Nutrition & Culinary Dermatology

PSORIASIS and ACTINIC KERATOSIS

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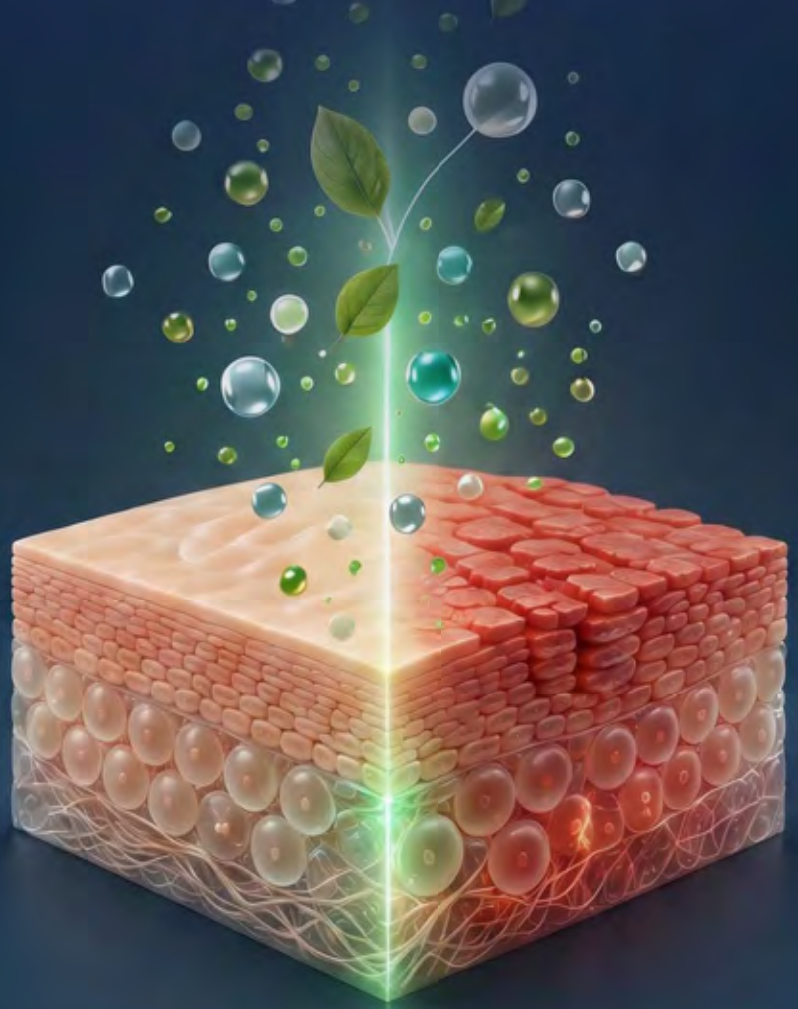

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List of abbreviations

All abbreviations used in this book are listed below in alphabetical order.

12-HETE 12-hydroxyeicosatetraenoic acid
24HDR 24-hour dietary recall
AGE Advanced glycation end products
AhR Aryl hydrocarbon receptor
AK Actinic keratosis
ALA Alpha-linolenic acid (ω-3)
aMED Alternate Mediterranean Diet score
APE Apurinic/apyrimidinic endonuclease
ATP Adenosine triphosphate
BCC Basal cell carcinoma
BMI Body mass index
BSA Body surface area
CCL C-C motif chemokine ligand
CDAI Composite dietary antioxidant index
CEL N-carboxyethyl-lysine
CLRs C-type lectin receptors
CM Culinary Medicine
CML N-carboxymethyl-lysine
CRP C-reactive protein
CXCL C-X-C motif chemokine ligand
CYP11A1 Cytochrome P450, family 11, subfamily A, polypeptide 1
DAMPs Damage-associated molecular patterns
DASH Dietary approaches to stop hypertension (dietary pattern)
DGAI Dietary guidelines for Americans Adherence Index
DHA Docosahexaenoic acid
DII Dietary Inflammatory Index
DIS Dietary Inflammation Score
DNCB 2,4-dinitrochlorobenzene
EAACI European Academy of Allergy and Clinical Immunology
E-DII Energy-adjusted Dietary Inflammatory Index
EDIP Empirical dietary inflammatory pattern
EGCG Epigallocatechin-3-gallate
EPA Eicosapentaenoic acid
ESR Erythrocyte sedimentation rate
FFAR2 Free fatty acid receptor 2
FFQ Food frequency questionnaire
FXR Farnesoid X receptor
GLUT4 Glucose transporter type 4
GM-CSF Granulocyte-macrophage colony-stimulating factor
GPR41 G protein-coupled receptor 41
GPR43 G protein-coupled receptor 43
GPR109A G protein-coupled receptor 109A
GPx Glutathione peroxidase
GWAS Genome-wide association studies
HbA1c Glycated haemoglobin A1c
HBD Human beta-defensin
HEI-2020 Healthy Eating Index 2020
HS Hidradenitis suppurativa
IBD Inflammatory bowel disease
ICAM-1 Intercellular adhesion molecule 1
IFN-γ Interferon gamma
IgE Immunoglobulin E
IGF-1 Insulin-like growth factor 1
IL Interleukin
IMID Immune-mediated inflammatory disease
IRF3 Interferon regulatory factor 3
JAK-STAT Janus kinase – signal transducer and activator of transcription
K17 Keratin 17
LL-37 Human cathelicidin antimicrobial peptide 37
LPS Lipopolysaccharide
LTB4 Leukotriene B4
MAC Microbiota-accessible carbohydrates
MAL MyD88 adaptor-like protein
MAPK Mitogen-activated protein kinase
MDA Malondialdehyde
MDS Mediterranean Diet Score
MEDAS Mediterranean Diet Adherence Screener
MEDIPSO Mediterranean Diet in Psoriasis Trial
MHC-II Major histocompatibility complex class II
MMP-1 Matrix metalloproteinase 1
NAD^+ Nicotinamide adenine dinucleotide
NCCN National Comprehensive Cancer Network
NER Nucleotide excision repair
NF-κB Nuclear factor kappa-light-chain-enhancer of activated B cells
NHS / HPFS Nurses' Health Study / Health Professionals Follow-up Study
NLRs NOD-like receptors
NMSC Non-melanoma skin cancer
NOD Nucleotide-binding oligomerisation domain
NPCT Nutritional Prevention of Cancer Trial
Nrf2 Nuclear factor erythroid 2-related factor 2
OGG1 8-oxoguanine DNA glycosylase 1
ONTRAC Oral nicotinamide to reduce actinic cancer trial

ONTRANS Oral Nicotinamide Trial in Renal Transplant Recipients and Non-melanoma Skin Cancer
p38 MAPK p38 mitogen-activated protein kinase
PAMP Pathogen-associated molecular patterns
PARP Poly(ADP-ribose) polymerase
PASI Psoriasis area and severity index
PGE2 Prostaglandin E2
PPAR Peroxisome proliferator-activated receptor
PPARγ Peroxisome proliferator-activated receptor gamma
PREDIME Prevención con Dieta Mediterránea (study)
PRR Pattern recognition receptors
PUFA Polyunsaturated fatty acids
RAGE Receptor for advanced glycation end products
RDA Recommended daily allowances
RELMα Resistin-like molecule alpha
RIG-I Retinoic acid-inducible gene I
RLR RIG-I-like receptors
ROS Reactive oxygen species
SAF Skin autofluorescence
SALT Skin-associated lymphoid tissue
SCC Squamous cell carcinoma
SCFA Short-chain fatty acids
SCORAD Scoring Atopic Dermatitis Index
SIBO Small Intestinal Bacterial Overgrowth
SKICAP-AK Skin Cancer Prevention Activity – Actinic Keratosis Trial
SOD Superoxide dismutase
sRAGE Soluble receptor for advanced glycation end products
T2DM Type 2 diabetes mellitus
TGR5 G protein-coupled bile acid receptor 5
Th1 / Th2 / Th17 T helper cell subsets (type 1, 2 and 17)
TLRs Toll-like receptors
TMA Trimethylamine
TMAO Trimethylamine N-oxide
TNF-α Tumour necrosis factor alpha
TP53 Tumour protein 53 (tumour suppressor gene)
TRAF3 TNF receptor-associated factor 3
TRIF TIR-domain-containing adaptor inducing interferon-β (TICAM-1)
TSLP Thymic stromal lymphopoietin
UV Ultraviolet (radiation)
UVA Ultraviolet A radiation
UVB Ultraviolet B radiation (290–320 nm)
VLCKD Very low-calorie ketogenic diet

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Forewords

The relationship between diet and skin health has for decades been a matter intuitively accepted by patients and clinicians alike, yet insufficiently explored from a rigorous scientific perspective. In recent years, the evidence accumulated around the influence of diet, the systemic inflammatory profile and the microbiota on various dermatological conditions has begun to provide concrete answers to questions that until recently remained unresolved. This book is born of that conviction: the need to address the connection between nutrition, culinary medicine and dermatology in an orderly, critical and clinically applicable manner.

