Explore Medical Science and Global Health; Vol.3; 2026
E-ISSN: 3079-1790 P-ISSN: 3079-1782
DOI: https://doi.org/10.70267/emsgh.v3.141151
Published by: Zeus Press

Mechanisms of Traditional Chinese Medicine Enema Therapy in the Treatment of Atopic Dermatitis: A Gut–Skin Axis Perspective

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Abstract

Atopic dermatitis (AD) is closely associated with dysbiosis of the gut microbiota. Based on the "gut–skin axis" theory, this review comprehensively examines the mechanisms underlying traditional Chinese medicine (TCM) enema therapy in AD. Gut dysbiosis, intestinal barrier disruption, and depletion of microbial metabolites can activate systemic immunity, driving Th2/Th17 polarization and elevated IgE levels. Integrated with TCM principles of "intestinal damp–heat" and "spleen deficiency with dampness excess," TCM enema administration achieves high local rectal concentrations through rectal delivery, exerting therapeutic effects via multidimensional mechanisms: remodeling the gut microbiota, repairing the intestinal barrier (upregulating ZO-1/Occludin), inducing regulatory T cell (Treg) differentiation, suppressing systemic inflammation through TLR4/NF-κB and vagus nerve pathways, and modulating the neuro–endocrine–immune network to alleviate the itch–anxiety cycle. Compared with the limitations and adverse effects of conventional Western therapies, TCM enema represents a "treating the gut to modulate the skin" strategy that demonstrates unique advantages in moderate-to-severe and refractory AD, offering a novel integrated approach for the prevention and management of AD.

Keywords

atopic dermatitis, gut–skin axis, traditional Chinese medicine enema, gut microbiota

1. Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease for which conventional topical therapies remain curatively insufficient [1]. The "gut–skin axis" theory has elucidated its systemic underpinnings: gut dysbiosis, impaired intestinal barrier function, and abnormal microbial metabolites can remotely drive cutaneous Th2/Th17 polarization and elevated IgE via circulating inflammatory mediators [2,3], suggesting that targeted intestinal intervention is therapeutically pivotal [2]. TCM enema therapy, grounded in traditional medical theory, achieves high local concentrations via rectal administration and can directly reshape the gut microbiota and repair the intestinal barrier [4], upregulating tight-junction proteins, inhibiting the TLR4/NF-κB pathway, and modulating neuro–immune networks to intervene in AD on multiple dimensions [5,6]. Compared with the limitations of Western pharmacotherapy, it demonstrates therapeutic potential and safety

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in moderate-to-severe and refractory AD [7]. This review summarizes its mechanisms to provide a reference for integrated Chinese–Western diagnosis and treatment [8].

2. Gut Dysbiosis and Atopic Dermatitis

2.1 Correlation Between Gut Microbiota Dysbiosis and Cutaneous Inflammation in AD

Children with AD exhibit gut dysbiosis characterized by reduced microbial diversity, decreased abundance of beneficial genera (Bifidobacterium, Lactobacillus), and overgrowth of pathogenic organisms (Staphylococcus aureus, Clostridium spp., Escherichia coli) [9,10]. Pathogenic bacteria activate dendritic cells, driving Th2 differentiation and secretion of pro-inflammatory cytokines including IL-4 and IL-13 [11,12]; dysbiosis also increases absorption of food allergens, eliciting hypersensitivity reactions. Clinically, SCORAD scores are negatively correlated with gut α-diversity and accompanied by elevated IgE and eosinophil counts, indicating that the gut microbiome is a key driver of AD progression [10,13].

2.2 Intestinal Mucosal Barrier Disruption and Systemic Immune Activation

In AD patients, gut dysbiosis and pro-inflammatory cytokines downregulate the expression of tight-junction proteins (ZO-1, Occludin), resulting in "leaky gut" [14,15]. Food antigens and pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS), subsequently translocate into the circulation, activating the NF-κB pathway and promoting secretion of TNF-α, IL-6, and IL-1β [11], thereby sustaining chronic inflammation and reducing cutaneous threshold sensitivity. Concurrently, Treg function is suppressed and the Th1/Th2 and Th17/Treg balances are disrupted, establishing a Th2-dominant vicious cycle [16,17]. Supplementation with glutamine or probiotics can upregulate tight-junction proteins and restore the intestinal barrier [18,19].

