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THE NEURO-IMMUNO-CUTANEOUS-ENDOCRINE (NICE) MODEL: BIOLOGICAL MECHANISMS LINKING PSYCHOLOGICAL STRESS AND SKIN DISEASES

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Abstract: *Psychological stress is increasingly recognized as an important modifier of dermatological disease activity. Advances in psychoneuroimmunology have demonstrated that the skin functions as an active neuroimmunoendocrine organ capable of responding to both environmental and psychological stressors. These discoveries have culminated in the development of the Neuro-Immuno-Cutaneous-Endocrine (NICE) model, which provides a comprehensive framework for understanding the biological mechanisms connecting stress and skin diseases. The objective was to review current evidence regarding the neuroendocrine, immunological, inflammatory, and microbiological pathways involved in stress-related skin disease and to discuss future developments in precision psychodermatology. Regarding the methods, a narrative review of the literature was performed using PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar databases. Landmark studies, systematic reviews, meta-analyses, and recent publications addressing psychodermatology, psychoneuroimmunology, skin–brain interactions, biomarkers, microbiome science, and precision medicine were analyzed. The results showed that Psychological stress influences skin physiology through activation of the hypothalamic–pituitary–adrenal axis, sympathetic nervous system stimulation, neurogenic inflammation, mast cell activation, cytokine dysregulation, epidermal barrier impairment, oxidative stress, and microbiome alterations. These interconnected mechanisms form the basis of the NICE model and contribute to the pathogenesis of numerous inflammatory and autoimmune dermatological disorders. Emerging evidence suggests that biomarkers of stress, microbiome profiling, artificial intelligence, and digital health technologies may facilitate the development of personalized psychodermatological care. To conclude, the NICE model provides a robust biological framework for understanding the bidirectional relationship between psychological stress and skin disease. Future advances in systems biology, biomarker discovery, and precision medicine are expected to transform psychodermatology into a predictive and individualized discipline.*

Key words: *psychodermatology; psychological stress, psychoneuroimmunology, NICE model, skin-brain axis, microbiome, biomarkers, precision medicine.*

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1. Introduction

Psychodermatology is an interdisciplinary field that investigates the complex interactions between psychological processes and dermatological diseases. Over recent decades, growing evidence has demonstrated that the skin and the nervous system are intimately connected through shared embryological origins, neuroendocrine pathways, immune mediators, and bidirectional signaling mechanisms. Both structures derive from the ectoderm during embryogenesis, establishing a biological foundation for lifelong communication between the brain and the skin [1,2].

Historically, the relationship between emotional states and skin disease has been recognized for centuries. Ancient medical writings described associations between emotional disturbances and cutaneous manifestations, while early psychosomatic medicine proposed that psychological factors could influence dermatological conditions. However, only during the last three decades have advances in psychoneuroimmunology provided a robust scientific framework explaining how psychological stress may directly influence cutaneous physiology and pathology [3,4].

Psychological stress represents a normal adaptive response that enables organisms to react to environmental challenges. Acute stress may exert beneficial effects by enhancing alertness, promoting survival mechanisms, and facilitating immune responses. In contrast, chronic or excessive stress may disrupt homeostatic regulatory systems and contribute to disease development. Increasing evidence suggests that chronic psychological stress affects neuroendocrine, immune, metabolic, and inflammatory pathways involved in the pathogenesis of numerous dermatological disorders [5,6].

The skin is no longer regarded as a passive target organ responding to systemic signals. Contemporary research demonstrates that the skin functions as an active neuroimmunoendocrine organ capable of synthesizing hormones, neurotransmitters, neuropeptides, cytokines, and growth factors. Furthermore, the skin possesses a peripheral equivalent of the hypothalamic-pituitary-adrenal (HPA) axis, allowing local responses to environmental and psychological stressors [7,8].

The clinical significance of stress in dermatology is substantial. Epidemiological studies indicate that between 30% and 70% of dermatological patients report stressful life events preceding disease onset or exacerbation [9]. Stress has been implicated in a wide range of dermatological conditions, including psoriasis, atopic dermatitis, vitiligo, alopecia areata, acne vulgaris, chronic spontaneous urticaria, seborrheic dermatitis, chronic pruritus, and hyperhidrosis [10,11].

Importantly, the relationship between stress and skin disease is bidirectional. While psychological stress may contribute to disease onset and progression, chronic dermatological disorders frequently generate considerable emotional distress. Visible lesions, chronic pruritus, pain, disfigurement, and social stigma may lead to anxiety, depression, sleep disturbances, body image dissatisfaction, social isolation, and impaired quality of life. These psychological consequences may further aggravate disease activity, creating a self-perpetuating vicious cycle [12,13].

Recent developments in psychoneuroimmunology have led to the emergence of the Neuro-Immuno-Cutaneous-Endocrine (NICE) model, which provides a comprehensive framework for understanding the interactions among psychological stress, the nervous system, endocrine pathways, immune responses, and cutaneous homeostasis. This model has become one of the most influential concepts in contemporary psychodermatology and offers valuable insights into disease pathogenesis and therapeutic intervention [14,15].

The growing recognition of psychiatric comorbidity among dermatological patients has also stimulated interest in integrated treatment approaches. Psychodermatological interventions, including cognitive behavioral therapy, mindfulness-based stress reduction, biofeedback, habit reversal therapy, and multidisciplinary psychodermatology clinics, have demonstrated encouraging results in improving both psychological well-being and dermatological outcomes [16,17].

In parallel, emerging fields such as microbiome research, biomarker discovery, artificial intelligence, and personalized medicine are transforming our understanding of the skin–brain axis and opening new perspectives for individualized patient care [18,19].

The aim of this narrative review is to summarize current evidence regarding the biological mechanisms linking psychological stress and dermatological disease, evaluate the psychosocial burden associated with chronic skin disorders, discuss major stress-sensitive dermatoses, and review evidence-based psychodermatological interventions and future developments in the field.

2. Materials and Methods

A narrative review was conducted to provide a comprehensive overview of current knowledge regarding the biological mechanisms linking psychological stress and dermatological disease.

Literature searches were performed between January 10 and February 28, 2026 using PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar databases.

The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords including: (“psychodermatology” OR “psychological stress”) AND (“psychoneuroimmunology” OR “skin–brain axis” OR “NICE model”) AND (psoriasis OR atopic dermatitis OR vitiligo OR alopecia areata OR chronic urticaria OR acne vulgaris) AND (biomarkers OR microbiome OR artificial intelligence OR precision medicine).

Approximately 930 records were initially identified. After removal of duplicates and screening of titles and abstracts, 126 full-text articles were evaluated for eligibility.

Publications considered particularly relevant for this review included landmark studies, systematic reviews, meta-analyses, randomized controlled trials, prospective cohort studies, consensus statements, and recent publications addressing psychodermatology, psychoneuroimmunology, neuroendocrine regulation, microbiome science, biomarker discovery, artificial intelligence, and precision medicine.

Articles published between 2000 and 2025 were preferentially selected, although earlier seminal studies were retained because of their historical importance.

Conference abstracts, duplicate reports,

animal studies without translational relevance, and non-English language publications were excluded.

The retrieved literature was critically analyzed and organized into thematic sections focusing on neuroendocrine mechanisms, neuroimmune interactions, oxidative stress, microbiome alterations, biomarker development, precision psychodermatology, and future perspectives.

3. Historical Development of Psychodermatology

3.1. Early Concepts Linking Mind and Skin

The relationship between psychological factors and skin disease has fascinated physicians for centuries. Early medical traditions recognized that emotional states could influence bodily functions and contribute to disease manifestations, including cutaneous disorders. Although these interpretations were largely based on philosophical and humoral concepts and lacked scientific validation, they represented some of the earliest attempts to explain interactions between the mind and the body [1–4].

During the nineteenth century, the emergence of dermatology as a distinct medical specialty stimulated renewed interest in the potential influence of emotional distress on skin disease. Clinicians increasingly reported observations suggesting that stressful life events frequently preceded the onset or exacerbation of chronic inflammatory dermatoses, including eczema, psoriasis, urticaria, and alopecia. However, in the absence of biologically plausible mechanisms, these observations remained largely descriptive and failed to gain widespread scientific acceptance [5].

A major conceptual shift occurred during the second half of the twentieth century with the emergence of psychoneuroimmunology, which provided experimental evidence supporting bidirectional communication among the nervous, endocrine, and immune systems. These discoveries transformed psychodermatology from a predominantly psychosomatic discipline into a biologically grounded field of investigation and ultimately paved the way for the development of contemporary neuroimmune models of skin disease, including the Neuro-Immuno-Cutaneous-Endocrine (NICE) model [6–10].

3.2. Psychosomatic Medicine and Dermatology

The early twentieth century marked the development of psychosomatic medicine, a discipline dedicated to understanding the influence of psychological processes on physical illness. Dermatological diseases quickly became important subjects of psychosomatic investigation because of their visible nature and apparent sensitivity to emotional influences [6].

Pioneering psychosomatic researchers proposed that unconscious conflicts, emotional trauma, and chronic psychological stress could contribute to the development of several dermatological disorders. Conditions such as eczema, urticaria, psoriasis, neurodermatitis, and alopecia were frequently discussed within psychoanalytic frameworks [7].

Although many early psychosomatic theories relied heavily on speculative interpretations and lacked biological evidence, they stimulated considerable

interest in the relationship between psychological stress and skin disease. Dermatologists increasingly observed that emotional disturbances often coincided with disease exacerbations and that improvement in psychological well-being occasionally paralleled clinical improvement [8].

By the mid-twentieth century, psychocutaneous medicine had become an emerging area of interest. However, the field continued to face skepticism because objective biological mechanisms linking psychological stress to skin pathology remained poorly understood. Consequently, psychosomatic dermatology occupied a peripheral position within mainstream dermatological research for several decades [9].

3.3. Emergence of Psychoneuroimmunology

A major scientific breakthrough occurred during the 1970s and 1980s with the emergence of psychoneuroimmunology (PNI), an interdisciplinary field investigating interactions among the nervous, endocrine, and immune systems. This new discipline fundamentally challenged traditional concepts that viewed these systems as largely independent entities [10].

Seminal studies demonstrated that psychological stress could influence immune function through neuroendocrine pathways. Research revealed that stress-induced activation of the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system could alter immune responses, inflammatory activity, and susceptibility to disease [11].

At the same time, evidence accumulated showing that immune cells express receptors for neurotransmitters and hormones, while neurons respond to cytokines and other immune mediators. These discoveries established the existence of bidirectional communication between the nervous and immune systems and provided the first biologically plausible explanation for how psychological experiences might influence physical disease processes [12].

For dermatology, psycho-neuroimmunology proved particularly relevant because the skin contains extensive networks of sensory nerves, immune cells, endocrine mediators, and vascular structures. The skin therefore emerged as an ideal model for studying neuroimmune interactions in vivo [13].

3.4. The Skin as a Neuroimmunoendocrine Organ

During the 1990s and early 2000s, a series of groundbreaking discoveries fundamentally transformed our understanding of skin biology. Research led by Slominski, Paus, Arck, Peters, Theoharides, and other investigators demonstrated that the skin possesses many characteristics traditionally associated with classical neuroendocrine organs [14], [18]. Studies revealed that the skin is capable of producing and responding to numerous neuroendocrine mediators, including: corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), cortisol and corticosteroid derivatives, catecholamines, neuropeptides, and cytokines. These findings established the concept of the skin as an active neuroimmunoendocrine organ rather than a passive barrier separating the organism from the external environment [19].