Psoriasis and actinic keratosis are two of the most prevalent dermatological entities in daily clinical practice and, at the same time, two illustrative examples of how systemic factors, among them diet and lifestyle, can contribute to modulating the course, severity and therapeutic response. In psoriasis, chronic low-grade inflammation, imbalance in the omega-3/omega-6 fatty acid profile, oxidative stress and alterations in the intestinal microbiota constitute a pathophysiological terrain upon which diet exerts a demonstrable influence. In actinic keratosis, the role of antioxidants, zinc, selenium and vitamin D, together with protection against cumulative actinic damage, likewise opens a pathway for nutritional intervention with growing scientific support.

As dermatologists, we know that our patients arrive at the consultation with specific questions: what they should eat, what they should avoid, whether certain habits may worsen or improve their condition. For too long, the clinical response has oscillated between excessive caution — acknowledging that sufficient evidence is lacking — and improvisation based on intuition or unfounded recommendations. This work therefore seeks to move beyond that dichotomy: to offer the dermatologist a robust frame of reference, grounded in the available evidence, that enables the integration of nutritional guidance into the therapeutic approach in a coherent and safe manner.

Culinary medicine contributes, in this context, a dimension that dermatology cannot afford to overlook. It is not enough to identify which nutrients or dietary patterns exert a beneficial effect on the skin; it is equally necessary to translate that knowledge into recommendations that the patient can incorporate into everyday life in a sustained fashion. The selection of foods, cooking methods and the impact of specific culinary techniques on nutrient bioavailability are variables that significantly influence the actual effect of diet on skin health. And it is precisely in that space where the collaboration with the team at GOe Tech Center and Basque Culinary Center has proved not merely enriching, but indispensable.

We wish to express our gratitude to Almirall for having championed and supported this project, and to the experts at Basque Culinary Center for their scientific rigour and their invaluable contribution from the fields of nutritional science and gastronomy.

We trust, finally, that this work will prove useful to those who, from the field of dermatology, wish to incorporate the emerging evidence on nutrition and culinary medicine into their daily clinical practice.

Dra. Montserrat Fernández-Guarino

At GOe Tech Center (the technology centre specialising in gastronomy at Basque Culinary Center), and particularly within the Health and Gastronomy Division, we work with the conviction that food and cooking represent far more than a physiological necessity: they constitute factors with the capacity to influence health and quality of life in a meaningful way. Our activity takes place precisely at the intersection of science, health and gastronomy, exploring how scientific knowledge can be translated into applicable and sustainable strategies for everyday life.

The rise in chronic diseases associated with inflammatory and metabolic processes has highlighted the need to move towards broader approaches to health. In parallel, dermatology has begun to pay increasing attention to the possible role of diet and certain lifestyle factors in the course and management of various cutaneous conditions. Although significant scientific challenges and numerous unresolved questions remain, the available evidence makes it clear that the skin cannot be addressed in complete isolation from the rest of the body's physiological systems.

At present, concepts such as low-grade systemic inflammation, microbiota, oxidative stress, barrier function and metabolic health form part of a new scientific landscape that calls for a re-examination of the relationship between nutrition and skin health from a broader and more rigorous perspective. At the same time, patients show a growing interest in understanding how their dietary habits might influence the health of their skin, seeking answers that they frequently encounter in settings with scant scientific backing or through overly simplified messages.

This guide has been conceived with the purpose of offering an up-to-date, critical and evidence-based overview of the link between diet, culinary medicine and dermatology. The aim is to provide tools that enable a better understanding of how certain dietary patterns, culinary practices and lifestyle-related factors might be integrated, in a complementary manner, within the clinical management of specific dermatological conditions.

In this context, culinary medicine becomes of particular relevance by placing the focus not solely on what to eat, but also on how to translate nutritional recommendations into everyday practice. The way in which we select, cook and consume food determines not only the nutritional quality of the diet but also its feasibility, adherence and long-term sustainability. Bridging the gap between scientific evidence and people's daily reality constitutes, precisely, one of the great current challenges in the field of health.

At GOe Tech Center, we believe that collaboration among researchers, healthcare professionals and gastronomy experts is essential for advancing the translation of scientific knowledge into tools and strategies with potential application in clinical practice. With this work, we hope to contribute not only to generating reflection and knowledge around the relationship between diet, culinary medicine and skin health, but also to offering practical and useful support for the dermatology professional in daily clinical practice.

We wish to express our gratitude to the professionals and institutions that have participated in the development of this project, and especially to Almirall for championing an initiative aimed at exploring new approaches to the relationship between dermatology, nutrition and culinary medicine. We trust that this guide may serve as a reference and support resource for dermatology professionals interested in incorporating the emerging evidence on diet and culinary medicine into clinical dermatology practice.

Dra. Usune Etxeberria Aranburu **Dra. Cecilia Galbete Ciáurriz**

MEDICAL and IMMUNOLOGICAL FOUNDATIONS

I. Introduction: dermatological foundations for nutritional intervention

1. The skin as an immune and metabolic organ

The skin represents much more than a protective barrier. As the largest organ of the human body, it constitutes a metabolically active interface that performs highly complex immune, neuroendocrine and metabolic functions.[1-3]

The cutaneous immune system includes skin-associated lymphoid tissue (SALT), a highly organised network integrating components of innate and adaptive immunity.[1,4] The skin harbours diverse populations of dendritic cells, macrophages, resident T lymphocytes, innate lymphoid cells and mast cells, each with specialised roles in immune surveillance.[2,5] In addition, cutaneous neurons directly participate in antimicrobial defence and in the modulation of immune responses through neuropeptides and neurotransmitters, explaining why psychological factors may influence the severity of dermatological diseases.[6]

Moreover, the skin functions as a metabolically active organ that synthesises, processes and metabolises structural molecules, lipids and signalling mediators.[3,7,8] For example, the skin expresses all components of the hypothalamic-pituitary-adrenal axis, including CYP11A1, which initiates steroid synthesis.[9] This steroidogenic capacity enables the local production of corticosteroids, sex hormones and unique metabolites such as vitamin D derivatives.[9]

Metabolomic studies show that factors affecting the skin — such as radiation, xenobiotics, ageing and disease — induce convergent metabolic changes: oxidative stress affecting antioxidant systems (coenzyme Q10, glutathione), alterations in lipid metabolism with activation of β-oxidation, and modifications in glycolysis, the Krebs cycle and purine metabolism.[10]

2. Scientific rationale for an integrative approach

Understanding the skin as an integrated immune and metabolic organ provides the scientific basis for nutritional interventions. Experimental, epidemiological and clinical evidence demonstrates that specific nutrients and dietary patterns modulate fundamental pathophysiological processes in skin diseases.

In psoriasis, several systematic reviews show that certain pro-inflammatory foods — alcohol, dairy products, sugars, gluten — exacerbate the disease, whereas the Mediterranean diet, caloric restriction, fibre, probiotics and ω-3 fatty acids are associated with lower disease severity.[11]

The MEDIPSO trial showed that adherence to the Mediterranean diet reduces systemic inflammation and oxidative stress through antioxidants (β-carotene, vitamins C and E), polyphenols, cyclooxygenase inhibition by oleocanthal, and inhibition of pro-inflammatory eicosanoids by ω-3 fatty acids.[12] In addition, the Mediterranean diet was associated with improved lipid profiles and insulin sensitivity.[12]

In paediatric atopic dermatitis without food allergy, meta-analyses have shown that probiotic supplementation reduces disease severity as measured by the SCORAD scale.[13]

Despite growing interest, evidence regarding the safety and efficacy of dietary supplementation remains limited due to the scarcity of large randomised clinical trials, heterogeneous dosing and the absence of adverse event reporting.[14] The most promising evidence concerns nicotinamide and the prevention of non-melanoma skin cancer.[14]

Dermatologists play a key role in diagnosing and managing nutritional deficiencies, which frequently present with cutaneous manifestations. In developed countries, the main organic risk factors for malnutrition are chronic liver disease, alcohol use, bariatric surgery, inflammatory bowel disease and haemodialysis.[15]

3. Chapter objective

This chapter provides a rigorous scientific foundation supporting the rational use of nutritional interventions in inflammatory and metabolic dermatological diseases.

The specific objectives are:

- To characterise the immune and metabolic architecture of the skin that underlies the response to nutritional interventions.
- To examine the evidence on specific nutrients — polyunsaturated fatty acids, antioxidants, vitamins, carbohydrates — in modulating cutaneous inflammation.
- To analyse the molecular mechanisms through which dietary factors influence the pathogenesis of psoriasis and atopic dermatitis.
- To critically assess the quality of the available scientific evidence.

This integrative approach is based on the concept that chronic inflammatory dermatological diseases are not merely skin disorders but manifestations of systemic immunometabolic dysregulation.

Nutrition emerges as a modifiable factor that simultaneously influences multiple components of this pathophysiological network. Anti-inflammatory dietary patterns reduce systemic inflammatory markers, improve insulin sensitivity, modulate the gut microbiota, increase short-chain fatty acid production and provide substrates for specialised pro-resolving lipid mediators.

The evidence presented adopts a critical perspective that acknowledges the strengths and limitations of current research, distinguishing between epidemiological associations, experimental mechanisms and clinical efficacy demonstrated in controlled trials.