2.3 Depletion of Gut Metabolites Weakens Cutaneous Immune Homeostasis

Short-chain fatty acids (SCFAs, including acetate, propionate, and butyrate) are the primary products of microbial fermentation of dietary fiber. They possess dual activity as histone deacetylase (HDAC) inhibitors and as ligands for G-protein-coupled receptors (GPR43, GPR109A), thereby participating in immune modulation. In AD patients, the abundance of SCFA-producing taxa (Faecalibacterium, Roseburia) is reduced, leading to diminished SCFA levels [9,20]. This depletion compromises several key functions: promoting Treg differentiation and suppressing Th2 responses [14,15]; enhancing epithelial barrier integrity and antimicrobial peptide synthesis [21]; inhibiting pathogenic bacterial colonization [22,23]; and regulating neuroendocrine signaling to attenuate pruritic signals [2,24]. Dietary interventions or probiotic supplementation can restore SCFA levels [18,25].

3. Bidirectional Regulation along the Gut–Skin Axis

3.1 Molecular Basis of the Gut–Skin Axis

The gut–skin axis exerts bidirectional regulation through microbial metabolites and immune cell trafficking. SCFAs inhibit HDAC activity, strengthen the cutaneous barrier, and suppress inflammation. Under dysbiotic conditions, LPS and other microbial products enter the circulation, triggering systemic inflammation and compromising cutaneous immune tolerance [26,27]. Gut-derived Th17 cells migrate to the skin guided by chemokines; IL-6 and TNF-α activate the cutaneous NF-κB pathway via the bloodstream, establishing a "intestinal inflammation–immune activation–cutaneous injury" cycle [28].

3.2 Neuroendocrine Pathways Mediating Gut-Axis-Driven Pruritus

The neuro–endocrine system constitutes a gut–brain–skin network that plays a pivotal role in gut-axis-mediated pruritus. Gut microbiota influences cortisol secretion via the vagus nerve or hypothalamic–pituitary–adrenal (HPA) axis; HPA-axis hyperactivity promotes release of neuropeptides (substance P, calcitonin gene-related peptide [CGRP]), activating mast cells to release histamine and tryptase, upregulating TRPV1, and lowering the pruritic threshold [24,29]. Microbially derived neuroactive metabolites (5-HT, GABA, dopamine) modulate cutaneous neuronal excitability; AD patients exhibit abnormalities in intestinal 5-HT-producing

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bacteria, and serum 5-HT fluctuations exacerbate pruritus through corresponding receptors. Keratinocytes release TSLP to activate IL-31 receptors, and sensory neurons release neurotrophic factors, forming a neuro–immune positive feedback loop that chronifies pruritus [30,31]. Acupuncture and TCM can modulate this network, restore HPA-axis balance, and reduce neuropeptide levels, thereby alleviating pruritus [2,32].

3.3 Gut-Axis Dysregulation Drives Th2/Th17 Polarization and IgE Elevation

Dysbiosis increases barrier permeability, permitting antigen translocation and uptake by dendritic cells. Under IL-4/IL-13 induction, Th2 differentiation is promoted; Th2-derived IL-4/IL-13 stimulate B-cell production of IgE and suppress filaggrin, thereby weakening the cutaneous barrier [33,34]. Dysbiosis also activates the IL-23/IL-17 axis, promoting Th17 expansion. Th17-derived IL-17A/IL-22 participate in epidermal hyperplasia and neutrophil recruitment during the chronic phase of AD. In children with AD, intestinal Clostridium abundance is positively correlated with serum IgE and eosinophil counts; Th2/Th17 immune deviation renders the skin hyper-reactive, resulting in recurrent AD flares [27,35].

4. Application of Traditional Chinese Medicine Enema

4.1 TCM Theoretical Framework: “Intestinal Damp–Heat” and “Spleen Deficiency with Dampness Excess” in Relation to the Gut Axis

The “intestinal damp–heat” syndrome is observed in acute-phase ulcerative colitis or infectious enteritis, presenting with abdominal pain, tenesmus, bloody purulent stool, and a red tongue with yellow greasy coating. Its microscopic basis comprises impaired intestinal mucosal barrier, downregulation of tight-junction proteins, LPS translocation activating the TLR4/NF-κB pathway, reduced microbial diversity, expansion of opportunistic pathogens (E. coli, Bacteroides fragilis), and depletion of beneficial bacteria (Bifidobacterium, Lactobacillus), driving Th1/Th17 immune polarization [36,37].