Particularly influential was the discovery of a functional peripheral equivalent of the HPA axis within the skin. This local stress-response system enables cutaneous tissues to respond directly to environmental and psychological stressors, thereby contributing to maintenance of local and systemic homeostasis [20]. The recognition of the skin as a neuroimmunoendocrine organ provided a mechanistic foundation for understanding the biological effects of psychological stress on cutaneous physiology and pathology.

Despite major advances in psychoneuroimmunology, several important questions remain unresolved. Much of the available evidence derives from experimental studies, animal models, or relatively small clinical cohorts, and direct causal relationships between psychological stress and chronic inflammatory skin diseases remain difficult to establish. Furthermore, individual variability in stress responsiveness, differences in environmental exposures, and methodological heterogeneity among studies may contribute to inconsistent findings. Additional longitudinal investigations integrating neuroendocrine, immunological, microbiome, and behavioral assessments are needed to better characterize the temporal dynamics underlying stress-associated dermatological disorders [14–17].

Although the concept of the skin as a neuroimmunoendocrine organ is now widely accepted, several aspects of local neuroendocrine regulation remain incompletely understood. In particular, the relative contribution of cutaneous versus systemic neuroendocrine pathways in different inflammatory dermatoses requires further investigation, and standardized methodologies are needed to facilitate comparisons among studies [9,10], [13].

3.5. Development of the Neuro-Immuno-Cutaneous-Endocrine (NICE) Model

Building upon advances in psychoneuroimmunology and skin neuroendocrinology, O'Sullivan and colleagues introduced the Neuro-Immuno-Cutaneous-Endocrine (NICE) model in the late 1990s [21]. The NICE model represented a conceptual milestone by integrating previously separate biological systems into a unified framework. According to this model, the nervous system, immune system, endocrine pathways, and skin communicate continuously through a complex network of signaling molecules and cellular interactions [22].

Within the NICE framework, psychological stress initiates coordinated neuroendocrine responses that influence: immune regulation, inflammatory activity, epidermal barrier function, wound healing, microbial homeostasis, disease susceptibility. The model emphasizes that communication among these systems is bidirectional rather than unidirectional. Consequently, skin inflammation may influence central nervous system activity just as psychological stress may influence skin physiology [23].

Over the following decades, the NICE model became one of the most influential theoretical frameworks in psychodermatology. It provided a scientific basis for understanding the association between stress and numerous dermatological diseases, including psoriasis, atopic dermatitis, vitiligo,

alopecia areata, acne vulgaris, and chronic urticaria [24].

The NICE model represented an important conceptual advance by integrating previously independent neuroendocrine, immunological, and cutaneous pathways into a unified framework capable of explaining stress-associated inflammatory skin disease. Nevertheless, the relative contribution of each component may vary considerably among dermatological disorders, and the interactions between neuroendocrine signaling, microbiome dysbiosis, oxidative stress, and environmental exposures remain incompletely characterized. Further multidisciplinary studies employing multi-omics technologies, longitudinal designs, and systems biology approaches are required to refine the model and improve its translational applicability [7–10].

3.6. Contemporary Concepts of the Skin–Brain Axis

Recent advances have further expanded the NICE model through incorporation of concepts such as the gut–brain–skin axis, microbiome science, systems biology, and precision medicine. Increasing evidence suggests that microbial communities inhabiting the skin and gastrointestinal tract play important roles in regulating immune responses, neuroendocrine signaling, and inflammatory activity [25–27]. Simultaneously, technological innovations have facilitated the emergence of novel research approaches involving: multi-omics technologies, biomarker discovery, artificial intelligence, wearable devices, digital health platforms. These developments are transforming psychodermatology from a largely descriptive discipline into a mechanistically driven field capable of integrating biological, psychological, environmental, and digital data [28].

Today, psychodermatology is increasingly viewed as a translational science situated at the intersection of dermatology, neuroscience, immunology, endocrinology, and behavioral medicine. The historical progression from anecdotal observations to sophisticated neuroimmunological models illustrates the remarkable evolution of our understanding of the skin–brain connection and provides the foundation for future advances in precision psychodermatology [29].

4. The Neuro-Immuno-Cutaneous-Endocrine (NICE) Model

4.1. Conceptual Foundations

The Neuro-Immuno-Cutaneous-Endocrine (NICE) model represents one of the most influential conceptual frameworks in contemporary psychodermatology. Originally proposed by O'Sullivan and colleagues in 1998, the model emerged from growing evidence demonstrating extensive bidirectional communication among the nervous, immune, endocrine, and cutaneous systems [21]. Historically, these biological systems were investigated as relatively independent entities. However, advances in psychoneuroimmunology and skin neuroendocrinology revealed that they function as highly interconnected networks that continuously exchange information through hormones, neurotransmitters, neuropeptides, cytokines, and cellular interactions [3],[7]. Within the NICE framework, the skin is no longer viewed as a passive target of systemic regulation but rather as an active

neuroimmunoendocrine organ capable of sensing environmental stimuli, generating local stress responses, and participating in systemic homeostasis [4,9].

The NICE model proposes that psychological stress initiates coordinated biological responses involving:

- activation of the hypothalamic–pituitary–adrenal (HPA) axis;
- stimulation of the sympathetic nervous system;
- release of neuropeptides and neurotransmitters;
- activation of mast cells and immune cells;
- cytokine production;
- modulation of epidermal barrier function;
- alterations in microbial homeostasis.

These responses collectively influence skin physiology and may contribute to the development or exacerbation of numerous dermatological disorders [1], [3], [8].

Importantly, communication within the NICE network is bidirectional. Cutaneous inflammation may influence central nervous system function through cytokines and neuroimmune mediators, while psychological stress may directly affect cutaneous immune responses and barrier integrity. This dynamic interplay forms the biological basis of the skin–brain connection [2],[22].

4.2. Hypothalamic–Pituitary–Adrenal Axis Activation

The HPA axis represents one of the primary physiological systems involved in adaptation to stress and constitutes a central component of the NICE model [14–17]. Psychological stress activates neurons within the hypothalamus, resulting in the release of corticotropin-releasing hormone (CRH). CRH stimulates the anterior pituitary gland to secrete adrenocorticotropic hormone (ACTH), which subsequently promotes glucocorticoid production by the adrenal cortex, primarily cortisol [15]. Under physiological conditions, cortisol exerts multiple protective functions, including: regulation of immune responses, maintenance of metabolic homeostasis, limitation of excessive inflammation, adaptation to environmental challenges. Acute activation of the HPA axis is generally beneficial and facilitates appropriate responses to stressors. However, chronic or repeated activation may result in dysregulation of neuroendocrine signaling and contribute to disease pathogenesis [16].

The Cutaneous HPA Axis

A landmark discovery in skin biology was the identification of a peripheral equivalent of the HPA axis within the skin itself [9],[13]. Keratinocytes, melanocytes, sebocytes, hair follicle cells, and dermal fibroblasts have been shown to express: CRH, CRH receptors, ACTH, melanocortin receptors, steroidogenic enzymes. These findings indicate that the skin possesses an autonomous stress-response system capable of responding directly to environmental and psychological challenges [18]. Local activation of the cutaneous HPA axis influences: epidermal differentiation, barrier function, immune surveillance, pigmentation, wound healing. Consequently, disturbances in local HPA-axis regulation may contribute to inflammatory skin diseases and impaired tissue homeostasis [20].

Chronic Stress and HPA-Axis Dysregulation

Persistent psychological stress may lead to altered cortisol secretion, flattened circadian cortisol rhythms, glucocorticoid resistance, impaired anti-inflammatory responses. Such abnormalities have been described in psoriasis, atopic dermatitis, chronic urticaria, and alopecia areata [25,26]. Reduced responsiveness to glucocorticoids may promote chronic inflammation by diminishing the ability of endogenous cortisol to suppress inflammatory pathways effectively.

4.3. Sympathetic Nervous System Activation

The sympathetic nervous system (SNS) represents a second major component of the physiological stress response. Psychological stress stimulates sympathetic nerve activity and promotes release of catecholamines, including: norepinephrine, epinephrine, dopamine. These mediators influence cardiovascular function, metabolism, immune activity, and cutaneous physiology [17].

Sympathetic Innervation of the Skin

The skin receives extensive sympathetic innervation that regulates: vascular tone, sweat gland activity, immune responses, hair follicle function. Catecholamines released from sympathetic nerve endings interact with keratinocytes, endothelial cells, immune cells, and dermal structures through adrenergic receptors [19].

Effects on Immune Regulation

Catecholamines influence both innate and adaptive immunity. Potential effects include modulation of cytokine production, altered leukocyte trafficking, changes in antigen presentation, regulation of T-cell activity. Although acute sympathetic activation may exert anti-inflammatory effects, chronic stimulation frequently promotes immune dysregulation and persistent inflammation [27].

Sympathetic nervous system activation has been implicated in psoriasis, atopic dermatitis, hyperhidrosis, rosacea, chronic pruritus. These observations highlight the importance of autonomic regulation within the broader NICE framework [21].

4.4. Neuropeptides and Neurogenic Inflammation

Neuropeptides represent key mediators linking psychological stress to cutaneous inflammation. Produced by sensory nerve fibers, immune cells, and skin cells, neuropeptides participate in complex neuroimmune communication networks that regulate inflammation, vascular responses, and immune activity [19], [22].

Substance P

Substance P is among the most extensively studied neuropeptides in dermatology. Stress-induced release of Substance P promotes vasodilation, mast cell activation, cytokine production, leukocyte recruitment, pruritus. Elevated levels of Substance P have been documented in psoriasis, atopic dermatitis, chronic urticaria, and chronic prurigo [23].

Calcitonin Gene-Related Peptide (CGRP)

CGRP contributes to neurogenic inflammation, vascular regulation and immune modulation. Interactions between CGRP and immune cells may amplify inflammatory responses in stress-sensitive dermatoses [22].

Neurogenic Inflammation

The collective actions of neuropeptides give rise to neurogenic inflammation, a process characterized by vasodilation, plasma extravasation, immune cell recruitment, enhanced inflammatory signaling. Neurogenic inflammation represents one of the most direct biological pathways through which psychological stress influences skin disease [20].

4.5. Mast Cell Activation and Neuroimmune Communication

Mast cells occupy a central position within the NICE model because they function as critical interfaces between the nervous and immune systems [23–25]. Located in close proximity to cutaneous nerve fibers, mast cells respond rapidly to neuropeptides, hormones, cytokines, and environmental stimuli.

Stress-Induced Mast Cell Activation

Psychological stress may stimulate mast cell activation through: CRH, substance P, neurotensin, catecholamines. Activated mast cells release numerous mediators, including histamine, tryptase, TNF-α, IL-6, leukotrienes, prostaglandins. These mediators contribute to inflammation, pruritus, vascular changes, and immune activation [24].

Neuroimmune Feedback Loops

Mast cells and nerve fibers engage in bidirectional communication. Neuropeptides activate mast cells, while mast cell mediators influence neuronal function and sensory perception. This reciprocal interaction creates self-amplifying inflammatory loops that may sustain chronic disease activity [25].

4.6. Cytokine Dysregulation and Chronic Inflammation

Cytokines constitute the primary molecular language of the immune system and represent essential mediators within the NICE network. Psychological stress influences cytokine production through both neuroendocrine and neuroimmune pathways [27].

