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NEW INSIGHTS INTO SAFE AND EFFECTIVE MANAGEMENT OF DERMATITIS WITH POLYHERBAL FORMULATION

Muhammad Osama Alam[1*], Muhammad Noman Khan[1], Sheraz Muhammad Siddiqui[1], Taseer Ahmed Khan[2], Safila Naveed[3]

[1*,1]Faculty of Eastern Medicine, Hamdard University, Karachi, 74600, Pakistan
m.osama.alam@hotmail.com , nomankhan.phd@hotmail.com

[2] Department of Physiology, University of Karachi, Karachi, 75270, Pakistan

[3]Department of Pharmaceutical Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences, University of Karachi, Karachi, 75270, Pakistan
safila117@gmail.com

***Corresponding author:** Muhammad Osama Alam
* Faculty of Eastern Medicine, Hamdard University, Karachi, 74600, Pakistan.
m.osama.alam@hotmail.com

Abstract

Dermatitis, a chronic inflammatory skin disorder characterized by cutaneous hyperactivity to environmental stimuli, serve as a pivotal point in the dermatitis rhythmic stride, often initiating a cascade leading to asthma, allergic rhinitis, and other associated manifestations. The clinical phenotype of dermatitis results from a complex interplay involving susceptibility genes, compromised skin barrier functions, and immunologic responses to environmental triggers. This review explores these multifaceted aspects, providing a comprehensive overview of the recent advancements in dermatitis research and their implications for innovative management strategies.

Keywords:

Dermatitis, Immunological response of dermatitis, Pathology of dermatitis, herbal treatment

Introduction

A common inflammatory skin condition is called dermatitis. The quality of life is significantly impacted by dermatitis, which also results in a dry skin rash with itching (1). According to contemporary research, there is a 20% prevalence of dermatitis in children in the USA and Europe and a 7% to 14% prevalence in adults, with significant regional heterogeneity (2). Dermatitis is the

leading global cause of disability related to skin disorders, which has significant social and financial consequences. In around 80% of cases, dermatitis develops during the first few years of life, and in about 60% of cases it remits during adolescence (3). Adult onset dermatitis may exist, according to recent studies, although the incidence across age groups and nations is still unknown (4). The reported prevalence and incidence data are heterogeneous, which is caused by variations in the method of research and the description of dermatitis (5). Variations in studies study designs, research teams, geographic locations, and methodologies lead to heterogeneity in estimates of the prevalence and incidence of dermatitis, which may under or overestimate the true prevalence and incidence of dermatitis in children and adults (6). Additionally, Dermatitis frequently has sporadic symptoms and indicators, which can vary depending on age group and skin types. Understanding the prevalence and incidence of dermatitis across various age groups and countries is essential for healthcare planning and patient counselling (7). The recommended method is frequent diagnosis that made using verified diagnostic criteria, especially therapeutic diagnosis, identification of biomarkers and epidemiological information associated with dermatitis. The diagnostic standards used by stringently regulated healthcare system are a reliable tool for assessing dermatitis (8).

Historical Perspective of Dermatitis

Dermatitis which is chronically inflamed skin that hallmark with cutaneous hypersensitivity to environmental stimuli that are safe for healthy non infected individuals (9). Despite its documented existence since the early 1800s, there is lack of exact diagnostic test available for the dermatitis. Clinical signs such as Pruritus, facial and extensor eczema in infants and children, and flexural eczema in adults are relied upon for the diagnostic purposes of dermatitis. Although it predominantly manifests in early life, can initiate or persist into adulthood, in addition to childhood and adolescence (10). Eczema is prevalent, affecting 1 to 3% of adults and 10 to 80% of children throughout their lifetimes. Over the past three decades, its prevalence has doubled or tripled in industrialized nations, while remaining less common in regions with substantial agricultural or rural populations. Significant variations in incidence among nations with comparable genetic backgrounds underscore the crucial role of environmental influences in the manifestation of dermatitis. Understanding the underlying mechanisms of dermatitis is pivotal for developing more effective management strategies.