The “spleen deficiency with dampness excess” syndrome is observed in chronic protracted disease or functional bowel disorders, presenting with loose stools, abdominal distension, poor appetite, fatigue, and a pale tongue with white greasy coating. Its pathogenesis involves dysfunction of spleen–stomach transformation, corresponding to intestinal dysmotility, digestive enzyme insufficiency, and chronic inflammation; abnormal SCFA metabolism and reduced butyrate lead to colonic epithelial energy deficit, impaired goblet cell function, and a thinner mucus layer, often accompanied by gut–brain axis dysregulation, HPA-axis abnormalities, and neurotransmitter disturbances [38,39].

4.2 Pharmacokinetic Advantages and Concentration Mechanisms of Enema Administration

As a rectal delivery route, TCM enema offers significant pharmacokinetic advantages: it bypasses hepatic first-pass metabolism, enhances bioavailability, and is particularly suitable for orally labile compounds; the drug directly contacts the lesional mucosa, achieving high local concentrations that favor tissue penetration; and after retention enema, the formulation remains in situ for several hours, creating a “drug reservoir effect” that facilitates mucosal repair and inflammation suppression [40,41].

The enema temperature should be maintained at 37–40°C; supplementation with suspending agents or thickeners can increase viscosity and prevent rapid expulsion. The peak concentration (Cmax) is 3–5-fold higher than oral administration, with a shorter Tmax enabling rapid onset. Additionally, enema provides mechanical flushing to eliminate toxins and improve the microenvironment, embodying the TCM principle of “providing an outlet for pathogenic factors” [40,42].

4.3 Clinical Advances in Enema Formulations Modulating the Intestinal Microenvironment

TCM enema formulations improve disease prognosis through multi-target modulation of the intestinal microenvironment. Weng-She decoction enema for large-intestine damp–heat ulcerative colitis achieves a total effective rate exceeding 90%, superior to mesalazine suppositories, reducing IL-6 and TNF-α, upregulating IL-10, restoring microbial balance, and repairing the barrier [41,43]. A self-designed ulcerative-colitis enema formulation combined with mesalazine improves symptoms and modulates Tfh cell homeostasis in spleen-deficiency/damp-accumulation patients [44,39]. In functional constipation and irritable bowel syndrome,

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modified Da-Cheng-Qi decoction enema modulates the microbiota–gut–brain axis, restores microbial balance, and promotes evacuation [45]; Ban-Xia-Xie-Xin decoction enema modulates SCFA metabolism, attenuates inflammation, and restores gastrointestinal function [46,47].

5. Mechanisms and Pathways of TCM Enema in Regulating the Gut Axis for AD

5.1 Remodeling Gut Microbiota Structure: Bidirectional Regulation Promoting Probiotic Colonization and Inhibiting Pathogenic Overgrowth

Gut dysbiosis is the initiating factor of cutaneous inflammation in AD. AD patients exhibit an elevated Firmicutes/Bacteroidetes (F/B) ratio, reduced beneficial bacteria (Lactobacillus, Bifidobacterium), and overgrowth of pathogens (S. aureus, E. coli). TCM enema formulations contain polysaccharides, saponins, and other prebiotics that, upon rectal absorption, promote probiotic colonization. Animal studies demonstrate that after enema intervention in AD model mice, intestinal Lactobacillaceae and Muribaculaceae increase, Ruminococcus and other pro-inflammatory taxa are suppressed, and the F/B ratio normalizes [48]; microbiota remodeling via SCFAs inhibits cutaneous pathogenic colonization, breaking the gut–skin cycle [6,8].

Berberine, present in Coptis chinensis and Phellodendron chinense, locally disrupts pathogenic bacterial cell walls and inhibits biofilm formation in the intestinal lumen, reducing toxin entry into the bloodstream; local antimicrobial activity avoids the systemic microbial disturbance caused by oral antibiotics, embodying the TCM principle of "treating disease at its root." Restoration of microbial diversity and stability provides the foundation for immune modulation and can attenuate systemic allergic responses [5,33].

5.2 Repairing the Intestinal Epithelial Barrier: Upregulating ZO-1/Occludin and Reducing Serum DAO and LBP

Impaired intestinal barrier with endotoxin translocation is a key trigger of systemic inflammation in AD. In AD animal models, ZO-1 and Occludin expression is downregulated and intestinal permeability is increased; after TCM enema treatment, expression of both is restored and permeability improved [49,50], with mechanisms involving activation of the Wnt/β-catenin pathway or inhibition of MLCK phosphorylation to maintain epithelial integrity. Serum diamine oxidase (DAO) and lipopolysaccharide-binding protein (LBP) are biomarkers of intestinal mucosal injury and endotoxin entry; in AD patients treated with enema, both levels decrease and correlate positively with SCORAD scores [3,2]. By "conserving the intestinal collaterals," TCM enema reduces endotoxin entry into the bloodstream, mitigates hepatic burden and cutaneous immune responses, and creates conditions for cutaneous repair [51,52].