Pro-Inflammatory Cytokines

Stress-related increases have been reported for IL-1β, IL-6, TNF-α, IFN-γ. These mediators promote inflammatory activation and contribute to disease progression [28].

The IL-23/IL-17 Axis

Particularly important in psoriasis is the IL-23/IL-17 pathway. Emerging evidence suggests that stress-related immune dysregulation may enhance activation of this pathway, thereby contributing to disease exacerbation [29].

Chronic Low-Grade Inflammation

Persistent activation of inflammatory pathways may result in chronic low-grade systemic inflammation, increasingly recognized as a hallmark of chronic stress exposure [30].

4.7. Epidermal Barrier Dysfunction

The epidermal barrier constitutes the first line of defense against environmental insults and microbial invasion. Psychological stress has been shown to impair barrier function through multiple mechanisms, including altered lipid synthesis, reduced keratinocyte differentiation, and dysregulated immune responses [31]. Experimental studies have

demonstrated that stress may increase transepidermal water loss, delay barrier recovery, impair antimicrobial defense, promote cutaneous inflammation. These effects may increase susceptibility to disease and exacerbate existing inflammatory conditions [33,34]. Barrier dysfunction is particularly relevant in atopic dermatitis, psoriasis, chronic pruritic disorders. Restoration of barrier integrity therefore represents an important therapeutic objective in stress-sensitive dermatoses [32].

4.8. Oxidative Stress and Cellular Damage

Oxidative stress represents another important component of the NICE model. Reactive oxygen species (ROS) are generated during normal cellular metabolism and participate in physiological signaling pathways. However, excessive ROS production may result in cellular damage and inflammation [35].

Psychological stress may enhance oxidative stress through sympathetic activation, mitochondrial dysfunction, inflammatory cytokine production, impaired antioxidant defenses. These mechanisms contribute to cumulative cellular injury and tissue dysfunction [37]. Oxidative stress has been implicated in psoriasis, vitiligo, alopecia areata, photoaging, chronic wounds. Particularly strong evidence exists for vitiligo, where oxidative damage is believed to contribute directly to melanocyte dysfunction and destruction [36].

Oxidative stress interacts closely with neuroendocrine, immune, and inflammatory pathways. Consequently, it should be viewed not as an isolated mechanism but as an integral component of the broader neuro-immuno-cutaneous-endocrine network [35], [37].

5. The Skin Microbiome and the Gut–Brain–Skin Axis

The human body hosts trillions of microorganisms that collectively constitute the microbiome, a complex ecological community composed of bacteria, fungi, viruses, and archaea. These microbial populations colonize various anatomical sites, including the skin, gastrointestinal tract, respiratory system, and mucosal surfaces, where they participate in numerous physiological processes essential for health and homeostasis [38], [42].

Historically, microorganisms were viewed primarily as potential pathogens. However, advances in high-throughput sequencing technologies and microbiome research have transformed our understanding of host–microbe interactions. It is now recognized that resident microbial communities contribute fundamentally to immune development, metabolic regulation, barrier maintenance, and protection against pathogenic invasion [40,41].

Within psychodermatology, increasing attention has focused on the role of microbial ecosystems in mediating communication between psychological stress and skin disease. The concept of the gut–brain–skin axis, originally proposed by Stokes and Pillsbury in 1930, has experienced renewed interest as emerging evidence demonstrates extensive bidirectional interactions among the central nervous system, intestinal microbiota, immune system, and skin [43].

These discoveries have expanded the traditional NICE framework by

incorporating microbial factors as active participants in neuroimmunoendocrine regulation. Consequently, the microbiome is increasingly viewed as a critical component of the biological pathways linking psychological stress and dermatological disease [44].

5.1. The Skin Microbiome and Cutaneous Homeostasis

The skin is colonized by a diverse array of microorganisms that vary according to anatomical location, environmental conditions, age, sex, and host genetics. Dominant bacterial genera include: Cutibacterium spp., Staphylococcus spp., Corynebacterium spp., Micrococcus spp. In addition, fungi such as Malassezia species and numerous viral communities contribute to the overall composition of the skin microbiome [40,41].

Far from being passive inhabitants, these microorganisms actively participate in maintaining cutaneous homeostasis. The skin microbiome contributes to pathogen exclusion through competitive colonization, regulation of innate immune responses, maintenance of epidermal barrier integrity, modulation of inflammatory pathways, wound healing and tissue repair, production of antimicrobial peptides. Through these mechanisms, microbial communities help preserve a balanced relationship between the host and the external environment [42].

Keratinocytes and resident immune cells continuously interact with microbial communities through pattern-recognition receptors such as Toll-like receptors (TLRs). Controlled activation of these pathways promotes immune surveillance while preventing excessive inflammation [45]. Microbiota-derived signals influence dendritic cell maturation, T-cell differentiation, regulatory T-cell development, cytokine production. Consequently, alterations in microbial composition may profoundly affect cutaneous immune homeostasis [46].

5.2. Psychological Stress and the Skin Microbiome

Psychological stress influences microbial ecosystems through multiple neuroendocrine mechanisms. Activation of the HPA axis and sympathetic nervous system results in the release of cortisol, catecholamines, and neuropeptides that may directly or indirectly affect microbial communities [47]. Experimental studies suggest that stress may alter microbial diversity, bacterial abundance, microbial metabolic activity, host–microbe interactions. Stress-related changes in sebum production, sweating, skin pH, and barrier integrity may further modify the cutaneous environment, creating conditions that favor microbial imbalance [48].

Neuroendocrine Effects on Microorganisms

An emerging field known as microbial endocrinology has demonstrated that microorganisms can respond directly to host neuroendocrine mediators. Catecholamines such as norepinephrine may influence bacterial growth, biofilm formation, virulence factor expression, microbial communication systems. These findings suggest that microorganisms actively participate in host stress responses rather than merely responding passively to environmental changes [49].

Stress-induced alterations in microbial communities may contribute to disease exacerbation in atopic dermatitis, acne vulgaris, rosacea, seborrheic dermatitis,

psoriasis. Although causal relationships remain under investigation, growing evidence supports the role of microbial dysregulation as a mediator of stress-related skin pathology [50].

5.3. The Gut–Brain–Skin Axis

The gut–brain–skin axis has emerged as one of the most important concepts in modern psychodermatology. This model describes bidirectional communication among: the central nervous system, the enteric nervous system, intestinal microbiota, immune pathways, endocrine signaling systems, the skin. Through this network, psychological stress may influence gastrointestinal function and microbial composition, while microbial metabolites and immune mediators may affect both brain function and cutaneous physiology [38],[43].

Neuroendocrine Regulation of Gut Function

Psychological stress influences intestinal physiology through activation of the HPA axis and autonomic nervous system. Potential effects include altered gastrointestinal motility, changes in secretion, increased intestinal permeability, altered mucosal immunity, and modifications of microbial composition. These changes create conditions favorable for dysbiosis and immune activation [51].

Microbial Signaling to the Brain

Microbial communities communicate with the central nervous system through several mechanisms. These include neural pathways (particularly the vagus nerve), immune mediators, microbial metabolites, and endocrine signaling. Such interactions may influence mood, cognition, stress responsiveness, neuroinflammatory activity. Consequently, the microbiome is increasingly regarded as an important regulator of mental health and emotional well-being [52].

Microbial Metabolites

Short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, represent some of the most extensively studied microbiota-derived signaling molecules. SCFAs contribute to epithelial barrier maintenance, immune regulation, anti-inflammatory activity, modulation of oxidative stress, and neuroimmune communication. Reduced SCFA production has been associated with several inflammatory disorders and may contribute to dysregulated immune responses [53].

5.4. Microbiome Dysbiosis and Chronic Inflammation

The maintenance of cutaneous and systemic homeostasis depends on a balanced relationship between microbial communities and host immune responses. Disruption of this equilibrium, known as dysbiosis, has been increasingly implicated in the pathogenesis of numerous inflammatory and autoimmune diseases [54]. Psychological stress may promote dysbiosis through neuroendocrine activation, altered barrier function, and immune dysregulation. Reduced microbial diversity, depletion of beneficial commensal organisms, and expansion of opportunistic species may collectively contribute to chronic inflammation [55].

Intestinal Barrier Dysfunction

Stress-related dysbiosis may

compromise intestinal barrier integrity, facilitating translocation of lipopolysaccharides (LPS), microbial metabolites, bacterial DNA fragments, and pathogen-associated molecular patterns. These molecules activate systemic immune responses and promote production of pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β, and IL-17 [56].

Cutaneous Dysbiosis

Alterations in skin microbial communities have been documented in several dermatological diseases. Examples include atopic dermatitis (reduced microbial diversity; overgrowth of Staphylococcus aureus), psoriasis (altered cutaneous and intestinal microbial profiles; enhanced inflammatory activation), acne vulgaris (strain-specific dysbiosis involving Cutibacterium acnes) and rosacea (microbial imbalance and altered innate immune responses). These observations suggest that dysbiosis may represent a common pathogenic mechanism across multiple inflammatory dermatoses [57], [59].

Chronic Systemic Inflammation

Through activation of immune pathways and disruption of barrier function, dysbiosis may contribute to chronic low-grade systemic inflammation. Particularly important are Th1 responses, Th17 activation, IL-23/IL-17 signaling, and oxidative stress pathways. These mechanisms closely interact with the neuroimmune pathways described within the NICE model [60].

5.5. Microbiome-Based Therapeutic Perspectives

Recognition of the microbiome as an active participant in skin disease has generated considerable interest in microbiome-targeted therapies. Potential strategies include:

Probiotics

Administration of beneficial micro-organisms may help restore microbial balance and modulate immune responses. Several studies have reported improvements in atopic dermatitis and acne following probiotic supplementation, although results remain heterogeneous [61].

Prebiotics and Synbiotics

Prebiotics promote the growth of beneficial microorganisms, while synbiotics combine probiotic and prebiotic approaches. These interventions may contribute to restoration of microbial homeostasis and reduction of inflammatory activity [62].

Postbiotics

Postbiotics refer to bioactive microbial metabolites or cellular components capable of exerting beneficial effects without administration of live organisms. This emerging therapeutic field may offer important advantages regarding safety and stability [63].

Dietary Modulation

Diet profoundly influences microbiome composition and function. Dietary patterns rich in fiber, fruits and vegetables, fermented foods, and polyphenols, may support microbial diversity and anti-inflammatory activity, whereas highly processed diets may promote dysbiosis [64].

Future Directions

Future therapeutic approaches may include personalized microbiome profiling, targeted microbial modulation, engineered probiotics, and microbiome transplantation strategies. Such

developments may facilitate more individualized management of stress-sensitive dermatological diseases [65].

6. Biomarkers of Stress in Dermatology

6.1. Neuroendocrine Biomarkers

One of the major challenges in psychodermatology is the objective quantification of psychological stress and its biological consequences. While psychological questionnaires and quality-of-life instruments provide valuable clinical information, they remain inherently subjective and may not fully reflect the underlying physiological alterations associated with stress exposure [43-46].

The neuroendocrine system constitutes the primary biological interface between psychological stress and systemic physiological responses. Activation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic-adrenal-medullary system results in the release of hormones and neuroendocrine mediators that influence immune regulation, inflammatory activity, metabolism, and skin homeostasis [14–18].