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II. The gut-skin axis: pathophysiological foundations

1. Introduction

The concept of the gut-skin axis represents a paradigm shift in the understanding of the pathophysiology of several inflammatory dermatoses, recognising that the skin and the gastrointestinal tract, despite their anatomical separation, maintain a complex bidirectional communication mediated by multiple molecular, cellular and immune pathways.[1,2] This axis emerges as a signalling system in which intestinal dysbiosis can trigger barrier dysfunction and cutaneous inflammatory alterations, and vice versa.[1,3,4]

2. Bidirectional gut-skin communication

Fundamentals of communication

The skin and the intestine share several physiological properties: both are extensive barrier tissues colonised by diverse microbial communities, are richly vascularised and maintain active immune components that constantly respond to environmental stimuli.[1,5,6]

The gut and skin microbiota constitute the central core of gut-skin communication.[1,2] Intestinal microbial metabolites, particularly short-chain fatty acids (SCFAs) such as acetate, propionate and butyrate, act as signalling molecules that enter the systemic circulation to modulate skin barrier function and immune responses.[2,7,8]

Recent studies show that gut–skin communication is bidirectional. Exposure of the skin to ultraviolet B radiation can beneficially modulate both the microbiome and intestinal health.[1] This reciprocity suggests that interventions directed at one organ may exert therapeutic effects on the other.

Molecular signalling pathways

Several major pathways mediate gut-skin communication: the innate and adaptive immune systems, the vitamin D receptor signalling pathway, the neuroendocrine pathway — through the hypothalamic–pituitary-adrenal axis and intestinal neuropeptides — and the aryl hydrocarbon receptor (AhR) signalling pathway.[1] AhR deserves particular attention because of its dual role in both organs. This xenobiotic receptor detects ligands derived from the microbiota and the diet (SCFAs, polyamines and tryptophan derivatives such as indole and indole-3-acetic acid), regulating the integrity of the intestinal and skin barriers.[1,2,6,9-12]

In the skin, AhR activation by microbial metabolites promotes keratinocyte differentiation, stratum corneum formation and the expression of antimicrobial peptides.[9,11]

Chronic cutaneous inflammation can alter the neuroimmune-endocrine axis, modify sympathetic and parasympathetic tone and thereby influence intestinal motility, secretion and permeability.[1,6,13] Likewise, psychosocial stress amplified by visible skin diseases tends to activate the stress axis and alter dietary and sleep patterns, factors that in turn impact the composition and function of the gut microbiota.[1,6,13]

Intestinal barrier dysfunction

The intestinal barrier is a dynamic system regulated by the microbiota composition, mucus, tight intercellular junctions between epithelial cells, the mucosal immune system and the enteric neuroendocrine system.[2,13-15]

Multiple factors can compromise intestinal barrier integrity: bacterial dysbiosis, fungal infections and parasitic infestations, oxidative stress, diets high in saturated fatty acids, low-fibre diets, alcohol exposure and chronic allergens.[14,16]

Barrier disruption due to altered tight junction proteins (occludin, claudins and zonulin), known as leaky gut syndrome, is characterised by the excessive release of bacterial metabolites and antigens such as lipopolysaccharide (LPS) and peptidoglycans into the systemic circulation, activating pattern recognition receptors (PRRs) and triggering systemic inflammatory responses.[8,13,14,16-18]

Systemic inflammation and cutaneous manifestations

Intestinal dysbiosis and increased intestinal permeability favour the production of IL-1β, IL-6, IL-23 and TNF-α. These cytokines drive the differentiation of Th1 and Th17 lymphocytes whilst reducing Treg stability, promoting a systemic immune profile prone to chronic inflammation.[1,6,8,13,19]

At the cutaneous level, systemic inflammation induces increased expression of adhesion molecules on dermal vascular endothelium, increased recruitment of neutrophils and T lymphocytes, amplification of signalling pathways such as NF-κB and JAK-STAT, and alteration of stratum corneum lipids, with consequent impairment of epidermal barrier function.[1,6,8]

Patterns of intestinal dysbiosis and increased permeability markers have been described in individuals with acne, rosacea and atopic dermatitis, suggesting that part of cutaneous susceptibility is mediated by the state of the intestinal barrier and low-grade systemic inflammation.[20]

On the other hand, the strongest clinical evidence for this connection comes from the association between inflammatory bowel disease (IBD) and psoriasis. Bidirectional Mendelian randomisation studies demonstrate a causal effect of IBD — particularly Crohn's disease — on psoriasis, but not in the opposite direction. Thus, patients with psoriasis have a 1.6-fold higher risk of developing ulcerative colitis compared with the general population.[5]

3. Participation of cytokines, T cells and toll-like receptors

IL-23/IL-17 axis and Th17 cells

The IL-23/IL-17 axis represents the most important immune pathway in the gut–skin axis.[5,21] The *IL23R* and *IL12B* genes, encoding components of the IL-23 receptor and the p40 subunit shared by IL-12 and IL-23, respectively, have been identified as shared genetic susceptibility loci for psoriasis and IBD.[5]

IL-23 is essential for the differentiation and activation of Th17 lymphocytes, which in turn produce IL-17.[5] In psoriasis, IL-17 stimulates keratinocyte proliferation and differentiation, maturation of myeloid dendritic cells and recruitment of neutrophils and macrophages.[5] In the gastrointestinal tract, increased IL-17 expression in the intestinal mucosa and plasma of patients with IBD supports its pathogenic role.[5]

Paradoxically, whilst IL-23 inhibition is clinically beneficial in both psoriasis and Crohn's disease, IL-17A inhibition may exacerbate or trigger IBD.[21] This therapeutic divergence reveals that cytokine networks are tissue-dependent.[21]

Regulatory T cells and immune memory

Regulatory T cells (Treg) specific to cutaneous commensals generated during neonatal colonisation may be altered by intestinal inflammation.[22] In experimental models of chemical colitis, epithelial damage induces increased intestinal colonisation by *Staphylococcus epidermidis*, reducing commensal-specific Treg lymphocytes in both intestinal and cutaneous lymph nodes, ultimately leading to increased cutaneous neutrophil density.[22]

Similarly, experimental studies show that intestinal dysbiosis can promote cutaneous inflammation in psoriasis through enhancement of the Th17 response.[23] Germ-free mice and conventional mice treated with broad-spectrum antibiotics are more resistant to imiquimod-induced skin inflammation than conventional mice, with lower local and systemic Th17 activation.[23]

Toll-like receptors (TLRs)

TLRs are fundamental receptors in innate immunity, recognising pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs).[24,25] However, their aberrant activation can induce type IV hypersensitivity responses and autoimmune T-cell activation.[24,25]

When intestinal permeability is increased, chronic systemic stimulation of TLRs by lipopolysaccharides and other PAMPs favours persistent low-grade inflammation and subclinical activation of resident immune cells in the skin. In the skin, TLR expression in keratinocytes, Langerhans cells and dermal dendritic cells allows circulating microbial products, or even secondary changes in the skin microbiota, to amplify these signals and maintain self-perpetuating inflammatory loops.[1,13]

TLRs participate in the pathogenesis of psoriasis and atopic dermatitis through multiple mechanisms: delayed barrier repair, promotion of Th2-mediated dermatitis, shift towards Th1 response in the chronic phase, establishment of the itch-scratch cycle and mediation of UV-induced effects.[26]

TLR7 deserves special attention for its role in bidirectional skin-gut communication. In the murine model of imiquimod-induced psoriasis, TLR7-dependent eosinophil degranulation links psoriatic skin inflammation with inflammatory changes in the small intestine.[27] TLR7-deficient mice do not exhibit intestinal eosinophil degranulation and show attenuated inflammation in both skin and small intestine after imiquimod administration.[27]

4. Relevant experimental and clinical evidence

Experimental models

Animal models have been fundamental in establishing causal relationships in the gut-skin axis. The imiquimod-induced psoriasis model in mice has shown that gut microbiota is necessary for the full development of cutaneous inflammation.[23,27] Mice devoid of intestinal microorganisms develop significantly milder skin lesions, with reduced immune cell infiltration and expression of pro-inflammatory cytokines.[23]

On the other hand, the 2,4-dinitrochlorobenzene (DNCB)-induced atopic dermatitis model has revealed the protective role of SCFAs.[8,28,29] Dietary supplementation with butyrate strengthens skin barrier function by modulating mitochondrial metabolism in epidermal keratinocytes and the production of structural components.[8] Thus, a diet rich in fermentable fibre alleviates systemic allergen sensitisation and the severity of atopic dermatitis.[8]

Acetate significantly improves DNCB-induced atopic dermatitis through binding to free fatty acid receptor 2 (FFAR2), inhibiting the transcription factor GATA-3 and suppressing the Th2 pathway, with a consequent reduction in serum levels of IgE and thymic stromal lymphopoietin.[28]

Finally, propionate, mediated by ginsenoside F2, positively affects the gut–skin axis in mice with atopic dermatitis, inhibiting inflammatory responses in both organs through the GPR43/NF-κB pathway.[29]

Clinical evidence

Epidemiological and genetic studies provide robust evidence of the gut–skin connection. A meta-analysis demonstrated a statistically significant association between psoriasis and IBD, with an odds ratio of 2.49 for Crohn's disease and 1.64 for ulcerative colitis in patients with psoriasis.[5] Genome-wide association studies (GWAS) have identified shared genetic susceptibility loci, including the 6p21 chromosomal locus (PSORS1 in psoriasis, IBD3 in IBD) and other genes such as *IL23R* and *IL12B*.[5]