5.3 Reprogramming the Gut Immune Microenvironment: Cellular and Molecular Basis for Inducing Treg Differentiation and Reversing Th2/Th17 Imbalance

The immunopathology of AD is characterized by Th2 predominance and Th1/Th2 and Treg/Th17 imbalance. TCM enema modulates gut-associated lymphoid tissue (GALT) to increase the proportion of Foxp3+ Tregs in the lamina propria, suppressing effector T-cell differentiation; this effect is associated with elevated butyrate, which as an HDAC inhibitor promotes epigenetic modification and functional maturation of Tregs [53,54]. Concurrently, enema downregulates Th2 cytokines (IL-4, IL-5, IL-13) in serum and lesional skin while upregulating Th1 cytokines (IFN-γ); it suppresses RORγt transcriptional activity, reduces IL-17A and IL-22 secretion, and attenuates neutrophil infiltration [55,56]. These multi-target modulations help resolve acute-phase inflammation, establish immune homeostasis, and reduce AD relapse [18,57].

5.4 Suppression of Systemic Inflammatory Responses

Intestinal inflammatory signals are transmitted to the skin via the circulatory and neural pathways, amplifying systemic inflammation. LPS binds to intestinal epithelial TLR4, activating NF-κB nuclear translocation and upregulating TNF-α, IL-6, and TSLP; TSLP, as an upstream factor in Th2 inflammation, acts on cutaneous Langerhans cells and induces their maturation and migration. Baicalin, matrine, and other TCM components can bind TLR4 or inhibit IκBα degradation, blocking NF-κB activation and reducing the levels of the aforementioned inflammatory mediators [58,59]. Furthermore, enema exerts anti-inflammatory effects via

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the vagus nerve anti-inflammatory pathway: intestinal stimulation is transmitted afferently via the vagus nerve to the central nervous system, with efferent release of acetylcholine to suppress macrophage inflammatory cytokine production. TCM modulates the microenvironment and neurotransmitters, enhancing reflex-arc sensitivity to form a "gut–brain–skin" negative feedback that contains inflammatory spread [2].

5.5 Modulation of the Neuro–Endocrine–Immune Interactive Network

In AD patients, pruritus and anxiety constitute a reciprocal vicious cycle associated with dysregulation of the neuro–endocrine–immune network. Microbial metabolism of tryptophan produces serotonin precursors that influence central function; TCM enema modulates the HPA axis through improving microbiota, reducing abnormal cortisol levels and alleviating anxiety [3,60]. Intestinal inflammation sensitizes sensory nerve endings, promoting release of neuropeptides such as substance P; substance P mediates pruritus and promotes mast-cell degranulation with histamine release. TCM enema can reduce serum and cutaneous levels of substance P and nerve growth factor (NGF), suppressing excessive sensory nerve excitation and thereby alleviating pruritus [61,48]. This modulation improves cutaneous symptoms, enhances sleep and quality of life, embodying the TCM advantage of treating both body and mind [62,63].

6. Integrated Chinese–Western Medicine: From "Treating the Skin" to "Modulating the Gut to Treat the Skin"

6.1 Limitations and Relapse Risk of Western Therapies

The conventional Western "treating the skin" strategy focuses on localized cutaneous anti-inflammation and immunosuppression. Topical glucocorticoids are first-line effective, but long-term use entails significant adverse effects and high relapse rates; systemic immunosuppressants (cyclosporine A, methotrexate) are limited by toxicity [64,65]. Biologics represented by dupilumab and JAK inhibitors have ushered in the era of targeted therapy: dupilumab blocks IL-4/IL-13 receptors, significantly improving symptoms and quality of life [66,67,68], but is associated with conjunctivitis and rebound upon discontinuation [69]; JAK inhibitors are convenient but carry safety concerns including thrombosis and infection [70,71]. These therapies focus on downstream inflammatory blockade without correcting upstream gut dysbiosis; dupilumab has limited effect on microbiota, which may be a key reason for relapse [72]. A single target cannot address the complex pathological network of AD, necessitating holistic modulation for etiological treatment [73,74].