Consequently, biomarkers reflecting neuroendocrine activity have emerged as promising tools for assessing stress-related biological responses in dermatological diseases. These biomarkers may facilitate objective measurement of stress burden, identification of stress-sensitive patients, prediction of disease exacerbations, monitoring of therapeutic interventions, and development of personalized psychodermatological strategies.

Among the currently available neuroendocrine biomarkers, cortisol remains the most extensively studied. However, growing attention has also focused on salivary cortisol, hair cortisol concentration, catecholamines, dehydro-epiandrosterone sulfate (DHEA-S), and neuropeptide-related biomarkers [43,44].

Cortisol: The Principal Stress Hormone

Cortisol is the final effector hormone of the HPA axis and remains the most widely investigated biomarker of stress. Following exposure to psychological or physical stressors, activation of the hypothalamus stimulates secretion of corticotropin-releasing hormone (CRH), leading to adrenocorticotropic hormone (ACTH) release from the anterior pituitary gland and subsequent cortisol production by the adrenal cortex [14,15]. Under physiological conditions, cortisol contributes to maintenance of metabolic homeostasis, regulation of immune responses, modulation of inflammatory activity, adaptation to environmental challenges.

Acute elevations in cortisol are generally adaptive and facilitate stress resilience. However, chronic stress may result in sustained HPA-axis activation, altered cortisol secretion patterns, and glucocorticoid resistance, all of which have been implicated in inflammatory skin diseases [16,17]. Several studies have reported abnormal cortisol responses in patients with psoriasis, atopic dermatitis, chronic urticaria, alopecia areata, chronic pruritus. These findings suggest that dysregulation of cortisol signaling may contribute to disease pathogenesis and exacerbation [25,26].

Salivary Cortisol

Salivary cortisol measurement has gained popularity because it provides a simple, non-invasive, and reproducible

method for assessing HPA-axis activity. Unlike serum cortisol, salivary cortisol reflects the biologically active free fraction of circulating cortisol and is less influenced by variations in cortisol-binding proteins [43]. Advantages include non-invasive collection, suitability for repeated sampling, home-based monitoring, assessment of circadian cortisol rhythms. Numerous studies have demonstrated altered salivary cortisol profiles in patients with chronic inflammatory skin diseases. Reduced morning cortisol responses, flattened diurnal rhythms, and abnormal cortisol awakening responses have all been described in psoriasis and atopic dermatitis [44]. Because repeated measurements can be obtained under real-world conditions, salivary cortisol remains one of the most practical neuroendocrine biomarkers currently available for psychodermatological research.

Hair Cortisol Concentration

Hair cortisol concentration (HCC) has emerged as one of the most promising biomarkers of chronic stress. In contrast to serum or salivary cortisol, which primarily reflect acute or short-term physiological states, HCC provides information regarding cumulative cortisol exposure over weeks or months. Human scalp hair grows approximately one centimeter per month, allowing retrospective assessment of long-term HPA-axis activity [43,44]. Advantages of HCC include assessment of chronic stress exposure, reduced influence of short-term fluctuations, easy sample collection, long-term biological integration.

Elevated hair cortisol concentrations have been reported in patients with psoriasis, chronic spontaneous urticaria, atopic dermatitis, and chronic pruritic disorders. Several studies have also demonstrated associations between HCC and perceived stress levels, disease severity, and quality-of-life impairment [43]. Given its ability to reflect long-term neuroendocrine activity, HCC is increasingly regarded as one of the most informative biomarkers for future psychodermatological investigations.

Catecholamines

The sympathetic-adrenal-medullary system represents another major component of the physiological stress response. Activation of sympathetic pathways results in increased secretion of norepinephrine, epinephrine and dopamine. These catecholamines influence vascular regulation, immune function, inflammatory responses, and skin physiology [17].

Elevated catecholamine levels have been associated with acute psychological stress, chronic stress disorders, inflammatory activation, autonomic dysregulation.

Although catecholamine measurement is less commonly employed in routine dermatological research due to methodological challenges, these mediators provide important insights into autonomic nervous system activity and may complement HPA-axis biomarkers [45].

Dehydroepiandrosterone Sulfate (DHEA-S)

DHEA-S is an adrenal steroid hormone frequently evaluated alongside cortisol. Unlike cortisol, DHEA-S possesses anti-inflammatory properties, neuroprotective effects, potential stress-buffering functions. The cortisol-to-DHEA-S ratio has been proposed as a more informative indicator of chronic stress than cortisol

alone because it reflects the balance between catabolic and protective neuroendocrine influences [46]. Lower DHEA-S levels and altered cortisol/DHEA-S ratios have been associated with chronic stress, depression, immune dysregulation, and inflammatory disease. Future studies may clarify the role of DHEA-S as a biomarker in psychodermatological disorders.

Neuropeptide-Associated Biomarkers

Neuropeptides occupy a central position within the NICE model and may serve as additional indicators of stress-related biological activity. Potential candidates include substance P, Calcitonin Gene-Related Peptide (CGRP), neurotensin and neuropeptide Y. These mediators participate in neurogenic inflammation, mast cell activation, pruritus pathways, and immune modulation.

Elevated concentrations have been reported in several inflammatory skin diseases and may correlate with disease activity and symptom severity [19–23]. Although neuropeptide measurements remain largely confined to research settings, they represent promising future biomarkers for psychodermatology.

Circadian Rhythms and Neuroendocrine Assessment

An important consideration in neuroendocrine biomarker research is the strong influence of circadian rhythms. Cortisol secretion follows a characteristic daily pattern characterized by a morning peak, progressive decline throughout the day, and minimal nocturnal levels. Psychological stress may disrupt these physiological rhythms, resulting in flattened cortisol curves, altered cortisol awakening responses, and impaired neuroendocrine adaptation.

Assessment of circadian neuroendocrine patterns may therefore provide additional information beyond single biomarker measurements [44].

Clinical Relevance and Future Perspectives

Although no single neuroendocrine biomarker currently provides a complete assessment of stress-related biological activity, combinations of complementary markers may offer valuable clinical insights.

Future psychodermatological research will likely focus on integrating: cortisol measurements, hair cortisol concentration, catecholamine profiles, DHEA-S levels, neuropeptide biomarkers, digital physiological indicators. Such multidimensional approaches may facilitate more accurate characterization of stress responsiveness and support the development of personalized therapeutic strategies.

As precision psychodermatology continues to evolve, neuroendocrine biomarkers are expected to play an increasingly important role in identifying vulnerable patients, predicting disease trajectories, and monitoring treatment responses [47–50].

6.2. Inflammatory Biomarkers

Inflammation represents one of the principal biological mechanisms linking psychological stress and dermatological disease. Increasing evidence from psychoneuroimmunology demonstrates that chronic stress may alter immune regulation through activation of neuroendocrine pathways, resulting in enhanced production of pro-inflammatory

mediators and disruption of immune homeostasis [27], [45].

The hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system exert profound effects on immune function through cortisol, catecholamines, and neuropeptides. Under physiological conditions, these mediators help maintain immune balance. However, prolonged stress exposure may lead to glucocorticoid resistance, persistent immune activation, and chronic low-grade inflammation [14–17].

Consequently, inflammatory biomarkers have emerged as important tools for evaluating stress-related biological responses and disease activity in dermatological disorders. These biomarkers may facilitate assessment of systemic inflammatory burden, identification of stress-sensitive disease phenotypes, prediction of disease exacerbations, monitoring of treatment response, development of personalized therapeutic strategies.

Among the most extensively investigated inflammatory biomarkers are cytokines, acute-phase proteins, and immune mediators associated with chronic inflammatory activation [27], [46].

Interleukin-6 (IL-6)

Interleukin-6 (IL-6) is one of the most consistently studied cytokines in psychoneuroimmunology and stress research. Produced by macrophages, dendritic cells, keratinocytes, endothelial cells, and fibroblasts, IL-6 plays a central role in coordinating inflammatory responses and regulating communication between the immune and neuroendocrine systems [27].

Numerous studies have demonstrated elevated circulating IL-6 levels in individuals exposed to chronic psychological stress. Potential mechanisms include sympathetic nervous system activation, glucocorticoid resistance, persistent immune stimulation, and oxidative stress. Elevated IL-6 concentrations have also been associated with anxiety, depression, sleep disturbance, and perceived stress [45].

In dermatology, increased IL-6 levels have been reported in psoriasis, atopic dermatitis, hidradenitis suppurativa, and chronic urticaria. Because IL-6 participates in both stress responses and inflammatory disease pathways, it represents one of the most promising biomarkers linking psychological stress and cutaneous inflammation [28].

Tumor Necrosis Factor-Alpha (TNF-α)

TNF-α is a key pro-inflammatory cytokine involved in numerous inflammatory and autoimmune diseases. Produced primarily by macrophages, T lymphocytes, mast cells and keratinocytes, TNF-α promotes leukocyte recruitment, endothelial activation, and amplification of inflammatory cascades [29].

Psychological stress has been shown to enhance TNF-α production through multiple neuroimmune pathways. Persistent elevation of TNF-α may contribute to chronic inflammation, endothelial dysfunction, oxidative stress, tissue damage. These mechanisms help explain the association between chronic stress and inflammatory disease exacerbation [46].

TNF-α plays a central role in psoriasis, hidradenitis suppurativa, and chronic inflammatory dermatoses. The remarkable clinical success of TNF inhibitors further underscores the biological importance of this cytokine in dermatological disease [29].

Interleukin-1 Beta (IL-1β)

IL-1β is an important mediator of innate immune activation and inflammatory signaling. Stress-related activation of inflammatory pathways may promote increased IL-1β production, resulting in enhanced leukocyte recruitment, activation of inflammatory cascades, and amplification of cytokine networks.

IL-1β has been implicated in several inflammatory skin disorders and may contribute to systemic inflammatory responses associated with chronic stress [46]. Because IL-1β also influences central nervous system function, it represents an important mediator within the broader skin–brain axis.

The IL-23/IL-17 Axis

The IL-23/IL-17 pathway represents one of the most important immunological discoveries in modern dermatology and is central to the pathogenesis of psoriasis [27], [29].

Produced primarily by dendritic cells and macrophages, IL-23 promotes differentiation of Th17 lymphocytes, maintenance of inflammatory responses, and cytokine amplification.

IL-17 stimulates keratinocyte activation and promotes production of chemokines, antimicrobial peptides, and pro-inflammatory cytokines. These effects contribute directly to epidermal hyperproliferation and chronic inflammation [27].

Emerging evidence suggests that chronic psychological stress may influence Th17-mediated immune responses through neuroendocrine and neuroimmune pathways. Although the precise mechanisms remain incompletely understood, stress-related dysregulation of the IL-23/IL-17 axis may contribute to disease exacerbations in psoriasis and other inflammatory dermatoses [52].

Interferon-Gamma (IFN-γ)

IFN-γ is a major cytokine associated with Th1 immune responses. Its biological functions include activation of macrophages, enhancement of antigen presentation, and promotion of cellular immunity. Stress-induced alterations in IFN-γ production may contribute to immune imbalance and inflammatory activation [30]. Elevated IFN-γ levels have been reported in several autoimmune and inflammatory skin diseases, including vitiligo, psoriasis, and alopecia areata.

C-Reactive Protein (CRP)

C-reactive protein is one of the most widely used biomarkers of systemic inflammation. Synthesized by the liver in response to IL-6 stimulation, CRP reflects overall inflammatory burden rather than disease-specific immune activity [45]. CRP offers several practical advantages: inexpensive measurement, widespread availability, standardized laboratory methods, and good reproducibility. However, CRP lacks specificity and may be influenced by infection, obesity, cardiovascular disease, and metabolic disorders. Despite these limitations, elevated CRP levels have been associated with chronic stress, depression, psoriasis, and systemic inflammatory activity [46].