16S rRNA sequencing studies in patients with psoriasis reveal significant alterations in the diversity and relative abundance of intestinal microbial communities compared with healthy controls.[30,31] Distinctive features include changes in the *Firmicutes/Bacteroidetes* ratio, intestinal dysbiosis and reduced SCFA production.[31] These microbial alterations are corrected after treatment with systemic immunosuppressants, suggesting that the gut microbiota may serve as a predictive biomarker.[31]

In atopic dermatitis, epidemiological evidence indicates that children with food allergies have lower levels of SCFAs derived from dietary fibre.[8] Paediatric patients with atopic dermatitis also show reduced alpha diversity of the gut microbiota, with lower abundance of *Faecalibacterium prausnitzii, Bifidobacterium* spp. and *Akkermansia muciniphila*.[32] Clinical and preclinical studies have shown that restoration of gut microbial homeostasis through interventions such as faecal microbiota transplantation, probiotics and prebiotics may improve symptoms of several skin diseases.[2]

Rosacea shows significant epidemiological associations with several gastrointestinal disorders, including IBD, coeliac disease, irritable bowel syndrome, small intestinal bacterial overgrowth (SIBO) and *Helicobacter pylori* infection.[33]

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III - Cutaneous microbiota, immunity and nutrition

1. The skin as a living ecosystem

The skin constitutes a complex biological ecosystem in which multiple microbial communities coexist dynamically. On its surface and within its adnexal structures — including hair follicles, sebaceous glands and sweat glands — a diverse microbiota composed of bacteria, fungi, viruses, mites such as *Demodex,* and archaea becomes established. The totality of these microorganisms, together with their genetic material, constitutes the cutaneous microbiome, a fundamental element in the regulation of skin homeostasis and immune response.[1]

Far from behaving as passive entities, these microbial communities fulfil essential functions in cutaneous physiology. These include the maintenance of epidermal barrier integrity, the regulation of lipid metabolism, the inhibition of colonisation by pathogenic microorganisms through ecological competition, and the modulation of both innate and adaptive immune responses.[2-4] Furthermore, the cutaneous microbiota participates in the production of bioactive metabolites, such as short-chain fatty acids and antimicrobial peptides, which contribute to defence against external insults.[3,6]

The fungal component is primarily composed of species of the genus *Malassezia*, which exhibit a high degree of adaptation to lipid-rich environments.[2,6] From a taxonomic perspective, the bacterial microbiota of the skin is dominated by the phyla *Actinobacteria*, *Firmicutes* and *Proteobacteria*, with a lesser representation of *Bacteroidetes.*[4] At the genus level, *Cutibacterium* (formerly *Propionibacterium*), *Staphylococcus, Streptococcus* and *Corynebacterium* predominate, with their relative distribution varying according to the microenvironmental characteristics of each body region.[5]

Variability according to anatomical site

The structural and functional heterogeneity of the skin determines the existence of distinct ecological niches that shape the composition of the microbiome. In this context, three major types of cutaneous habitats have been described: sebaceous, moist and dry.[7] A positive association between *Cutibacterium* and the lipid content of the skin has been reported. Conversely, genera such as *Streptococcus* exhibit negative correlations with hydration, transepidermal water loss and sebum — that is, a preference for dry sites.[5]

Sebaceous areas, such as the forehead, the retroauricular region or the upper trunk, are characterised by high sebum production and the predominance of lipophilic microorganisms, particularly *Cutibacterium acnes* and *Malassezia* species. These regions display lower microbial diversity, associated with the selection of species highly specialised in lipid metabolism. Several studies have demonstrated an inverse correlation between sebum production and the alpha diversity of the cutaneous microbiome.[5,8]

Moist zones, such as skin folds, the umbilicus or interdigital areas, favour the proliferation of genera such as *Staphylococcus* and *Corynebacterium*. These regions exhibit intermediate diversity and are strongly influenced by local humidity and occlusion.[9,10]

Dry areas, such as the forearms or lower limbs, present the greatest microbial diversity and richness. In these locations, genera such as *Streptococcus*, *Rothia* and other less specialised taxa predominate, reflecting a more ecologically permissive environment.[8,9,11]

Taken together, parameters such as sebum secretion and hydration level emerge as key determinants of microbial composition.

Modulatory factors of the cutaneous microbiome

The composition of the cutaneous microbiome is subject to dynamic variations over time, influenced by multiple intrinsic and extrinsic factors (Figure 1).

Age constitutes one of the most relevant modulators. Throughout life, progressive changes occur in the diversity and structure of microbial communities, with a general trend towards increasing bacterial diversity. In parallel, a decrease in the relative abundance of genera such as *Cutibacterium* and *Lactobacillus* is observed, in relation to physiological modifications inherent to ageing, such as reduced sebaceous gland activity and hormonal changes.[12,13]

Topical preparations, including cosmetics, cleansers and dermatological treatments, represent another significant modulatory factor. These may induce changes in microbial composition, both transiently and in a sustained manner. Of particular interest, dermatological treatments for atopic dermatitis or psoriasis have been shown to partially restore a microbial equilibrium closer to the physiological state.[7,14]

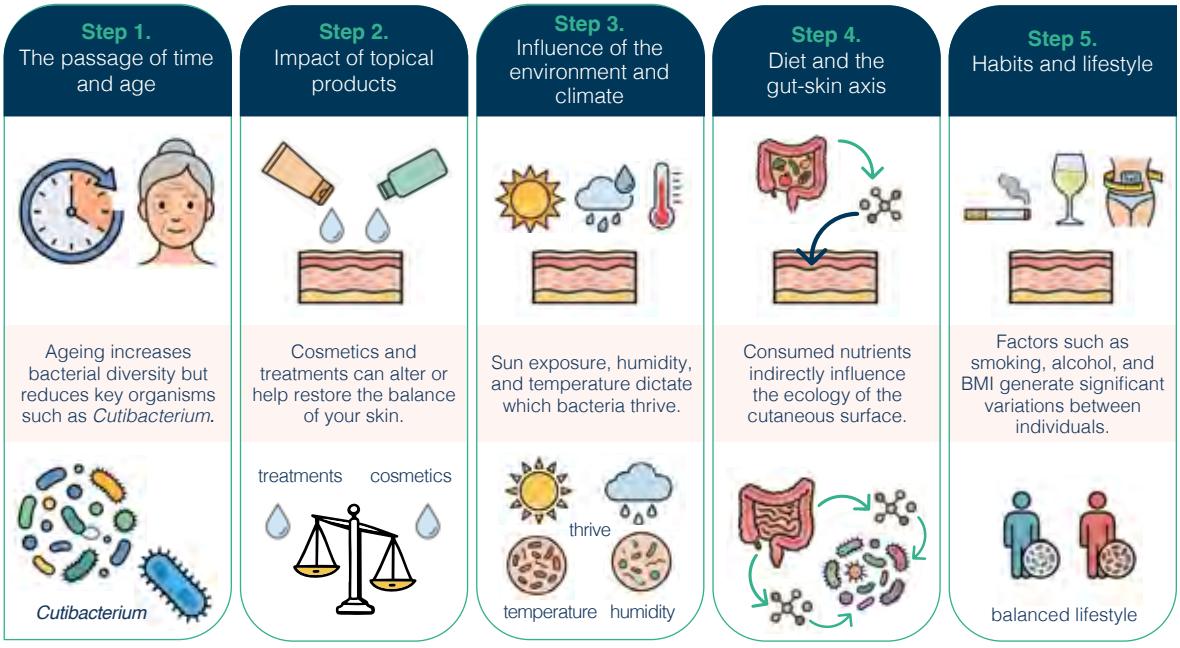

Figure 1. Factors modulating the cutaneous microbiome.

The environmental setting also exerts a considerable influence. Exposed areas generally present greater alpha diversity compared with covered regions, suggesting a relevant role for interaction with the external milieu. Variables such as temperature, hours spent outdoors, ambient humidity, cutaneous pH and solar exposure contribute to the configuration of these communities.[10,15,16]

In recent years, diet has emerged as a potentially relevant factor in the modulation of the cutaneous microbiome. Associations have been described between macronutrient intake and the relative abundance of *Propionibacterium*, *Corynebacterium* and *Staphylococcus,* pointing to the existence of a gut–skin axis through which nutrition could indirectly influence cutaneous microbial ecology.[15]

Finally, other factors such as sex, body mass index, smoking, alcohol consumption and sociodemographic variables have also been associated with variations in microbiome composition. Collectively, these lifestyle and physiological determinants account for approximately 12–20% of the variability in microbiome composition.[17]

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2. Cutaneous dysbiosis and immunological impact

Concept of cutaneous dysbiosis

Cutaneous dysbiosis is defined as a disturbance in the balance of the skin microbiota, which may involve changes in the abundance, composition or distribution of resident microorganisms. Dysbiosis generally entails a reduction in microbial diversity and a shift in the proportion between commensal species and pathobionts (commensal species with inflammatory potential).[1,2] In this context, dysbiosis represents a disruption of the homeostatic state between the host and its microbiota, in which microorganisms with protective functions are displaced by opportunistic species with pro-inflammatory potential[3] (Figure 2).