6.2 Advantages of TCM Enema in Moderate-to-Severe and Refractory AD

Based on the association between AD and intestinal function, TCM enema provides a holistic "modulating the gut to treat the skin" approach. It bypasses upper-gastrointestinal enzymatic degradation and hepatic first-pass metabolism, acting directly on the rectal mucosa and being rapidly absorbed via the hemorrhoidal venous plexus to modulate the gut microbiome and repair the intestinal barrier [40]. TCM theory holds that "the lung and large intestine are internally–externally related"; intestinal damp–heat toxic pathogens manifest outwardly on the skin. Enema formulations typically include Coptis chinensis and Phellodendron chinense to clear heat, drain dampness, and detoxify, thereby eliminating turbid pathogens and cutting off the source of inflammatory mediators [40,75]. Clinical studies demonstrate that enema combined with Western therapy enhances efficacy and reduces relapse: Shen-Ling-Bai-Zhu powder combined with dupilumab improves lesional scores, downregulates serum IgE and eosinophil (EOS) levels, repairs the cutaneous barrier, and is well tolerated [76,77]. Its mechanism lies in the multi-component, multi-target action of herbal combinations—modulating microbiota structure, enriching beneficial bacteria, suppressing pathogens, regulating TLR4/NF-κB, JAK-STAT, and MAPK pathways, inhibiting Th2 transcription, inducing Treg differentiation, and re-establishing immune homeostasis [5,8,55,78,79,80].

7. Summary and Future Perspectives

7.1 Therapeutic Effects and Advantages of TCM Enema in AD

As an external TCM therapy for internal disease, TCM enema achieves efficient absorption via rectal administration, bypassing hepatic first-pass metabolism, and aligns with the "lung–large intestine" internally–

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externally related theory. Modern research confirms its modulation of the gut–skin axis, suppression of Th2 inflammatory cytokines (IL-4, IL-13), and alleviation of cutaneous pruritus and inflammation [55,56]; simultaneously, it improves the gut microbiome, repairs the intestinal barrier, and reduces systemic inflammation caused by endotoxin entry [8,5]. Compared with oral administration, enema offers clear advantages in refractory AD patients with concomitant gastrointestinal symptoms, avoiding gastrointestinal irritation and improving compliance. Clinical evidence shows that heat-clearing dampness-resolving enemas reduce serum IgE and eosinophil counts, improve SCORAD scores, and exhibit low adverse-event rates [63,81]. Its multi-target holistic modulation compensates for the limitations of Western single-target anti-inflammation, showing promising prospects in improving sleep, reducing glucocorticoid dependence, and preventing relapse [2,57].

7.2 Standardization Needs for Enema Protocols

Although TCM enema is therapeutically effective, its clinical application faces non-standardized protocols and insufficient evidence-based support. Institutions vary widely in enema temperature, volume, retention time, and catheter insertion depth; the solution temperature typically ranges from 39°C to 42°C, but the optimal retention time remains to be defined by RCTs. Herbal combinations are largely based on individual experience, and the pharmacodynamic substance basis is unclear, hindering the development of treatment guidelines [82,83]. Future efforts should establish an evidence-based standardized system: conduct high-quality clinical research to define optimal dosage and treatment courses; strengthen quality control and establish fingerprint profiles to ensure drug efficacy stability; and elucidate the absorption and metabolism of active components through pharmacokinetic studies, providing a basis for precision medicine [78,80].

8. Conclusion

Based on the gut–skin axis theory, TCM enema represents an innovative strategy for shifting AD management from “treating the skin” to “modulating the gut”: via rectal administration that bypasses first-pass metabolism, it reshapes the gut microbiome, repairs the intestinal mucosal barrier, suppresses inflammation through TLR4/NF-κB and vagus nerve pathways, reverses Th2/Th17 immune deviation, and alleviates pruritus. Compared with single-target Western therapy, its multi-component, multi-target modulation improves dysbiosis, lowers serum IgE, and prolongs remission. However, issues of insufficient protocol standardization and unclear pharmacodynamic substance bases remain to be addressed. Future efforts should establish an evidence-based standardized system, define optimal dosage and treatment courses, explore synergistic mechanisms between TCM enema and fecal microbiota transplantation, optimize the “herb–microbiota–host” interaction network, and construct a precision diagnosis and treatment model, which holds promise for overcoming the therapeutic bottleneck in AD and improving patients' quality of life.

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Funding

This research received no external funding.

Conflicts of Interest

The author(s) declare no conflicts of interest.

Acknowledgment

This paper is an output of the science project.

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