Numerous studies emphasize the complexity of dermatitis etiology, indicating the involvement of multiple inflammatory and immunologic mechanisms (11). The clinical phenomenon which characterizing dermatitis results from an intricate interplay involving susceptibility genes, the host's environment, defects in epidermal barrier functions, and systemic and local immunological responses (12). Advancements in understanding the pathogenesis of dermatitis

have been achieved through various techniques, including the analysis of cellular and inflammatory cytokines gene expression in human dermatological skin lesions and the utilization of gene deletion and transgenic animal models associated with potential dermatitis oriented genes (13).

The Genetic Predisposition to Allergic Diseases as a Systemic Phenomenon

Asthma, food allergies, and allergic rhinitis, all symptomatic of this systemic condition, have been observed to correlate with dermatitis (14). These disorders share common features such as peripheral eosinophilia and elevated blood IgE levels. The onset of the atopic march, often commencing with dermatitis in a majority of affected patients, establishes a systemic connection. In animal models of dermatitis, the epicutaneous administration of allergens causing allergic skin inflammation has been found to enhance the systemic allergic response and airway hyper-reactivity characteristic of asthma (15).

Dermatitis itself is categorized into at least two distinct types: an extrinsic form, affecting 70 to 80% of patients, involving IgE-mediated sensitization, and an intrinsic form, affecting 20% to 30% of patients. Eosinophilia is a common symptom in both types of dermatitis (16). In extrinsic dermatitis, memory T cells expressing the skin-homing receptor, cutaneous lymphocyte-associated antigen (CLA), produce increased levels of Th2 cytokines, including IL-4 and IL-13. These cytokines play a pivotal role in triggering IgE production with an isotype switch, along with IL-5, crucial for the growth and survival of eosinophils. Interestingly, CLA+ T cells in extrinsic dermatitis exhibit little secretion of Interferon (IFN-gamma), a Th1 cytokine known for suppressing Th2 cell activity. In contrast, intrinsic dermatitis is associated with lower levels of IL-4 and IL-13 production when compared to extrinsic dermatitis (17, 18). Understanding of these intricate immune responses in dermatitis contributes to unraveling the systemic nature of allergic diseases, laying the foundation for targeted therapeutic interventions.

Immune Responses in Dermatitis Affected Skin

Clinically unchanged skin in dermatitis presents an aberrant profile, showcasing heightened dryness and increased sensitivity to irritants compared to healthy controls. Unlike healthy skin, unaffected dermatitis skin displays a perivascular T cell infiltrate, a distinctive feature detected through biopsy analyses. Investigations into biopsies from clinically unchanged skin of dermatitis patients reveal an abundance of Th2 cells expressing IL-4 and IL-13, but not IFN-gamma, mRNA, in comparison to normal non-atopic skin (19).

Acute eczematous skin lesions clinically manifest as intensely itchy, erythematous papules, accompanied by serous exudation and excoriation. The dermis of acute lesions exhibits a noticeable infiltration of CD4+ activated memory T cells. Contrasting with healthy or unaffected skin from dermatitis patients, acute lesions contain significantly more cells expressing mRNAs for IL-4, IL-5,

and IL-13, but fewer cells expressing mRNA for IFN or IL-12. IgE molecules are observed on antigen presenting cells (APCs) in both serous exudation and excoriation. The dermal mononuclear cell infiltrate in acute lesions is dominated by macrophages, while IgE-bearing Langerhans cells (LCs) and inflammatory dendritic epidermal cells (IDECs) are more prevalent in the epidermis (20, 21). Although eosinophils and T lymphocytes are present in lesser quantities than in acute dermatitis, they contribute to the ongoing inflammatory response.

Chronic dermatitis skin lesions exhibit a reduced presence of IL-4 and IL-13-expressing cells compared to acute lesions, but show an increase in IL-5, GM-CSF, IL-12, and IFN-expressing cells (22). Recent studies attribute collagen deposition in chronic dermatitis to heightened gene expression of the pro-fibrotic cytokine, IL-11 (23). The progression of dermatitis skin lesions is intricately regulated by the local production of pro-inflammatory cytokines and chemokines. Tissue necrotic factor (TNF) and IL-1, produced by resident cells such as keratinocytes, mast cells, and dendritic cells (DCs), stimulate cellular signaling, including the NF-B pathway. This stimulation leads to the creation of vascular endothelial cell adhesion molecules by binding to receptors on the vascular endothelium, initiating the process by which inflammatory cells adhere, anchor, and become activated to the endothelium. Inflammatory cells respond to chemotactic gradients produced by chemoattractant cytokines and chemokines originating from the sites of injury or infection once they have entered the tissue (24). These molecules play a pivotal role in determining the characteristics of the inflammatory infiltrate in dermatitis (10).