High-Sensitivity C-Reactive Protein (hs-CRP)

High-sensitivity CRP assays permit detection of low-grade inflammation that may not be apparent using conventional CRP measurements. Chronic psychological stress has been associated with modest elevations in hs-CRP, suggesting that this

marker may reflect subtle inflammatory consequences of long-term stress exposure [45]. In dermatology, hs-CRP may be particularly useful for assessing systemic inflammatory burden in patients with psoriasis and other chronic inflammatory diseases.

Inflammatory Biomarker Panels

Although individual biomarkers provide valuable information, no single inflammatory mediator fully captures the complexity of stress-related immune dysregulation. Future approaches will likely rely on integrated biomarker panels combining: IL-6, TNF-α, IL-1β, IL-17, IFN-γ, CRP and hs-CRP. Such multidimensional assessments may provide a more accurate representation of inflammatory status and disease activity [47].

6.3. Neuroimmune Biomarkers

The concept of neuroimmune communication represents one of the central pillars of the Neuro-Immuno-Cutaneous-Endocrine (NICE) model. Over the past three decades, substantial evidence has demonstrated that the nervous and immune systems engage in continuous bidirectional communication through a complex network of neurotransmitters, neuropeptides, cytokines, and cellular interactions [19–23].

Psychological stress activates neural pathways that directly influence immune responses, while immune mediators generated during inflammation can affect neuronal function, behavior, and emotional regulation. Within the skin, these interactions are particularly important because sensory nerve fibers, mast cells, keratinocytes, dendritic cells, and lymphocytes are located in close anatomical proximity, creating a highly integrated neuroimmune microenvironment [1–3].

Neuroimmune biomarkers represent measurable indicators of this communication network and may provide valuable information regarding stress-induced biological activity, inflammatory responses, disease severity, and treatment outcomes.

Among the most extensively investigated neuroimmune biomarkers are substance P (SP), Calcitonin Gene-Related Peptide (CGRP), Nerve Growth Factor (NGF), Brain-Derived Neurotrophic Factor (BDNF), neurotensin, mast cell mediators and neurokinins. These biomarkers are increasingly recognized as potential links between psychological stress and inflammatory skin disease [19–23].

Substance P

Substance P is one of the most extensively studied neuropeptides in psychodermatology and serves as a prototypical neuroimmune biomarker. Belonging to the tachykinin family of neuropeptides, substance P is produced primarily by sensory nerve fibers, keratinocytes, immune cells, endothelial cells. It exerts its biological effects mainly through activation of the neurokinin-1 receptor (NK-1R) [19].

Substance P participates in neurogenic inflammation, vasodilation, mast cell activation, leukocyte recruitment, cytokine production, and pruritus transmission. Because of these diverse actions, Substance P occupies a central position within the skin-brain axis [20].

Psychological stress stimulates the release of Substance P from peripheral nerve endings and central nervous system structures. Elevated Substance P levels

have been associated with acute stress responses, chronic psychological stress, anxiety disorders, depression. These observations suggest that Substance P functions as an important mediator linking emotional stress and inflammatory activity [21].

Increased expression of Substance P has been demonstrated in psoriasis, atopic dermatitis, chronic urticaria, prurigo nodularis, and alopecia areata. Several studies have reported correlations between Substance P concentrations and disease severity, particularly in pruritic disorders [22].

Calcitonin Gene-Related Peptide (CGRP)

CGRP is another important neuropeptide involved in neuroimmune communication. Produced by sensory neurons and peripheral nerve fibers, CGRP is widely distributed throughout cutaneous tissues and participates in inflammatory regulation [20]. CGRP contributes to vasodilation, vascular permeability, immune modulation, neurogenic inflammation, and wound healing. The peptide also influences dendritic cell activity and cytokine production, highlighting its role in immune regulation [22]. Elevated CGRP expression has been reported in several inflammatory dermatoses, including psoriasis, atopic dermatitis, and rosacea. Although less extensively studied than Substance P, CGRP is increasingly recognized as an important neuroimmune mediator within the NICE framework [23].

Nerve Growth Factor (NGF)

Nerve Growth Factor is a neurotrophin that plays a critical role in neuronal development, survival, and regeneration. In addition to its neurological functions, NGF possesses important immunomodulatory properties and participates in neuroimmune communication [24]. NGF is produced by keratinocytes, fibroblasts, mast cells, eosinophils, and lymphocytes. Its production may be enhanced by inflammatory cytokines and psychological stress [25]. NGF contributes to sensory nerve growth, neurogenic inflammation, mast cell activation, cytokine production, and pruritus sensitization. These actions suggest an important role in chronic inflammatory and pruritic disorders [24]. Increased NGF levels have been documented in atopic dermatitis, psoriasis, chronic pruritus, and alopecia areata. Several studies have demonstrated associations between NGF concentrations and itch intensity, supporting its potential utility as a biomarker of neuroimmune activation [25].

Brain-Derived Neurotrophic Factor (BDNF)

Brain-Derived Neurotrophic Factor is another neurotrophin increasingly investigated in psychoneuroimmunology. Traditionally associated with neuronal plasticity and cognitive function, BDNF also influences immune regulation and inflammatory processes [26]. BDNF participates in neuronal survival, synaptic plasticity, stress adaptation, and immune modulation. Psychological stress may alter circulating BDNF levels, and abnormalities have been reported in depression, anxiety disorders, and chronic inflammatory diseases [27]. Although research remains limited, emerging evidence suggests that BDNF may contribute to stress-related inflammatory responses, chronic pruritus, and neurogenic inflammation. Further studies are required to clarify its role in

psychodermatological disorders.

Neurotensin

Neurotensin is a neuropeptide involved in stress responses and neuroimmune regulation. Experimental studies have demonstrated that neurotensin may activate mast cells, promote cytokine release, enhance vascular permeability, and amplify inflammatory responses. Because mast cell activation is a central component of the NICE model, neurotensin has attracted increasing attention as a potential neuroimmune biomarker [23].

Mast Cell-Associated Biomarkers

Mast cells occupy a unique position at the interface between the nervous and immune systems and represent one of the most important cellular components of the NICE network. Stress-induced mast cell activation may result in release of numerous mediators, including histamine, tryptase, chymase, TNF-α, IL-6, leukotrienes, and prostaglandins. Measurement of these mediators may provide indirect evidence of neuroimmune activation [24].

Tryptase

Tryptase is among the most commonly used markers of mast cell activation. Elevated levels have been reported in chronic spontaneous urticaria, mast cell disorders, and inflammatory skin diseases. Because mast cells respond directly to neuropeptides such as Substance P and CRH, tryptase may serve as a useful indicator of neuroimmune interactions [25].

Histamine

Histamine contributes to pruritus, vasodilation, vascular permeability, and inflammatory activation. Although not specific for stress-related inflammation, histamine remains an important mediator linking mast cell activation and clinical symptoms [24].

Neurokinins and Related Peptides

Additional members of the tachykinin family, including neurokinin A and neurokinin B, have also been implicated in neuroimmune regulation. These mediators influence inflammatory responses, vascular function and sensory nerve activity. Although their roles in dermatological disease remain less well characterized than those of Substance P, they may contribute to the broader neuroimmune network involved in stress-sensitive dermatoses [22].

6.4. Oxidative Stress Biomarkers

Oxidative stress has emerged as an important biological mechanism linking psychological stress, immune dysregulation, and chronic inflammatory disease. Within the framework of the Neuro-Immuno-Cutaneous-Endocrine (NICE) model, oxidative stress represents a downstream consequence of neuroendocrine activation, inflammatory signaling, and cellular metabolic imbalance. Increasing evidence suggests that excessive production of reactive oxygen species (ROS) contributes not only to tissue damage but also to immune activation, neuroinflammation, and epidermal dysfunction [35–37].

Under physiological conditions, ROS are generated as natural by-products of cellular metabolism and participate in numerous signaling pathways involved in cell proliferation, differentiation, host defense, and tissue repair. However, when

ROS production exceeds the capacity of antioxidant defense systems, oxidative stress develops, resulting in damage to lipids, proteins, nucleic acids, and cellular organelles [35].

Psychological stress has been shown to enhance oxidative stress through multiple mechanisms, including activation of the hypothalamic–pituitary–adrenal (HPA) axis, sympathetic nervous system stimulation, mitochondrial dysfunction, and chronic inflammatory activation. Consequently, biomarkers reflecting oxidative damage have attracted increasing attention as potential indicators of stress-related biological activity in dermatological diseases [36].

Psychological Stress and Oxidative Stress

Psychological stress influences redox homeostasis through complex neuroendocrine and immunological pathways. Activation of the stress response results in: increased cortisol secretion, catecholamine release, enhanced inflammatory cytokine production, mitochondrial activation, altered antioxidant defenses. Collectively, these mechanisms contribute to increased generation of reactive oxygen and nitrogen species [37]. Chronic exposure to oxidative stress may subsequently promote: cellular senescence, DNA damage, immune dysregulation, chronic inflammation, impaired tissue repair. These effects are particularly relevant in dermatology, where oxidative stress has been implicated in numerous inflammatory, autoimmune, and degenerative skin disorders [35].

Malondialdehyde (MDA)

Malondialdehyde is one of the most widely used biomarkers of oxidative stress. MDA is generated during lipid peroxidation, a process in which reactive oxygen species attack polyunsaturated fatty acids within cellular membranes. Elevated MDA concentrations therefore reflect oxidative damage to membrane lipids and cellular structures [35]. Increased MDA levels indicate: enhanced lipid peroxidation, cellular membrane damage, chronic oxidative stress, inflammatory activation. Because lipid peroxidation represents a major consequence of oxidative injury, MDA has become a widely accepted marker of systemic oxidative burden [36].

Elevated MDA concentrations have been reported in: psoriasis, vitiligo, alopecia areata, atopic dermatitis, Chronic urticaria. Several studies have demonstrated correlations between MDA levels and disease severity, suggesting a potential role in disease monitoring [37].

8-Hydroxy-2’-Deoxyguanosine (8-OHdG)

8-Hydroxy-2’-deoxyguanosine (8-OHdG) is considered one of the most reliable biomarkers of oxidative DNA damage. Reactive oxygen species may attack guanine residues within DNA, generating 8-OHdG as a stable oxidation product. Measurement of 8-OHdG provides valuable information regarding cumulative oxidative injury at the genomic level [36].

Elevated 8-OHdG levels have been associated with chronic psychological stress, aging, inflammatory diseases, autoimmune disorders, and carcinogenesis. Because DNA damage represents a critical consequence of oxidative stress, 8-OHdG is increasingly used in both clinical and experimental studies [37]. In dermatology, increased 8-OHdG concentrations have been observed in: psoriasis, vitiligo, photoaging, skin

cancer, and chronic inflammatory dermatoses. These findings support the role of oxidative DNA damage in cutaneous pathology.

Advanced Oxidation Protein Products (AOPPs)

Advanced oxidation protein products are generated through oxidative modification of proteins by reactive oxygen species and chlorinated oxidants. AOPPs serve as indicators of protein oxidation, chronic inflammatory activity, and oxidative tissue injury. Unlike transient reactive oxygen species, AOPPs are relatively stable and therefore provide useful information regarding cumulative oxidative stress exposure [35]. Elevated AOPP levels have been documented in several chronic inflammatory diseases and may correlate with disease activity.