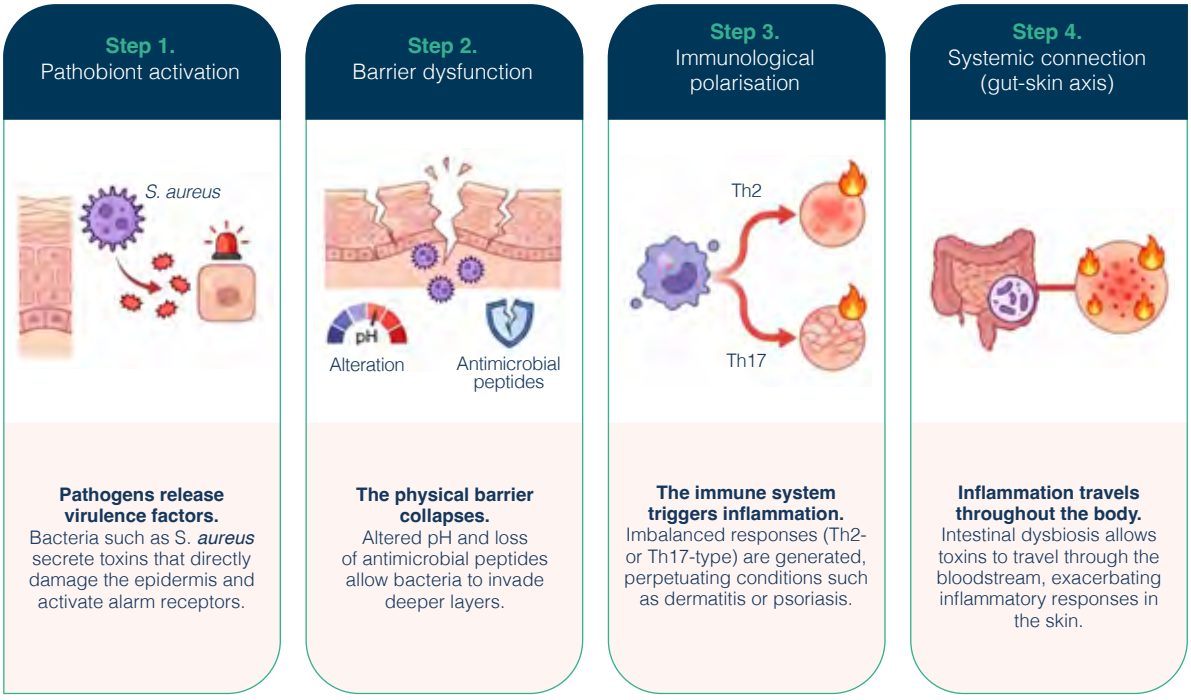

Figure 2. The dysbiosis–inflammation cycle.

Under physiological conditions, the cutaneous microbiota plays an active role in maintaining barrier function, defending against pathogens and preserving epidermal integrity.[4] However, in dysbiotic states, different patterns of alteration may be observed, including the loss of beneficial commensal functions, the excessive proliferation of certain species such as *Staphylococcus aureus*, or modifications in the expression of bacterial virulence factors, even in the absence of significant changes in relative abundance.[5,6]

Furthermore, interactions between microorganisms — both inter-species and inter-kingdom (bacteria, fungi and viruses) — may trigger cascading changes that favour the establishment and perpetuation of dysbiotic states, an aspect of increasing relevance in the understanding of various inflammatory dermatoses but still insufficiently characterised.[1]

Disruption of homeostasis and inflammation

Cutaneous dysbiosis is associated with a disruption of immunological homeostasis, promoting the activation of inflammatory responses through complex mechanisms involving both innate and adaptive immunity.[1,7]

One of the fundamental mechanisms is immune activation induced by pathobionts. Species such as *Staphylococcus aureus* produce toxins, proteases and other virulence factors capable of directly damaging the epidermal barrier and generating persistent antigenic stimulation.[4] These stimuli are recognised by pattern recognition receptors, such as toll-like receptors (TLRs), present on keratinocytes and immune cells, triggering inflammatory cascades and the production of pro-inflammatory cytokines.[8]

In parallel, dysbiosis contributes to cutaneous barrier dysfunction through multiple mechanisms, notably including decreased production of antimicrobial peptides, alteration of cutaneous pH and loss of physiological acidity. These modifications favour the adhesion and proliferation of pathogenic microorganisms, as well as structural damage to the stratum corneum.[4] Barrier disruption, in turn, facilitates the penetration of microorganisms or their products into deeper skin layers and even into the systemic circulation, thereby amplifying the inflammatory response.[9]

From an immunological standpoint, dysbiosis also influences the polarisation of the immune response. In atopic dermatitis, colonisation by *S. aureus* is predominantly associated with a Th2-type response.[5,6] Conversely, in psoriasis, dysbiosis favours the activation of Th17 pathways, with increased production of IL-17 and perpetuation of chronic inflammation.[9,10] In this context, bacterial regulatory systems such as the *S. aureus agr* quorum sensing system modulate the expression of toxins, including δ-toxin, contributing to the exacerbation of inflammation and the deterioration of barrier function.[6]

Moreover, cutaneous dysbiosis cannot be understood in isolation but rather within the framework of the gut-skin axis. Alteration of the intestinal microbiome may lead to increased intestinal permeability — the so-called “leaky gut syndrome” — facilitating the translocation of bacteria and endotoxins into the systemic circulation. This phenomenon induces systemic inflammatory activation that may directly affect the skin.[7,11] In this regard, the microbiome acts as a key regulator of the immune system, establishing bidirectional communication with various organs and tissues.

Relationship with inflammatory diseases

In psoriasis, dysbiosis is considered a central element in its pathophysiology, acting as an integrating node between genetic, immunological and environmental factors.[9,10] At the cutaneous level, psoriatic lesions exhibit a relative enrichment of genera such as *Corynebacterium* and *Staphylococcus*, together with a significant decrease in *Cutibacterium*.[12] In parallel, intestinal dysbiosis — characterised by reduced microbial diversity, an altered *Bacteroidetes/Firmicutes* ratio and a decrease in short-chain fatty acid (SCFA)-producing microorganisms — contributes to the loss of intestinal barrier integrity and diminished systemic immunoregulatory capacity.[10]

The reduction in SCFAs is associated with decreased anti-inflammatory signalling and greater polarisation towards Th17 responses.[10,13] Furthermore, cutaneous dysbiosis, with a predominance of pathobionts such as *S. aureus* and alterations in the fungal microbiota, potentiates IL-17-mediated inflammation, establishing a persistent inflammatory feedback loop.[10] Integrated microbiome and metabolome studies have additionally demonstrated that *Cutibacterium* correlates with antioxidant metabolic profiles, whilst *Staphylococcus* and *Corynebacterium* are associated with pro-inflammatory metabolites and oxidative stress.[12] The abundance of *Propionibacteriaceae* correlates strongly with glutathione levels (r = 0.821, P 0.001), indicating a role for microbiome-mediated oxidative stress.[12]

In the case of actinic keratosis (AK), a progressive pattern of dysbiosis has been described from healthy skin towards precancerous lesions and subsequently towards cutaneous squamous cell carcinoma. This process is characterised by a relative increase in *S. aureus* and a decrease in *Cutibacterium acnes*.[14] These findings suggest that dysbiosis is not merely an associated phenomenon but may play an active role in cutaneous carcinogenesis.[15,16]

Additionally, strain-level differences in *C. acnes* have been identified between healthy skin and lesions, pointing to specific functional changes in the microbiota during tumour progression to squamous cell carcinoma.[14] For their part, toxins produced by *S. aureus* may induce DNA damage and promote the sustained expression of pro-inflammatory cytokines, contributing to the tumour microenvironment.[15]

From a clinical perspective, certain therapies directed at the field of cancerisation have been observed to be associated with a reduction in *Staphylococcus* abundance in lesions, whilst elevated persistence of this genus is associated with a poorer therapeutic response.[17,18] Notably, patients who respond to field-directed therapies, such as diclofenac or cryotherapy, show a reduction in *Staphylococcus* abundance at weeks 24 and 36 compared with week 0, and a greater relative abundance of *S. aureus* at week 36 characterises non-responders.[17,18]

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3. Microbiota-immune system dialogue

Keratinocytes as active immune cells

Keratinocytes, which represent the predominant cell population of the epidermis, should not be regarded solely as structural elements of the cutaneous barrier. They are now recognised as immunocompetent cells with the capacity to detect microbial signals, respond to inflammatory stimuli and actively modulate cutaneous immunity. They act as immunological sentinels capable of integrating signals from the environment, the microbiota and the immune system, and of translating them into effector responses through the production of cytokines, chemokines and growth factors.[1] Figure 3 illustrates microbial recognition in the skin.