Elevated levels of IL-16, an LC-derived chemoattractant cytokine for CD4+ T cells, and C-C chemokine ligand 27 are associated with acute dermatitis skin lesions. Eosinophils, macrophages, and Th2 cells are likely attracted to dermatitis skin lesions by C-C chemokines RANTES, monocyte chemotactic protein-4, and eotaxin, which are increased compared to psoriasis. The selective recruitment of CCR4-expressing Th2 cells into dermatitis skin may be facilitated by thymus and activation-regulated cytokines, increased in dermatitis, and macrophage-derived chemokines (25). Increased IL-5 and GM-CSF expression in the skin may contribute to the ongoing inflammation observed in chronic lesions by promoting the survival of LCs, eosinophils, and monocyte-macrophages. Additionally, extracellular matrix elements have been found to support memory T cell survival in persistent skin lesions (26).

Role of T Lymphocytes as Primary Effector Cells in Dermatitis

The crucial involvement of immunological effector T cells in dermatitis is underscored by findings in individuals with primary T cell immunodeficiency disorders. These individuals often present with elevated serum IgE levels, and the resolution of eczematous skin lesions is observed following successful bone marrow transplants (27). Animal models further highlight the indispensability of T

cells, as the absence of these cells results in the absence of eczematous rash manifestation. House dust mite (HDM) allergen-induced skin lesions exhibit distinct phases, with an initial dominance of Th2 cells producing IL-4, followed by a subsequent phase, occurring 24 to 48 hours later, characterized by Th1 cells producing IFN (28). This observation is elucidated through the atopy patch test technique, simulating eczema production in patients. The invasion of eosinophils and/or IDECs, locally producing IL-12, is believed to trigger this transformation. Activated T lymphocytes expressing Fas ligand contribute to keratinocyte killing, thereby contributing to the spongiosis observed in acute dermatitis (29). This process is mediated by IFN-gamma, enhancing the Fas activity of keratinocytes. Some research also believe that IL-8 stimulation of CXCR1/2 receptors are involved in the progression of atopic dermatitis (30).

Experimental models employing targeted deletions or overexpression of Th1 and Th2 cytokines in mice underscore the pivotal role these cytokines play in the skin's inflammatory response. The local expression of Th2 cytokines is particularly critical for dermatitis, evident in transgenic mice engineered to overexpress IL-4 in their skin, presenting inflammatory and pruritic skin lesions reminiscent of dermatitis (31). In contrast to IL-4 knockout mice with normal skin layer thickening but reduced eosinophils, and IFN- knockout mice with reduced dermal thickening, IL-5 knockout mice exhibit no detectable eosinophils and decreased thickening (32).

Dermatitis affected skin showcases an augmented presence of LCs and IDECs expressing IgE, along with the high-affinity IgE receptor Fc receptor I (FcRI). Elevated IgE levels sustain heightened expression of the FcRI chain on DCs in atopic skin. LCs and IDECs play pivotal roles in presenting allergens to Th2 and Th1 cells, respectively (33). Fc-RI-bound IgE on LCs facilitates the collection and internal absorption of allergens in atopic skin before processing and presentation as antigens to T cells. FcRI+/IgE+ LCs can migrate to lymph nodes, activating naive T cells and amplifying the production of Th2 cells (34). Experimental models of aeroallergen-induced patch test reactions on atopic skin underscore the essential role of FcRI+/IgE+ LCs in producing eczematous skin lesions. Recent studies reveal that the development of Th2 cells in an animal model of dermatitis relies on the generation of IL-10 by T cells and APCs.

Epidermal keratinocytes from dermatitis patients exhibit a distinct profile of chemokines and cytokines in response to mechanical stimulation, such as scratching, or exposure to pro-inflammatory cytokines, including abnormally high levels of RANTES after stimulation with TNF- and IFN-gamma (34). They significantly contribute to the production of thymic stromal lymphopoietin, inducing DCs to activate naive Th cells and prepare them to secrete IL-4 and IL-13. These findings offer insights into the connection between scratching and the Th2-mediated development of skin inflammation in dermatitis. As demonstrated later, the compromised ability of

keratinocytes to produce antimicrobial peptides crucial for innate immune responses against pathogens is also noted in dermatitis (35).

