms have not been fully elucidated, they provide a physiologically plausible framework linking local mechanical stimulation with systemic biological responses. Collectively, these findings support the potential role of wet-cupping therapy as a complementary intervention capable of influencing immune, vascular, oxidative, and neurophysiological processes.

Table 3: Clinical conditions investigated in studies evaluating wet-cupping therapy and their reported outcomes

Condition	Reported Outcomes
Chronic pain disorders	Reduction in pain intensity and improvement in pain tolerance
Rheumatic diseases	Decrease in inflammatory symptoms and improvement in joint function
Metabolic disorders	Improvement in metabolic parameters including glucose and lipid profiles
Autoimmune diseases	Reduction in inflammatory activity and modulation of immune responses
Chronic fatigue syndrome	Improvement in fatigue severity and overall quality of life

Legend- *This table summarizes selected clinical conditions in which wet-cupping therapy (Hijama) has been investigated as a complementary therapeutic intervention. Reported outcomes from clinical and observational studies include reductions in pain severity, improvements in inflammatory and metabolic markers, modulation of immune responses, and enhancement of patient-reported quality of life. Although these findings suggest potential therapeutic benefits, further well-designed randomized controlled trials are required to establish the clinical efficacy and safety of wet-cupping therapy in these conditions.*

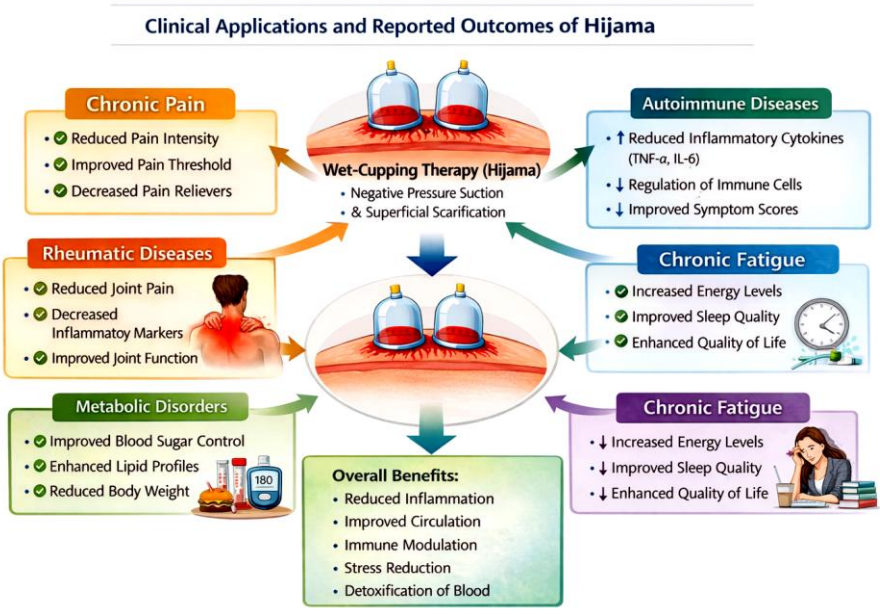

Fig. 3: Clinical applications and reported outcomes of wet-cupping therapy (Hijama).

Legends- *Clinical studies have explored the potential therapeutic applications of wet-cupping therapy across several conditions, including chronic pain disorders, rheumatic diseases, metabolic disturbances, autoimmune diseases, and chronic fatigue syndromes. Reported outcomes from clinical and observational studies include reductions in pain intensity, improvements in inflammatory markers, enhanced metabolic parameters, and improved patient-reported quality of life. Although these findings suggest potential benefits of wet-cupping therapy as a complementary treatment, the clinical evidence remains heterogeneous and further well-designed randomized controlled trials are required to confirm its therapeutic efficacy and establish standardized treatment protocols.*

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Current Evidence, Research Gaps, and Future Perspectives

Despite these promising findings, the current evidence should be interpreted cautiously. Considerable heterogeneity exists across published studies with respect to study design, participant characteristics, cupping techniques, treatment frequency, outcome measures, and duration of follow-up. In addition, many investigations are limited by relatively small sample sizes, methodological shortcomings, and inadequate standardization of treatment protocols, limiting direct comparisons and reducing the overall strength of the available evidence. [3,10]

Although the biological plausibility of wet-cupping therapy is increasingly supported, definitive conclusions regarding its clinical efficacy and underlying mechanisms cannot yet be established. Future research should prioritize adequately powered randomized controlled trials employing standardized treatment protocols, validated clinical outcome measures, and longer follow-up periods. Furthermore, mechanistic investigations incorporating molecular biomarkers, advanced imaging techniques, and neurophysiological assessments are needed to better characterize the interactions among immune regulation, oxidative stress, autonomic function, and neuroimmune signaling. Such studies will be essential for defining the role of wet-cupping therapy within evidence-based complementary and integrative medicine.

STRENGTHS

This narrative review provides a comprehensive synthesis of the current evidence regarding the physiological mechanisms underlying wet-cupping therapy by integrating findings from experimental studies, clinical trials, systematic reviews, and mechanistic investigations published over the past decade. Unlike reviews that primarily focus on clinical efficacy, the present review examines multiple biological domains including immune modulation, oxidative stress regulation, microcirculatory changes, and neuroimmune interactions to provide a broader understanding of the potential mechanisms underlying the therapeutic effects of Hijama. The inclusion of summary tables and illustrative figures further enhances the clarity and accessibility of the available evidence.

LIMITATIONS

Despite the increasing volume of research on wet-cupping therapy, several limitations remain within the current literature. Many available studies involve relatively small sample sizes and lack rigorous randomized controlled trial designs. Considerable heterogeneity in patient populations, cupping techniques, treatment frequency, cup placement, duration of therapy, and outcome measures further limits direct comparison across studies. In addition, many mechanistic findings are derived from experimental or observational research rather than high-quality clinical trials. These limitations highlight the need for standardized treatment protocols and more robust translational and clinical research before definitive conclusions regarding the effectiveness and mechanisms of wet-cupping therapy can be drawn.

CONCLUSIONS

Evidence from recent studies suggests that wet-cupping therapy may exert physiological effects through modulation of immune responses, reduction of inflammatory mediators, regulation of oxidative stress pathways, and activation of neuroimmune mechanisms. Although these findings provide preliminary support for the biological plausibility of Hijama as a complementary therapeutic approach, further high-quality clinical trials and mechanistic studies are necessary to establish standardized treatment protocols and confirm long-term clinical effectiveness. Future interdisciplinary research integrating clinical trials, molecular biomarkers, and neurophysiological assessments will be essential to further elucidate the therapeutic mechanisms and establish the clinical relevance of wet-cupping therapy.

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