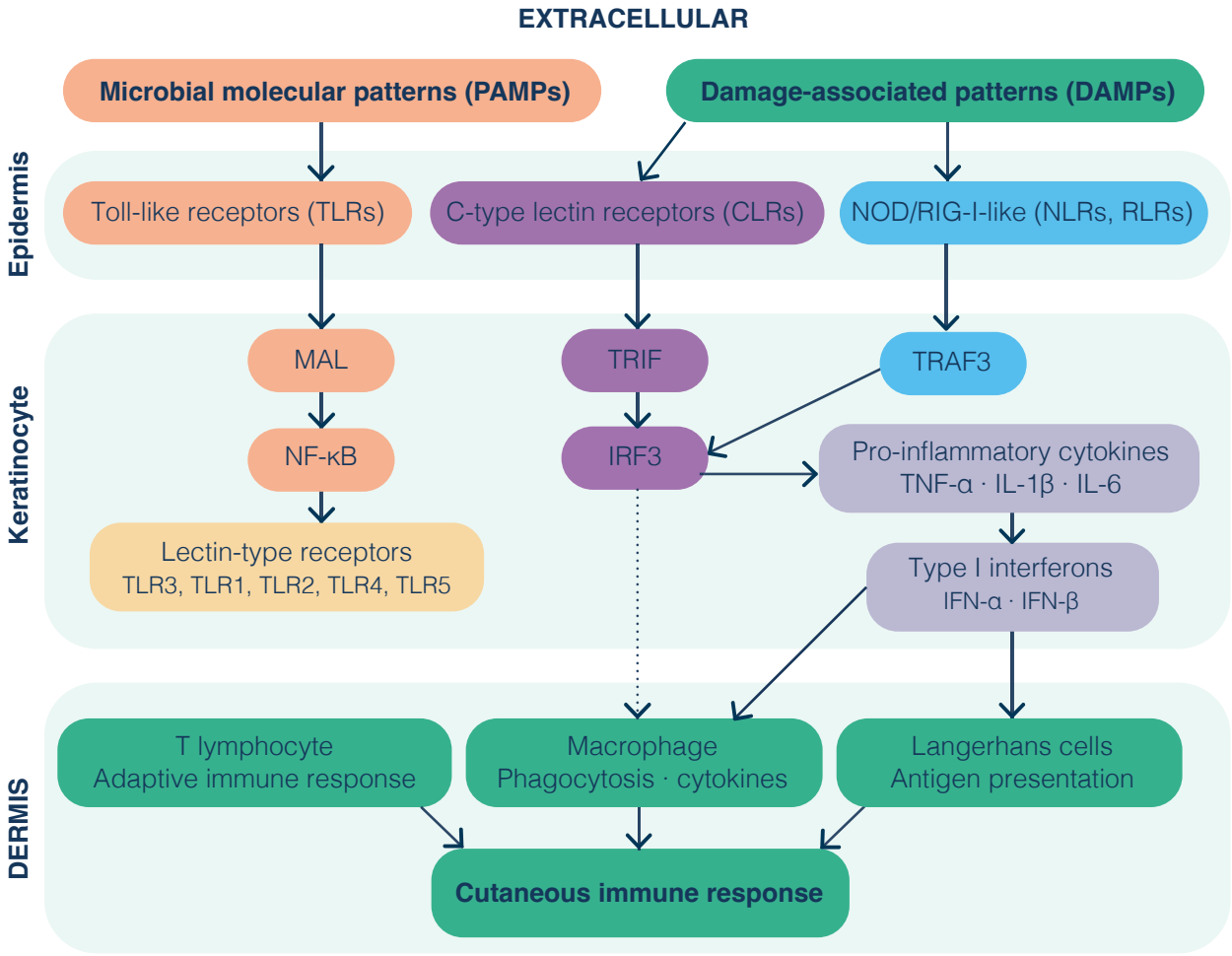

Figure 3. Microbial recognition in the skin.

CLR: C-type lectin receptor; DAMP: Damage-associated molecular pattern; IFN-α: Interferon alpha; IFN-β: Interferon beta; IL-1β: Interleukin-1 beta; IL-6: Interleukin-6; IRF3: Interferon regulatory factor 3; MAL: MyD88 adaptor-like protein; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; NLR: NOD-like receptor; NOD: Nucleotide-binding oligomerisation domain; PAMP: Pathogen-associated molecular pattern; RIG-I: Retinoic acid-inducible gene I; RLR: RIG-I-like receptor; TRAF3: TNF receptor-associated factor 3; TRIF: TIR-domain-containing adaptor inducing interferon-β (TICAM-1); TLR: Toll-like receptor; TNF-α: Tumour necrosis factor alpha.

From a functional standpoint, keratinocytes participate in both innate and adaptive immunity.[1,2] They produce pro-inflammatory mediators such as IL-1β, IL-6, TNF-α, TSLP and IL-33, promote the recruitment of immune cells and, in certain contexts, may acquire functions related to antigen presentation through the expression of major histocompatibility complex class II molecules and co-stimulatory molecules. Of particular interest is the observation that MHC-II expression by keratinocytes, induced by IL-22, contributes to the accumulation of IFN-γ-producing $CD4^+$ T lymphocytes in commensal microbiota-dependent responses.[1,3-5]

In this context, the concept of the "cytokinocyte" has emerged, reflecting the capacity of keratinocytes to receive multiple incoming inflammatory signals and generate specific profiles of outgoing mediators. This property enables them to integrate shared signalling pathways, such as NF-κB, JAK/STAT and MAPK, and to direct different immune responses according to the pathological context. Thus, in atopic dermatitis, Th2 polarisation programmes predominate, whilst in psoriasis and lichen planus, profiles closer to Th1/Th17 are observed.[1,3,4]

The dialogue between keratinocytes and the microbiota is, moreover, bidirectional. The commensal microbiota not only stimulates defensive responses but also contributes to the maintenance of barrier function and epidermal repair. A particularly relevant mechanism is signalling through the aryl hydrocarbon receptor (AhR) in keratinocytes. The absence of this pathway has been experimentally associated with greater barrier fragility and increased susceptibility to infection, whilst colonisation with cutaneous bacterial consortia can restore these functions in an AHR-dependent manner.[5,6]

Antimicrobial peptides: defensins and cathelicidins

Antimicrobial peptides constitute one of the principal effector mechanisms of cutaneous innate immunity. Some are expressed constitutively, whilst others are rapidly induced upon microbial invasion, tissue damage or exposure to inflammatory cytokines. Their function is not limited to direct microbicidal activity but also encompasses a marked immunomodulatory and epidermal homeostasis-regulating capacity.[7]

Among them, the sole human cathelicidin, LL-37, occupies a central position. This peptide exerts activity against bacteria, fungi, enveloped viruses and certain parasites, and additionally participates in the regulation of inflammation, angiogenesis and re-epithelialisation. Its expression is tightly regulated by, among other factors, vitamin D. Quantitative or qualitative alterations in LL-37 have been linked to several inflammatory dermatoses: in atopic dermatitis its production is reduced; in rosacea it undergoes aberrant processing with enhanced pro-inflammatory capacity; and in psoriasis it may complex with self-DNA and promote an auto-inflammatory cascade.[7,8]

The human β-defensins, in particular HBD-1, HBD-2, HBD-3 and HBD-4, are cationic peptides with broad-spectrum activity. Their antimicrobial action is exerted primarily through disruption of microbial membranes or interference with essential intracellular functions, yet their biological relevance extends beyond the direct control of pathogens. Defensins also regulate cellular recruitment, cytokine production and the functional connection between innate and adaptive immunity.[9-11]

The expression of these peptides is critical for barrier maintenance. In atopic dermatitis, the reduced expression of HBD-2 and LL-37 in lesional skin has been associated with increased susceptibility to infection by *Staphylococcus aureus*, viruses and fungi. Conversely, in psoriasis, a relative overexpression of various antimicrobial peptides is observed, which probably contributes to the lower frequency of cutaneous infections compared with other inflammatory dermatoses.[8,11,12]

In addition to cathelicidins and defensins, keratinocytes produce other peptides with antimicrobial and immunomodulatory activity, such as RNase 7 and various S100 proteins, including psoriasin, calprotectin and koebnerisin. These molecules participate not only in defence against bacteria but also in the response to viruses, either through direct action on viral particles or through modulation of the host immune response.[11-13]

Role of TLRs and microbial recognition

Toll-like receptors (TLRs) constitute an essential family of pattern recognition receptors involved in the detection of conserved microbial structures and tissue damage signals.[14] In the skin, they are expressed not only in keratinocytes but also in Langerhans cells, dendritic cells, macrophages, mast cells, lymphocytes, fibroblasts, endothelial cells and adipocytes, rendering the cutaneous compartment a highly competent network for immunological recognition.[15-17]

TLRs recognise both PAMPs (pathogen-associated molecular patterns) and DAMPs (damage-associated molecular patterns). In general terms, plasma membrane TLRs — such as TLR1, TLR2, TLR4, TLR5 and TLR6 — detect extracellular microbial components, particularly those of the bacterial cell wall, whilst TLRs localised in endosomal compartments — such as TLR3, TLR7, TLR8 and TLR9 — recognise nucleic acids and play a prominent role in antiviral responses.[15-18]

Activation of these receptors triggers intracellular signalling cascades, principally through the MyD88-dependent or TRIF-dependent pathways, culminating in the transcription of genes involved in inflammation, antimicrobial defence and activation of adaptive immunity. As a consequence, the production of cytokines, chemokines and antimicrobial peptides is increased, together with the expression of adhesion and co-stimulatory molecules.[15-17]

A particularly noteworthy aspect is that recognition by PRRs should not be interpreted solely in terms of defence against pathogens. Products derived from commensal microorganisms may also signal through these receptors and contribute to tissue development, homeostasis maintenance and immunological tolerance. This observation has reinforced the notion that PRRs participate in a stable bidirectional dialogue between host and microbiota, beyond their classical function in infection.[18,19]

Nevertheless, this same machinery may acquire a pathological role when its activation is aberrant or sustained. TLR overactivation has been associated with the amplification of autoimmune responses and with the development or perpetuation of inflammatory and neoplastic cutaneous diseases, including psoriasis, atopic dermatitis, lupus erythematosus, wound healing disorders and cutaneous cancer.[15,20] In parallel, other pattern recognition receptors, such as C-type lectin receptors, NOD receptors and RIG-I-like receptors, cooperate with TLRs to provide more comprehensive immune surveillance and maintain cutaneous homeostasis.[18,21]