Skin Barrier Dysfunction

Dry skin stands as a defining characteristic of dermatitis, extending its impact to both lesion and non-lesion skin, leading to an escalation in trans-epidermal water loss. The compromised skin barrier function in dermatitis results in an augmented absorption of antigens, further fueling the cutaneous hyper reactivity that characterizes this condition. A network of structural proteins linked to ceramides, acting as the primary water-retaining molecules within the extracellular space of the cornified envelope, is pivotal for maintaining the barrier function of these intricate structures (36). Examination of both lesion and non-lesion skin in dermatitis patients reveals diminished levels of ceramide in the cornified envelope. Consequently, the heightened irritability observed in dermatitis may be attributed to an inherent epidermal differentiation issue, exacerbated by the presence of skin damage induced by inflammation (37).

Herbs: Exploring Therapeutic Potentials

In the realm of medicinal history, the intertwined journey of drugs, herbs, and medications has paved the way for herbal treatments, often encapsulated in pills, capsules, tinctures, or nutritional supplements (38). A distinctive feature of herbal remedies lies in their considerably less regulated landscape, with marketing strategies often taking precedence over rigorous safety or efficacy testing, as permitted by federal legislation in the United States since 1994. The absence of mandated FDA reviews of packaging or sales material prior to market entry allows for broad and ambiguous claims, rendering consumers vulnerable to potentially misleading assertions by herbal product manufacturers. Unlike traditional medications, herbal products commonly bypass the stringent approval processes, lacking verifiable claims regarding safety and efficacy due to the absence of gold standard controlled clinical trials (39).

Chamomile: A Botanical Ally in Dermatitis

For centuries, the therapeutic use of the dried and fresh flowers of the chamomile plant has resonated globally. In vitro studies showcase the ability of chamomile extracts to suppress histamine release, lipoxygenase, and cyclooxygenase (40-42).

A specifically formulated chamomile extract, applied topically, demonstrated efficacy in treating dermatitis without eliciting chamomile-related allergies. In a partially double-blind, randomized study employing a half-side comparison, patients with moderate dermatitis received the chamomile cream, hydrocortisone 0.5% cream, or a placebo vehicle cream. After a two-week

course, a marginal advantage over hydrocortisone 0.5% and a negligible difference over placebo were reported (43). While chamomile's role in phytotherapy has shown promise, allergic contact dermatitis has been linked to its usage.

Evening Primrose Oil: Nurturing Dermatitis Management

Several studies suggest potential benefits of evening primrose oil for children with dermatitis when administered orally. Rich in gamma linoleic acid (GLA), evening primrose oil addresses a structural flaw related to the enzyme delta-6-desaturase, which is implicated in dermatitis development. Oral supplementation with evening primrose oil resulted in positive fatty acid alterations in the epidermis of dermatitis patients (44). Topically, evening primrose oil stabilized the stratum corneum barrier, particularly in a water-in-oil emulsion. The inclusion of GLA, known for its anti-pruritic and anti-inflammatory properties, highlights its potential efficacy in treating dermatitis. However, the presence of pyrrolizidine alkaloids in GLA warrants cautious use due to potential hepatotoxicity upon repeated application. Conflicting evidence persists regarding the effectiveness of GLA therapy for dermatitis, as highlighted by studies producing divergent outcomes (43, 44). The therapeutic potential of evening primrose oil formulations remains a subject of debate, necessitating further exploration and comprehensive toxicity assessments.

Chinese Herbal Treatments: Navigating Complexity for Dermatological Wellness

Chinese herbal preparations, rooted in a rich tradition, present a multifaceted approach to dermatitis management. The literature extensively explores the efficacy of these preparations, characterized by intricate combinations of herbs with potentially synergistic interactions (40). While the identification of active ingredients is essential for scientific inquiry, the holistic effectiveness of herbal combinations relies on the intricate interplay of numerous chemicals within them, opening avenues for the discovery of novel medicinal molecules.