Protein Carbonyls

Protein carbonyls represent another important marker of oxidative protein damage. Oxidative modification of amino acid side chains results in the formation of carbonyl groups, which accumulate during periods of increased oxidative stress. Elevated protein carbonyl levels have been associated with chronic inflammation, aging, autoimmune disease, and psychological stress. Although less frequently used in dermatological research than MDA or 8-OHdG, protein carbonyls provide complementary information regarding oxidative injury [36].

Total Antioxidant Capacity (TAC)

Assessment of oxidative stress should ideally include evaluation of antioxidant defense mechanisms in addition to markers of oxidative damage. Total antioxidant capacity (TAC) reflects the cumulative activity of enzymatic and non-enzymatic antioxidant systems, including glutathione, superoxide dismutase (SOD), catalase, vitamins C and E, and uric acid. Reduced TAC may indicate impaired ability to neutralize reactive oxygen species and increased susceptibility to oxidative injury [37]. Several studies have reported decreased antioxidant capacity in patients with psoriasis, vitiligo, alopecia areata, and atopic dermatitis. Such findings suggest that oxidative stress results not only from increased ROS production but also from inadequate antioxidant defenses.

Enzymatic Antioxidant Biomarkers
Superoxide Dismutase (SOD)

SOD represents one of the most important endogenous antioxidant enzymes. Its primary function is the conversion of superoxide radicals into hydrogen peroxide, thereby reducing oxidative damage. Altered SOD activity has been reported in numerous inflammatory skin diseases and may reflect disturbances in redox homeostasis [35].

Catalase

Catalase converts hydrogen peroxide into water and oxygen, preventing accumulation of potentially toxic oxidants. Reduced catalase activity has been documented in vitiligo, psoriasis, and photoaging. Particularly in vitiligo, decreased catalase activity is considered an important contributor to melanocyte vulnerability [36].

Glutathione Peroxidase (GPx)

GPx protects cells against oxidative injury by reducing hydrogen peroxide and lipid peroxides. Abnormal GPx activity has been associated with chronic

inflammatory and autoimmune conditions and may serve as an indicator of antioxidant system dysfunction.

Oxidative Stress in Major Dermatological Diseases

Psoriasis

Psoriasis is characterized by increased oxidative stress resulting from chronic immune activation and accelerated keratinocyte proliferation. Elevated levels of MDA, AOPPs and 8-OHdG have been reported, while antioxidant defenses are frequently reduced [27,35].

Vitiligo

Among dermatological diseases, vitiligo exhibits some of the strongest evidence implicating oxidative stress in pathogenesis. Accumulation of hydrogen peroxide, reduced catalase activity, and oxidative damage to melanocytes are believed to contribute directly to depigmentation [36].

Alopecia Areata

Oxidative stress may contribute to follicular immune dysregulation and hair follicle damage in alopecia areata. Several studies have demonstrated increased lipid peroxidation and altered antioxidant enzyme activity in affected patients [37].

Atopic Dermatitis

In atopic dermatitis, oxidative stress interacts with barrier dysfunction and immune activation, contributing to chronic inflammation and disease persistence.

6.5. Microbiome-Derived Biomarkers

The growing recognition of the microbiome as a key regulator of immune homeostasis, neuroendocrine signaling, and inflammatory responses has generated considerable interest in the identification of microbiome-derived biomarkers. Within the framework of the Neuro-Immuno-Cutaneous-Endocrine (NICE) model, microbial communities are increasingly viewed not merely as passive colonizers but as active participants in host physiological regulation and disease pathogenesis [38–42].

Advances in next-generation sequencing, metagenomics, metabolomics, and systems biology have enabled detailed characterization of microbial ecosystems inhabiting the skin and gastrointestinal tract. These technologies have revealed associations between microbial composition, psychological stress, immune dysregulation, and chronic inflammatory diseases, including numerous dermatological disorders [39,40]. Microbiome-derived biomarkers encompass a broad range of measurable parameters, including microbial diversity indices, taxonomic composition, microbial metabolites, functional gene profiles, and microbial-derived inflammatory mediators. These biomarkers provide valuable insights into host–microbe interactions and may contribute to future precision psychodermatology approaches [41].

Microbial Diversity as a Biomarker

One of the most widely investigated microbiome-derived biomarkers is microbial diversity.

Alpha Diversity

Alpha diversity refers to the richness and evenness of microbial species within a specific ecological niche. Reduced alpha diversity is frequently considered a marker of dysbiosis and has been associated with inflammatory bowel disease, obesity,

autoimmune diseases, atopic dermatitis, and psoriasis. Several studies have demonstrated that psychological stress may reduce microbial diversity, potentially contributing to immune dysregulation and inflammatory activation [42].

Beta Diversity

Beta diversity describes differences in microbial composition between individuals or populations. Alterations in beta diversity have been reported in numerous dermatological diseases and may help distinguish disease-specific microbial signatures [38]. Although diversity measures are not disease-specific, they provide useful indicators of microbial ecosystem stability and resilience.

Taxonomic Biomarkers

Specific microbial taxa have been proposed as potential biomarkers of health and disease.

Gut Microbiota Signatures

Numerous studies have reported alterations in the relative abundance of key bacterial groups in inflammatory and stress-related disorders. Examples include reduced Faecalibacterium prausnitzii, decreased Bifidobacterium spp., reduced Lactobacillus spp., increased Escherichia coli, and expansion of pro-inflammatory Proteobacteria. Many of these changes have been associated with increased intestinal permeability and systemic inflammation [39].

Skin Microbiota Signatures

Disease-specific microbial alterations have also been documented at the cutaneous level.

Atopic dermatitis

- increased *Staphylococcus aureus* colonization;
- reduced microbial diversity.

Psoriasis

- altered abundance of *Streptococcus, Corynebacterium,* and *Cutibacterium species.*

Acne vulgaris

- strain-specific alterations of *Cutibacterium acnes*.

Rosacea

- changes involving *Demodex*-associated microbial communities.

Such microbial signatures may eventually serve as diagnostic or prognostic biomarkers [40,41].

Short-Chain Fatty Acids (SCFAs)

Among microbiome-derived metabolites, short-chain fatty acids are among the most extensively studied. SCFAs are produced through bacterial fermentation of dietary fibers and include acetate, propionate, and butyrate. These metabolites exert profound effects on host physiology and immune regulation [60].

Biological Functions

SCFAs contribute to maintenance of intestinal barrier integrity, regulation of regulatory T-cell activity, suppression of pro-inflammatory cytokines, modulation of oxidative stress, and neuroimmune communication. Through these mechanisms, SCFAs help maintain immune tolerance and inflammatory balance [53]. Reduced SCFA production has been associated with chronic psychological stress, inflammatory bowel disease, psoriasis, atopic dermatitis, and metabolic disorders. Consequently, SCFA levels may serve as valuable indicators of microbiome

function and immune homeostasis [61].

Tryptophan Metabolites

The metabolism of tryptophan represents another important pathway linking the microbiome, immune system, and nervous system. Gut microorganisms influence tryptophan metabolism through several mechanisms, generating bioactive compounds capable of affecting both immune responses and central nervous system function [62].

Important microbiome-related tryptophan metabolites include indole derivatives, kynurenine, and serotonin precursors. These compounds influence mood regulation, stress responsiveness, immune activity, and epithelial barrier function. Alterations in tryptophan metabolism have been implicated in both psychiatric disorders and inflammatory diseases [63]. Because of their dual neuroimmune effects, tryptophan metabolites represent particularly attractive candidates for future psychodermatological biomarker research.

Lipopolysaccharide (LPS) and Microbial Translocation Markers

Increased intestinal permeability associated with dysbiosis may facilitate translocation of bacterial products into the systemic circulation. Among these products, lipopolysaccharide (LPS) is one of the most extensively studied.

LPS activates innate immune pathways through Toll-like receptor 4 (TLR4), resulting in cytokine production, macrophage activation, oxidative stress, and systemic inflammation. Elevated circulating LPS levels have been associated with chronic stress, metabolic disorders, and inflammatory diseases [54]. Markers reflecting microbial translocation may provide indirect evidence of intestinal barrier dysfunction, dysbiosis, and chronic inflammatory activation. Such biomarkers may prove useful in evaluating the gut–brain–skin axis in clinical research settings.

Microbial Functional Biomarkers

Traditional microbiome studies often focus on taxonomic composition. However, increasing evidence suggests that microbial function may be more informative than microbial identity alone. Metagenomic and metabolomic approaches allow assessment of microbial metabolic pathways, enzymatic activity, neurotransmitter synthesis, and inflammatory potential. Potential functional biomarkers include SCFA biosynthesis capacity, neurotransmitter production pathways, bile acid metabolism, and oxidative stress-related pathways. These approaches provide deeper insights into the biological consequences of dysbiosis [64].

Neuroactive Microbial Metabolites

One of the most intriguing discoveries in microbiome research is the ability of microorganisms to produce neuroactive compounds. Microbial communities can generate γ-aminobutyric acid (GABA), serotonin precursors, dopamine precursors, and acetylcholine-like molecules.

These substances may influence mood, cognition, stress responses, and neuroimmune communication. Consequently, microbial neuroactive metabolites are increasingly recognized as potential biomarkers of gut–brain communication [52].

6.6. Digital Biomarkers

The rapid development of digital health technologies has transformed the way physiological and behavioral data can be collected, analyzed, and integrated into clinical practice. In recent years, the concept of digital biomarkers has emerged as one of the most promising innovations in precision medicine and personalized healthcare. Digital biomarkers are defined as objective, quantifiable physiological and behavioral data collected through digital devices such as smartphones, wearable sensors, smartwatches, biosensors, and remote monitoring systems [51–55].

Within psychodermatology, digital biomarkers offer a unique opportunity to objectively assess stress-related physiological changes, behavioral patterns, and disease trajectories in real-world settings. Unlike conventional biomarkers obtained during isolated clinical visits, digital biomarkers enable continuous and longitudinal monitoring, providing dynamic information regarding patient health status and disease activity [56].

Because psychological stress plays a central role in many dermatological disorders, digital biomarkers may significantly enhance our ability to identify stress-sensitive patients, predict disease flares, monitor treatment responses, and implement preventive interventions. Consequently, digital biomarkers are increasingly viewed as an important component of future precision psychodermatology [57].

Concept and Characteristics of Digital Biomarkers

Digital biomarkers differ fundamentally from traditional laboratory biomarkers. Conventional biomarkers are typically measured through blood samples, saliva, urine or tissue biopsies. In contrast, digital biomarkers are derived from continuously collected physiological and behavioral data generated during daily life [54]. Advances in wearable technology have made it possible to monitor numerous physiological parameters without disrupting normal activities, thereby providing valuable insights into real-world stress responses and health behaviors [55].

Heart Rate Variability (HRV)

Heart rate variability is among the most extensively studied digital biomarkers of stress. HRV reflects fluctuations in the interval between consecutive heartbeats and provides an indirect measure of autonomic nervous system activity. HRV reflects the balance between sympathetic nervous system activity, parasympathetic nervous system activity. Higher HRV generally indicates better autonomic flexibility, greater stress resilience, and improved physiological adaptability. Conversely, reduced HRV has been associated with chronic stress, anxiety disorders, depression, and systemic inflammation [58]. Because stress plays an important role in many inflammatory dermatoses, HRV may provide valuable information regarding stress burden, autonomic dysregulation, disease susceptibility, and flare risk. Continuous HRV monitoring may therefore become a useful tool in psychodermatological research and clinical practice [59].