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4. Microbiota-nutrient interaction

Vitamins and their role in cutaneous immunity

Fat-soluble vitamins, in particular A, D and E, play a fundamental role in the regulation of skin immunity, acting upon the integrity of the epidermal barrier, the immune response and microbiome homeostasis (Figure 4).[1,2]

Vitamin A, through its active derivatives (retinoids), is essential for the maintenance of cutaneous epithelial structure and function. It regulates keratinocyte proliferation and differentiation and modulates both innate and adaptive immune responses.[3] Its deficiency is associated with increased susceptibility to skin infections.[4] At the molecular level, vitamin A controls the expression of antimicrobial molecules such as RELMα, produced by keratinocytes and sebocytes, with demonstrated bactericidal activity both *in vitro* and *in vivo*.[4] Furthermore, retinoids influence T lymphocyte polarisation, favouring Th2 and regulatory T cell responses whilst inhibiting Th1 and Th17 pathways.[3,5]

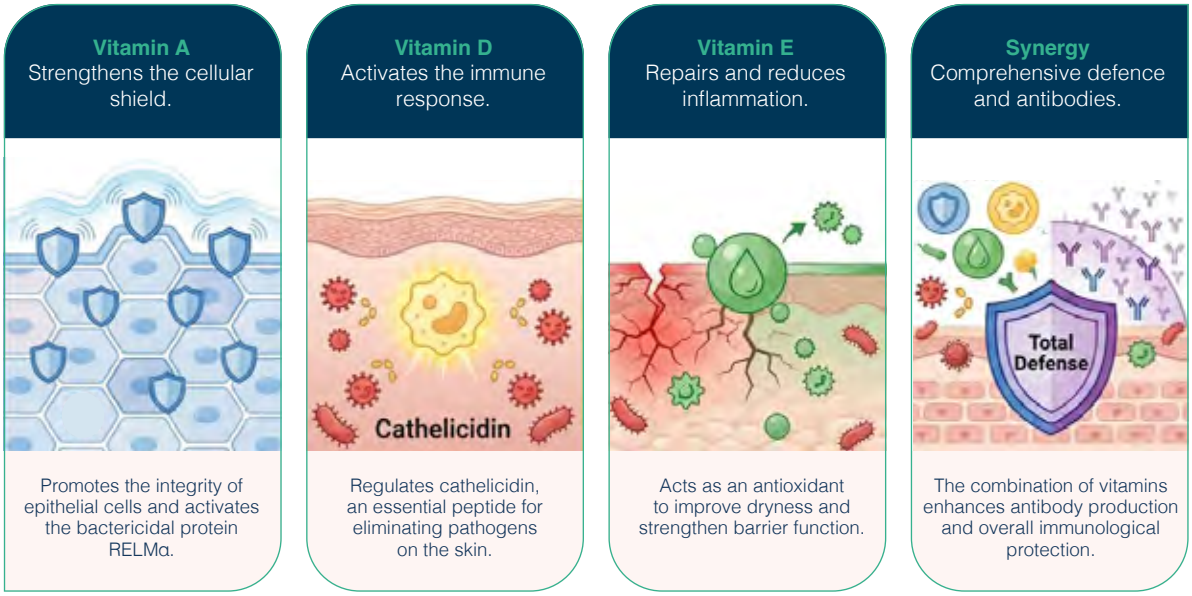

Figure 4. The role of vitamins.

Vitamin D exerts broad effects on the cutaneous immune system. It regulates innate immunity through the induction of antimicrobial peptides, particularly cathelicidin (LL-37), and modulates adaptive immunity by influencing T lymphocyte activation and differentiation as well as antibody production.[5-7] In the clinical setting, oral vitamin D supplementation, especially in combination with vitamin E, has been associated with improvement in symptoms such as dryness and pruritus in patients with atopic dermatitis.[8]

Vitamin E acts primarily as a fat-soluble antioxidant, protecting cell membranes from oxidative damage and modulating cutaneous inflammation.[1,2] Its beneficial effect on barrier function has been demonstrated in inflammatory diseases such as atopic dermatitis, where improvement in clinical parameters including dryness and lichenification has been observed.[8]

Collectively, these vitamins act synergistically with other micronutrients, including zinc, selenium and B-group vitamins, to sustain epidermal barrier function and optimise both cellular and humoral immune responses.[2]

Lipids and barrier function

Lipids constitute an essential component of the epidermal barrier and play a decisive role in the prevention of transepidermal water loss and in protection against external agents.[9,10]

Lipids are located principally in the stratum corneum, where at the extracellular level they are organised into highly specialised lamellar structures that limit the movement of water and solutes.[11] This lipid matrix exhibits a characteristic composition, formed predominantly by ceramides (≈50%), cholesterol (≈25%) and free fatty acids (≈15%), whose proportion and organisation are critical for the correct functioning of the epidermal barrier.[12]

Essential fatty acids, in particular linoleic acid and α-linolenic acid, play a key role in skin homeostasis. Their incorporation into cell membranes and epidermal lipids contributes to improved barrier function and modulation of the cutaneous lipid profile.[13] Conversely, their deficiency is associated with structural alterations of the stratum corneum and impairment of barrier function.[11]

The interaction between lipids and the microbiota is bidirectional. Certain cutaneous microorganisms have developed the capacity to utilise epidermal lipids as an energy source, whilst lipids, in turn, modulate microbial composition.[9,14] Integrative studies have demonstrated specific associations between microbial taxa and lipid profiles: *Cutibacterium* is associated with hydrophobic barrier components, whilst *Staphylococcus* is linked to metabolites involved in pH regulation and cutaneous hydration.[15]

Disruption of the lipid barrier, as occurs in atopic dermatitis, favours dysbiosis and colonisation by pathogens such as *Staphylococcus aureus*, facilitating antigen penetration and activation of the inflammatory response.[14] In this context, restoration of physiological lipids through topical interventions has been shown to improve barrier homeostasis and constitutes a relevant therapeutic strategy.[11]

Production of microbial metabolites

The cutaneous microbiota and the intestinal microbiota generate a broad range of bioactive metabolites that mediate the interaction between microorganisms and the host, modulating both barrier function and the immune response.[16,17]

Among the metabolites produced by the cutaneous microbiota are short-chain fatty acids (SCFAs), tryptophan derivatives, antimicrobial peptides and other bioactive molecules that participate in processes such as wound healing, colonisation resistance and immunological regulation.[16,18]

Tryptophan-derived metabolites play a particularly relevant role by acting as ligands of the aryl hydrocarbon receptor (AhR). These compounds, produced by commensal microorganisms, have been shown to enhance epidermal repair and strengthen barrier function through activation of this signalling pathway.[19]

Combined microbiome and metabolome analysis has enabled the identification of specific microbe–metabolite interaction patterns. Thus, *Cutibacterium* is associated with hydrophobic lipid profiles, whilst *Staphylococcus* is linked to amino acids involved in pH regulation and cutaneous hydration, and *Streptococcus* exhibits more independent associations.[15]

Short-chain fatty acids (SCFAs), particularly acetate, propionate and butyrate, represent a central axis in microbiota-host communication. These metabolites modulate inflammation, promote keratinocyte differentiation and contribute to the maintenance of epidermal barrier integrity.[20-22] Their effects are exerted through mechanisms such as the activation of G protein-coupled receptors and the inhibition of histone deacetylases, thereby influencing gene expression and the immune response.[21,22]

From a functional standpoint, SCFAs exhibit relevant anti-inflammatory properties. Butyrate has been shown to reduce cutaneous inflammation, induce regulatory T cells and modulate cytokine production, contributing to immunological equilibrium.[23,24]

In the context of the gut-skin axis, the production of SCFAs from dietary fibre fermentation indirectly influences skin health. These metabolites can act at a distance, modulating systemic immunity and barrier function in the skin.[21,22]

In diseases such as psoriasis, intestinal dysbiosis is associated with a reduction in SCFA production, which contributes to the loss of immunological control and the perpetuation of inflammation. The restoration of these metabolites thus emerges as a potential therapeutic strategy in inflammatory cutaneous diseases.[25,26]

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5. Nutrition as a modulator of the cutaneous microbiota

Prebiotics and probiotics: a realistic appraisal of the evidence

Nutrition can modulate the cutaneous microbiota indirectly, principally through its impact on the intestinal microbiota and the systemic immune response (Figure 5, gut-skin axis). In this context, probiotics, prebiotics and symbiotics have attracted growing interest as adjunctive tools in dermatology. Nevertheless, the available evidence remains heterogeneous and demands cautious interpretation, as studies differ in the strains employed, doses, duration, routes of administration and clinical variables analysed.[1-5]