Rustin and Poulter contextualize Chinese herbal treatment (CHT) within the yin and yang theory, interpreting skin ailments as a disruption in the crucial balance between yin sustenance and yang activity. This theoretical framework recognizes the subsequent invasion of pathogenic elements, such as wind, heat, and wetness, exacerbating skin conditions. CHT endeavors to eliminate harmful microorganisms and restore the equilibrium between yin and yang (41). Sheehan et al. bolster this perspective with double-blind clinical studies, showcasing the effectiveness of CHT and providing a comprehensive breakdown of the pharmacological activities of individual herbal components (refer to Table 1).

Herb	Double-blinded	Side-effects	Outcome	References
Chinese Herbal Therapy	yes	Mixed	Diarrhea, increase in transaminases, Reversible dilated cardiomyopathy, reversible acute hepatic illness related, fatal hepatic necrosis, nephropathy, exacerbation of disease	(42)
Chamomile Mild extract	yes	Mild superiority vs 0.5% hydrocortisone; marginal difference vs. placebo	Possible allergic contact dermatitis from non-trade brand	(43)
Evening Primrose oil	yes	Mixed	Rare	(44)
Shiunko	yes	Mixed	Not reported	(45)
Witch Hazel	no	Anecdotal	Not reported	(46)
Burdock	no	Anecdotal	Not reported	(47)
Aloe Vera	no	Anecdotal	Allergic contact dermatitis	(48)
Oolong Tea	no	Anecdotal	Not reported	(49)

Shiunko: Herbal Efficacy in Topical Dermatitis Treatment

Shiunko, a herbal extract-based topical treatment, emerges as a promising intervention for various ailments, including dermatitis. In a vehicle-controlled study involving nine patients, Shiunko demonstrated success when compared to petrolatum, while its efficacy was comparable to 3.5% saltwater in four patients. The suggested antibacterial mechanism of action on staphylococci aligns with the benefits observed with topical fusidic acid, an antibacterial agent distinct from herbal preparations (45). Additional natural treatments, such as witch hazel, burdock, aloe vera, and oolong tea, show potential for eczema management, although rigorous studies are scarce (48, 49).

Herbal Allergens: Unraveling Sensitivities in Dermatological Care

Compositae plant extracts, prevalent in cosmetics, shampoos, lotions, and internal herbal medicines and tonics, introduce a spectrum of herbal allergens. Artichoke, burdock, chamomile, chrysanthemum, marigold, ragweed, and sunflower, all part of the Compositae family, contain sesquiterpene lactones—the primary allergen in this category. Cases of composite dermatitis often manifest in middle-aged and elderly patients, reporting airborne or direct contact dermatitis (50).

In navigating the intricacies of Chinese herbal treatments, Shiunko's promising outcomes, and understanding herbal allergens, this discourse underscores the potential and challenges within herbal dermatological interventions.

Conclusion: A Holistic Approach to Dermatological Care Integrating Medicinal Plants

Throughout human history, spanning millennia, the utilization of medicinal plants has been ingrained in diverse cultural practices worldwide. Recent studies underscore the pharmacological significance of several herbs, elucidating their potent medical effects. In the contemporary milieu, a palpable surge in interest toward alternative therapies is evident, manifesting in the increasing adaption of over-the-counter herbal medicines among dermatology patients.

The evolving landscape of patient preferences and therapeutic choices necessitates a paradigm shift in dermatological practices. Dermatologists, as primary caregivers, are challenged to assimilate an expansive understanding of herbal therapies, aligning traditional wisdom with contemporary scientific insights. A nuanced comprehension of the complex interplay between phytochemical constituents and dermatological outcomes becomes imperative for clinicians. Dermatologists stand at the nexus, not merely as prescribers but as empathetic listeners, acknowledging and comprehending the unique perspectives and concerns of their patients. The patient-doctor relationship emerges as a cornerstone, fostering an environment conducive to shared decision-making and informed choices.

As medicinal plant-based therapies weave their way into the fabric of modern dermatology, the discipline stands at a juncture where tradition and scientific rigor converge. Embracing this integration, dermatologists can spearhead a new era of holistic care, where the potency of herbal therapies is harnessed synergistically with evidence-based medicine, enriching the therapeutic landscape and advancing patient outcomes.

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