Sleep-Related Digital Biomarkers

Sleep disturbances are highly prevalent among patients with chronic dermatological diseases, particularly those

characterized by pruritus and chronic inflammation. Wearable devices and smartphone-based applications can provide objective assessment of sleep duration, sleep efficiency, sleep fragmentation, circadian rhythm patterns, and nocturnal awakenings. Poor sleep quality has been associated with increased psychological stress, elevated inflammatory activity, impaired immune regulation, and worsening of dermatological symptoms.

In conditions such as atopic dermatitis and chronic pruritus, sleep disruption may contribute significantly to disease burden and reduced quality of life [60]. Consequently, sleep-related metrics represent valuable digital biomarkers of both psychological and dermatological health.

Physical Activity Monitoring

Physical activity represents another important digital biomarker. Modern wearable devices allow continuous monitoring of daily step counts, exercise duration, energy expenditure, and sedentary behavior. Reduced physical activity may reflect psychological distress, depressive symptoms, fatigue, and disease-related functional impairment. Conversely, regular physical activity is associated with improved stress resilience, reduced systemic inflammation, and better mental health outcomes. Monitoring activity patterns may therefore provide indirect information regarding disease burden and psychosocial functioning [61].

Skin Conductance and Electrodermal Activity

Electrodermal activity (EDA), also known as skin conductance, reflects sympathetic nervous system activation and emotional arousal. Stress-induced activation of sweat glands alters electrical conductivity of the skin, allowing continuous measurement through wearable sensors. Changes in EDA may provide information regarding, acute stress responses, emotional reactivity, autonomic nervous system activity, and physiological arousal. Because EDA responds rapidly to psychological stimuli, it may serve as a sensitive indicator of moment-to-moment stress fluctuations [62].

Wearable Biosensors

Recent technological advances have facilitated the development of increasingly sophisticated wearable biosensors capable of monitoring physiological and biochemical parameters in real time. Potential applications include continuous assessment of body temperature, heart rate, respiratory rate, sweat composition, hydration status, and cortisol levels. Although many of these technologies remain investigational, they have considerable potential for future psychodermatological applications [63].

Cortisol Monitoring

Particularly promising are emerging wearable systems capable of measuring cortisol in sweat or interstitial fluid. Continuous cortisol monitoring could provide valuable information regarding stress exposure, HPA-axis activity, and disease exacerbation risk. Such technologies may eventually complement traditional neuroendocrine biomarkers discussed earlier in this review [43,44].

Smartphone-Derived Behavioral Biomarkers

Smartphones generate large amounts of behavioral data that may serve as indirect

indicators of psychological health. Potential digital biomarkers include screen time, communication patterns, mobility data, typing behavior, and social interaction metrics. Several studies have demonstrated associations between these parameters and stress, anxiety, depression, emotional well-being. Although still in early stages of development, smartphone-derived biomarkers may provide valuable insights into psychosocial functioning [64].

Artificial Intelligence and Predictive Modeling

One of the greatest strengths of digital biomarkers lies in their ability to generate large volumes of continuous data suitable for machine-learning analysis. Artificial intelligence (AI) algorithms may integrate information from wearable sensors, smartphones, clinical assessments, laboratory biomarkers, patient-reported outcomes. Such systems may facilitate prediction of disease flares, identification of high-risk patients, treatment optimization, and personalized intervention strategies [53,54].

Predictive Psychodermatology

Future AI-driven models may identify subtle physiological changes that precede clinical disease exacerbation. Potential applications include prediction of psoriasis flares, atopic dermatitis exacerbations, chronic urticaria activity, and pruritus severity. These approaches represent important components of emerging precision psychodermatology frameworks.

Digital Biomarkers and Precision Psychodermatology

Digital biomarkers align closely with the principles of precision medicine because they provide individualized, real-time information regarding patient physiology and behavior. Potential advantages include continuous monitoring, early disease detection, personalized risk assessment, objective treatment evaluation, and enhanced patient engagement. When integrated with neuroendocrine, inflammatory, neuroimmune, oxidative stress, and microbiome-derived biomarkers, digital biomarkers may facilitate comprehensive characterization of stress-related biological responses [47–50].

Challenges and Limitations

Despite their promise, several challenges currently limit the widespread implementation of digital biomarkers.

These include technical challenges (device accuracy, sensor reliability, data standardization, interoperability issues), ethical considerations (privacy concerns, data security, informed consent, algorithmic transparency) and clinical validation. Many proposed digital biomarkers require further validation before routine clinical adoption. Large prospective studies are needed to establish their reliability, reproducibility, and clinical utility [54].

Future Perspectives

The next decade is likely to witness rapid expansion of digital biomarker research in dermatology and psychodermatology. Future developments may include continuous multimodal monitoring platforms, wearable stress-detection systems, AI-assisted flare prediction, digital phenotyping, and personalized psychodermatological interventions. Integration of digital biomarkers into clinical practice may facilitate a shift from

reactive disease management toward predictive, preventive, and personalized care. Within the broader NICE framework, digital biomarkers may eventually provide real-time assessment of neuroendocrine, neuroimmune, and behavioral processes, enabling more precise understanding of the dynamic interactions linking psychological stress and skin disease [65].

7. Precision Psychodermatology: From Systems Biology to Personalized Care

The growing complexity of psychodermatological research has revealed important limitations of traditional reductionist approaches to disease. Historically, dermatological disorders were often investigated through isolated biological pathways or individual risk factors. While such approaches have yielded significant advances, they are frequently insufficient to explain the considerable heterogeneity observed in disease susceptibility, clinical presentation, treatment response, and long-term outcomes [47–50].

Psychological stress-related skin diseases represent particularly complex conditions because they arise from dynamic interactions among genetic, immunological, neuroendocrine, microbial, environmental, and psychosocial factors. Consequently, increasing attention has shifted toward systems biology and precision medicine approaches capable of integrating multiple levels of biological and clinical information into comprehensive models of disease pathogenesis [47,48]. Within this evolving framework, precision psychodermatology may be defined as the application of systems biology, multi-omics technologies, biomarker science, artificial intelligence, and personalized healthcare principles to the assessment and management of stress-related dermatological diseases. Rather than treating all patients according to generalized disease classifications, precision psychodermatology seeks to identify individual biological and psychosocial profiles that can guide personalized prevention, diagnosis, monitoring, and treatment strategies [49].

7.1. Systems Biology and the NICE Framework

Systems biology represents an integrative scientific approach that examines biological systems as interconnected networks rather than collections of isolated components.

The NICE model itself can be viewed as an early systems biology framework because it recognizes continuous bidirectional communication among the nervous system, the immune system, endocrine pathways, and the skin. More recent developments have expanded this model to include the microbiome, metabolic pathways, environmental exposures, behavioral factors, and digital health data. As a result, psychodermatological diseases are increasingly understood as emergent properties of complex adaptive biological systems rather than consequences of single pathogenic mechanisms [48].

Systems biology offers several advantages identification of disease networks rather than isolated biomarkers, improved understanding of disease heterogeneity, recognition of feedback loops and non-linear interactions, discovery of novel therapeutic targets, and facilitation of personalized care

strategies. These characteristics are particularly relevant for stress-sensitive dermatoses, where multiple biological pathways interact simultaneously [47].

7.2. Multi-Omics Approaches in Psychodermatology

One of the major drivers of precision medicine has been the emergence of multi-omics technologies. The term "omics" refers to large-scale characterization of biological systems at multiple levels.

Genomics

Genomic analyses investigate inherited genetic variation associated with disease susceptibility and treatment response. Potential applications include identification of genetic predisposition to inflammatory diseases, stress-response polymorphisms, and susceptibility loci for psoriasis and atopic dermatitis. Genomic information may help explain why certain individuals exhibit greater biological sensitivity to psychological stress than others [49].

Transcriptomics

Transcriptomics evaluates gene expression patterns under specific physiological or pathological conditions. Stress-related alterations in transcriptional activity may reveal inflammatory activation, neuroendocrine dysregulation, oxidative stress pathways, and immune response signatures. Transcriptomic analyses have already identified characteristic molecular profiles in psoriasis, atopic dermatitis, and alopecia areata [50].

Proteomics

Proteomics focuses on large-scale characterization of proteins and signaling molecules. Potential applications include cytokine profiling, neuropeptide assessment, inflammatory pathway analysis, and therapeutic response monitoring. Because proteins represent functional mediators of biological activity, proteomic approaches may provide particularly relevant clinical information [49].

Metabolomics

Metabolomics evaluates small molecules generated by cellular metabolism. Examples include short-chain fatty acids, amino acid metabolites, oxidative stress products, and neurotransmitter precursors. Metabolomic profiling may provide valuable insights into interactions among stress, immunity, metabolism, and microbiome function [50].

Microbiomics

Microbiome analysis has become an increasingly important component of precision psychodermatology. Characterization of gut and skin microbial ecosystems may facilitate identification of dysbiosis patterns, prediction of inflammatory activity, and development of microbiome-targeted therapies. Integration of microbiomic and metabolomic data is expected to play a central role in future personalized treatment approaches [39–42].

7.3. Integrated Biomarker Signatures

Although individual biomarkers may provide useful information, complex diseases rarely depend on a single biological pathway. For this reason, future

psychodermatology will likely rely on integrated biomarker signatures rather than isolated laboratory measurements. Integration of these complementary datasets may facilitate a more comprehensive understanding of individual disease mechanisms [47–55].

7.4. Artificial Intelligence and Machine Learning

The increasing availability of large, multidimensional datasets has stimulated growing interest in artificial intelligence (AI) and machine learning applications within dermatology. AI systems are particularly valuable because they can identify complex relationships among variables that may not be apparent through conventional statistical methods [51–54].

Potential Applications

AI may assist in disease classification, patient stratification, biomarker discovery, flare prediction, treatment selection, and outcome prediction. For psychodermatology, AI offers the possibility of integrating biological, psychological, microbiological, and behavioral data into unified predictive models.

Predicting Disease Flares

One particularly promising application involves prediction of stress-related disease exacerbations. Machine-learning algorithms may eventually combine stress measurements, biomarker profiles, wearable sensor data, patient-reported outcomes, and environmental exposures, to identify patients at increased risk of disease flare before clinical symptoms become apparent [54].

7.5. Digital Phenotyping and Continuous Monitoring

Digital phenotyping refers to the real-time characterization of human behavior and physiology through data generated by digital devices. In psychodermatology, digital phenotyping may provide objective information regarding stress exposure, sleep patterns, physical activity, social engagement, and treatment adherence. These data can complement traditional clinical assessments and improve understanding of individual disease trajectories [55]. Future digital health platforms may continuously integrate information from smartphones, wearable devices, remote sensors, and electronic health records, creating dynamic models of patient health status and disease risk.

7.6. Personalized Therapeutic Strategies

The ultimate goal of precision psychodermatology is the development of individualized treatment plans based on each patient's unique biological and psychosocial profile.

Potential therapeutic components may include:

- **Targeted Pharmacological Therapy** - selection of biologics or small molecules based on inflammatory and molecular signatures.
- **Psychological Interventions** - identification of patients who may benefit from cognitive behavioral therapy, mindfulness-based stress reduction, and stress-management programs.
- **Microbiome-Based Therapies** - use of probiotics, prebiotics, postbiotics, dietary interventions.
- **Lifestyle-Based Interventions** - personalized recommendations regarding

sleep optimization, physical activity, nutrition, stress reduction.

Such approaches may improve both clinical outcomes and quality of life [48–50].

7.7. Challenges and Limitations

Despite its considerable promise, precision psychodermatology faces several important challenges.

Biological Complexity

Stress-related skin diseases involve numerous interacting biological pathways that remain incompletely understood.

Data Integration

Combining genomic, immunological, microbiome, digital, and clinical data requires sophisticated analytical approaches.

Cost and Accessibility

Many advanced technologies remain expensive and are not widely available in routine clinical practice.

Ethical Considerations

Important issues include patient privacy, data ownership, algorithm transparency, equitable access to precision medicine technologies.

Addressing these challenges will be essential for successful implementation of personalized psychodermatological care [51–55].

7.8. Future Perspectives

The future of psychodermatology will likely be characterized by increasing integration of systems biology, multi-omics technologies, artificial intelligence, and digital health. Emerging models of care may incorporate continuous biomarker monitoring, real-time stress assessment, microbiome profiling, predictive analytics, and individualized therapeutic recommendations. Within this framework, dermatologists may move beyond reactive treatment of disease flares toward proactive identification of biological vulnerability and early intervention.

Precision psychodermatology therefore represents a natural evolution of the NICE model, transforming our understanding of the skin–brain connection from a conceptual framework into a clinically actionable strategy for personalized patient care.

8. Artificial Intelligence and Digital Psychodermatology

Artificial intelligence (AI) is rapidly transforming modern medicine by enabling the analysis of complex datasets, facilitating clinical decision-making, and supporting personalized healthcare. In dermatology, AI applications have expanded dramatically over the past decade, driven by advances in machine learning, deep learning, computer vision, and digital health technologies [51–54].

While much of the early attention focused on automated image analysis and skin cancer detection, AI is increasingly being applied to broader aspects of dermatological care, including disease monitoring, treatment optimization, patient stratification, and predictive analytics. Simultaneously, the growing availability of wearable devices, mobile health applications, telemedicine platforms, and digital biomarkers has fostered the emergence of digital

psychodermatology, an interdisciplinary field integrating dermatology, behavioral science, psychoneuroimmunology, and digital medicine [55].

Within the framework of the Neuro-Immuno-Cutaneous-Endocrine (NICE) model, artificial intelligence offers unprecedented opportunities to integrate multidimensional data derived from neuroendocrine, inflammatory, neuroimmune, microbiome, behavioral, and environmental sources. Such approaches may facilitate a more comprehensive understanding of stress-related dermatological disease and support the transition toward predictive and personalized care [47–50].

8.1. Fundamentals of Artificial Intelligence in Healthcare

Artificial intelligence encompasses computational systems capable of performing tasks that traditionally require human cognitive abilities, including pattern recognition, prediction, classification, and decision-making [53].

Machine Learning

Machine learning (ML) represents a subset of AI in which algorithms identify patterns within data and improve performance through experience. Common ML approaches include supervised learning, unsupervised learning, reinforcement learning. These methods have been increasingly applied to disease prediction, risk stratification, and biomarker discovery [54].

Deep Learning

Deep learning utilizes artificial neural networks composed of multiple computational layers capable of extracting highly complex features from large datasets. In dermatology, deep learning has achieved remarkable success in lesion classification, melanoma detection, image interpretation, or disease recognition. Several studies have demonstrated diagnostic performances comparable to experienced dermatologists for selected image-based tasks [51,52].

8.2. Artificial Intelligence in Dermatology

Dermatology is particularly well suited for AI applications because of its strong reliance on visual assessment and pattern recognition.

Automated Image Analysis

Deep learning algorithms can analyze dermoscopic and clinical images to identify characteristic disease patterns. Applications include melanoma detection, non-melanoma skin cancer diagnosis, psoriasis severity assessment, acne grading, or inflammatory dermatosis classification. Automated image analysis may improve diagnostic accuracy, increase accessibility, and facilitate earlier detection of disease [51].

Disease Severity Assessment

AI systems may also assist in objective disease monitoring. Examples include Psoriasis Area and Severity Index (PASI) estimation, Eczema Area and Severity Index (EASI) assessment, automated lesion counting, and erythema quantification. These tools may reduce interobserver variability and improve standardization of clinical evaluations [54].

Teledermatology

The integration of AI with teledermatology platforms has expanded

access to dermatological expertise, particularly in underserved regions. Potential benefits include rapid triage, remote monitoring, early diagnosis, or improved healthcare accessibility. These advances became particularly relevant during and after the COVID-19 pandemic, which accelerated adoption of digital healthcare technologies [55].

8.3. Artificial Intelligence and Psychodermatology

Although AI applications in psychodermatology remain in early stages of development, the field presents unique opportunities for innovation. Stress-related dermatological diseases involve complex interactions among psychological factors, neuroendocrine pathways, immune responses, microbiome dynamics, and behavioral variables. Traditional clinical assessment often struggles to integrate these diverse sources of information effectively. Artificial intelligence offers powerful tools capable of identifying multidimensional patterns that may not be apparent through conventional analytical approaches [53].

Identification of Stress-Sensitive Phenotypes

Machine-learning algorithms may facilitate identification of patient subgroups characterized by heightened biological stress responses, increased disease susceptibility, distinct inflammatory profiles, and specific psychosocial characteristics. Such stratification could support more individualized treatment approaches [47].

Prediction of Disease Exacerbations

One of the most promising applications involves prediction of disease flares. Potential predictive variables include cortisol levels, inflammatory biomarkers, sleep patterns, heart rate variability, patient-reported stress, and environmental exposures. By integrating these factors, AI systems may identify early indicators of disease worsening before clinical manifestations become evident [54].

8.4. Digital Phenotyping in Psychodermatology

Digital phenotyping refers to the continuous and objective assessment of human behavior and physiology through data generated by digital devices. Smartphones, wearable sensors, and connected health platforms generate large amounts of information that may provide insights into psychological and physiological functioning [55].

Potential Variables

Digital phenotyping may capture physical activity levels, sleep quality, mobility patterns, social interactions, communication behavior, or physiological stress responses. These variables may serve as indirect indicators of emotional well-being, stress burden, and disease activity [56].

Relevance for Dermatological Disease

Several chronic dermatological disorders are associated with sleep disturbance, reduced social engagement, impaired quality of life, and psychological distress. Digital phenotyping may therefore provide objective measures of disease burden that complement traditional clinical assessments.

8.5. Wearable Technologies and Remote Monitoring

Wearable devices have become increasingly sophisticated and are capable of continuously monitoring multiple physiological parameters relevant to psychodermatology. Examples include heart rate, heart rate variability, skin temperature, electrodermal activity, sleep metrics, and physical activity. These technologies facilitate real-time assessment of stress responses and physiological adaptation [57].

Early Detection of Disease Activity

Continuous monitoring may identify subtle physiological changes that precede clinical deterioration. Potential applications include prediction of psoriasis flares, monitoring of atopic dermatitis activity, assessment of chronic urticaria triggers, and evaluation of pruritus-related sleep disruption. Such approaches may facilitate preventive interventions before overt disease exacerbation occurs.

8.6. Digital Therapeutics and Behavioral Interventions

Digital health technologies are increasingly being used not only for monitoring but also for therapeutic purposes. Digital therapeutics may include cognitive behavioral therapy applications, mindfulness-based interventions; stress-management programs, sleep optimization platforms, or behavioral coaching systems. Several studies have demonstrated beneficial effects of digital psychological interventions on stress reduction and quality of life [58].

Potential Role in Psychodermatology

Because psychological stress contributes significantly to disease activity in many inflammatory dermatoses, digital therapeutic platforms may become valuable adjunctive tools in comprehensive patient management. Potential benefits include improved treatment adherence, enhanced patient engagement, greater accessibility of psychological support, and continuous behavioral monitoring.

8.7. Artificial Intelligence and Multi-Omics Integration

One of the greatest challenges in precision psychodermatology is the integration of large and heterogeneous datasets. These may include genomic information, transcriptomic profiles, proteomic data, metabolomic signatures, microbiome analyses, biomarker panels, and digital health data. Artificial intelligence provides powerful analytical tools capable of identifying meaningful patterns within these multidimensional datasets [49,50].

Predictive Modeling

Future AI systems may generate individualized risk profiles by integrating biological biomarkers, psychological variables, environmental exposures, digital phenotyping data. Such predictive models could support personalized prevention strategies, early intervention, treatment selection, and disease monitoring.

8.8. Future Perspectives

Artificial intelligence and digital health technologies are likely to play increasingly

important roles in the future of psychodermatology.

Emerging developments may include continuous multimodal patient monitoring, AI-assisted disease prediction, personalized digital therapeutics, microbiome-informed treatment strategies, integration of wearable biomarkers into clinical care, and real-time stress assessment platforms. These innovations have the potential to transform psychodermatology from a reactive discipline focused on disease management into a predictive and preventive model centered on individualized care.

Within the broader NICE framework, AI may serve as the integrative platform capable of connecting biological, psychological, environmental, and behavioral dimensions of disease, thereby facilitating a more comprehensive understanding of the skin–brain connection and advancing the implementation of precision psychodermatology [47–55].

9. Future Perspectives

The future of psychodermatology is likely to be characterized by increasing integration of psychoneuroimmunology, systems biology, artificial intelligence, and precision medicine. Advances in biomarker discovery may facilitate objective assessment of stress-related disease activity, while microbiome science may identify novel therapeutic targets. The integration of multi-omics technologies, digital biomarkers, and machine-learning algorithms is expected to improve prediction of disease flares and treatment responses.

Future psychodermatological care will likely shift from reactive disease management toward predictive, preventive, and personalized strategies. Such developments may enable clinicians to identify vulnerable individuals before clinical deterioration occurs and to implement targeted interventions tailored to individual biological and psychological profiles.

Expansion of multidisciplinary psychodermatology services and incorporation of psychodermatology into dermatology training programs will be essential for translating scientific advances into clinical practice.

10. Conclusions

Psychological stress exerts profound effects on skin physiology through a complex network of neuroendocrine, immunological, inflammatory, and microbiological pathways. The Neuro-Immuno-Cutaneous-Endocrine (NICE) model has emerged as the most comprehensive framework for understanding these interactions and provides a scientific basis for contemporary psychodermatology.

Evidence accumulated during recent decades demonstrates that activation of the hypothalamic–pituitary–adrenal axis, sympathetic nervous system stimulation, neurogenic inflammation, mast cell activation, cytokine dysregulation, oxidative stress, epidermal barrier impairment, and microbiome alterations collectively contribute to stress-related skin disease. These mechanisms highlight the inseparable relationship between psychological processes and cutaneous biology.

Future advances in biomarker discovery, microbiome research, artificial

intelligence, and precision medicine are expected to transform psychodermatology into a predictive and individualized discipline. A comprehensive understanding of the NICE model may ultimately facilitate more effective prevention, diagnosis, and treatment of stress-sensitive dermatological disorders.

11. Conflict of Interest

The author declares no conflict of interest.

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13. Author Contributions

M.I. conceived the review, performed the literature analysis, drafted the manuscript, and approved the final version. C.I. contributed to literature acquisition, data curation, critical revision of the manuscript, and editing of the final version.

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