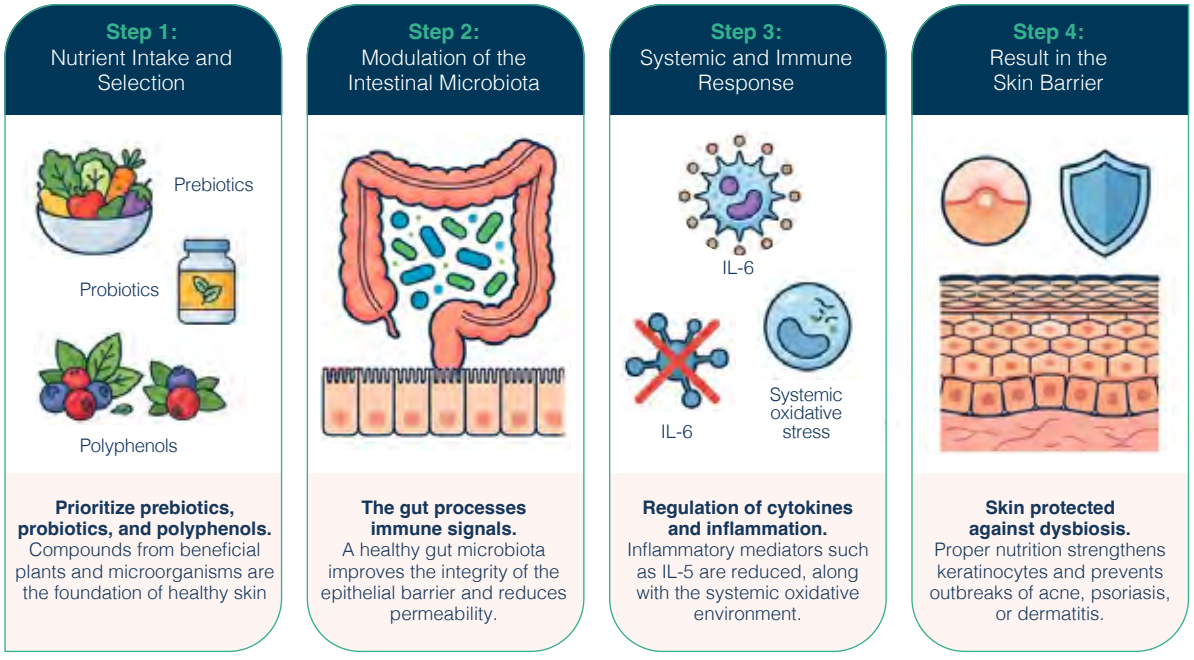

Figure 5. Gut-skin axis.

Atopic dermatitis is, to date, the most extensively studied entity. Recent reviews suggest that certain probiotic or prebiotic interventions may be associated with improvement in clinical severity, quality of life and, in some contexts, with a reduction in incidence during early life. However, results are not uniform, and the therapeutic benefit cannot be considered generalisable to any given preparation or patient profile.[1-4] In psoriasis, the evidence is considerably more limited, although some trials have described improvement in clinical indices and inflammatory markers, suggesting a possible immunomodulatory effect that still awaits confirmation in studies of higher methodological quality.[1,2,4,5] In acne, research is still in its early stages and points primarily to a possible adjunctive role alongside other therapies, rather than a robustly demonstrated autonomous effect.[1,3,4]

From a physiological standpoint, probiotics may influence cytokine production, epithelial barrier integrity and the synthesis of antimicrobial peptides, in addition to modulating keratinocyte differentiation and regeneration. Prebiotics, particularly certain oligosaccharides, may promote microbiota-host interactions with antioxidant, anti-inflammatory and reparative effects.[5,6] More recently, postbiotics have emerged as a strategy of interest, as they allow the exploitation of microbial components or metabolites without depending on the viability of the microorganism. Postbiotics derived from *Lactiplantibacillus plantarum* demonstrated antimicrobial activity, antioxidant capacity, suppression of inflammatory cytokines (IL-6, IL-8, TSLP) and improvement of cutaneous barrier function (involucrin, filaggrin, loricrin) in stimulated keratinocytes.[7-9] Postbiotics derived from *Bifidobacterium* breve, *Limosilactobacillus reuteri* and *Ligilactobacillus salivarius* improved the growth, differentiation and epithelial barrier integrity of keratinocytes in *ex vivo* human skin.[10]

Polyphenols and plant-rich diets

Polyphenols constitute a broad group of bioactive compounds present in fruits, vegetables, legumes, nuts, tea, cocoa and other plant-derived foods. Their dermatological interest stems from their antioxidant and anti-inflammatory capacity, as well as their potential to modulate pathways implicated in photoageing, oxidative stress and cutaneous inflammation.[11-15]

Various experimental studies have shown that polyphenols can attenuate collagen degradation, promote procollagen synthesis and reinforce the endogenous antioxidant systems of the skin. Furthermore, some compounds have demonstrated antimicrobial, antitumoral and photoprotective properties, which has driven their study in the field of nutricosmetics and as adjuncts in inflammatory cutaneous diseases.[12-15] Along these lines, dietary patterns rich in plant-based foods could provide a combination of micronutrients and phytochemicals with complementary effects on the cutaneous barrier, inflammation and redox balance.[11]

Direct clinical evidence remains limited, yet suggestive data exist. A randomised controlled trial showed that consumption of pomegranate juice or extract over 12 weeks increased resistance to UVB-induced erythema and was accompanied by changes in the composition of the cutaneous microbiome in healthy women.[16] This finding is particularly noteworthy because it reinforces the notion that certain dietary compounds act not only upon the host but may also modulate the cutaneous microbial ecosystem. Nonetheless, simplistic messages should be avoided: the majority of the evidence derives from *in vitro* models, animal studies or trials with specific extracts, such that precise recommendations regarding dose, duration or optimal formulations cannot yet be established.[11,13,16]

Sugars and the Western diet: dysbiosis

Conversely, the Western diet — rich in refined sugars, saturated fats and ultra-processed foods and poor in fibre — has been associated with alterations in the intestinal microbiota and, indirectly, with changes in skin homeostasis. This dietary pattern favours barrier dysfunction, low-grade systemic inflammation and disruption of the gut-skin axis.[17-22]

Experimental models support this association. In mice, a short-term Western diet was capable of promoting IL-23-mediated cutaneous and articular inflammation, accompanied by reduced microbial

diversity and intestinal dysbiosis; moreover, some of these changes were attenuated upon reversal of the dietary pattern, suggesting that diet-induced alterations may be, at least in part, reversible.[17] High sugar intake may contribute to increased intestinal permeability, altered mucosal immunity and a systemic pro-inflammatory milieu.[18,21]

These alterations may be relevant in diseases such as atopic dermatitis, psoriasis or acne. In atopic dermatitis, the Western diet has been linked to dysbiosis and epidermal barrier dysfunction.[19] In metabolic disorders such as obesity or type 2 diabetes, hyperglycaemia, advanced glycation end-products and changes in lipid composition may favour colonisation by pro-inflammatory microorganisms and modify the microbial ecology of the skin.[20]

Taken together, current evidence suggests that diet may act as a relevant modulator of the microbiota-immunity-cutaneous barrier axis. At present, sufficient data are not available to convert probiotics, prebiotics, postbiotics or specific bioactive compounds into universal, definitive recommendations for each dermatosis. It does, however, seem reasonable to consider that dietary patterns rich in plant-based foods and fibre, and low in refined sugars and ultra-processed products, could foster a metabolic and immunological milieu more compatible with skin homeostasis. This perspective opens the door to individualised nutritional interventions, conceived not as substitutes for dermatological treatment but as complementary tools within an integrative approach.[11,17,22]

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IV. Psoriasis: immunological mechanisms and nutrient connections

1. Immunological architecture of psoriasis

Psoriasis is defined as a chronic, multifactorial, immune-mediated inflammatory dermatosis characterised by well-demarcated erythemato-squamous plaques resulting from keratinocyte hyperproliferation and abnormal differentiation, associated with inflammatory infiltrates of T lymphocytes, dendritic cells and other immune cells in the dermis and epidermis. The skin lesions show acanthosis, parakeratosis and elongation of the epidermal rete ridges, reflecting an accelerated epidermal turnover rate in response to inflammatory mediators.[1,2]

Psoriasis is now regarded as a systemic disease associated with metabolic comorbidities such as obesity, insulin resistance, metabolic syndrome, hyperuricaemia and increased cardiovascular risk, suggesting the involvement of common inflammatory pathways between the skin and other organs.[3-7]

Advances in cutaneous immunology have identified the IL-23/Th17 axis as the predominant immune pathway in psoriasis pathogenesis, with IL-17 and TNF-α as key mediators.[8,9]

IL-23 is mainly produced by inflammatory myeloid dendritic cells and macrophages in psoriatic dermis and acts by maintaining and expanding pathogenic Th17 lymphocyte populations. Once stimulated by IL-23, these cells secrete cytokines such as IL-17A, IL-17F, IL-22, IL-26, IFN-γ and GM-CSF, which orchestrate the cutaneous inflammatory response.[10]

IL-17A and IL-17F, produced by Th17, Tc17 and dermal γδ T cells, induce keratinocyte proliferation and stimulate the expression of chemokines (e.g. CXCL8-CXCL11, CCL20), pro-inflammatory cytokines (TNF, IL-1β, IL-6) and antimicrobial peptides (β-defensins, LL-37) in the epidermis. These molecules recruit neutrophils, T lymphocytes and dendritic cells, reinforcing a self-amplifying inflammatory loop in psoriatic plaques.[11]

TNF-α, traditionally linked to the Th1 axis, also occupies a central place in the IL-23/Th17 axis by promoting dendritic cell activation and favouring Th17 differentiation and survival.[1] In addition, TNF-α stimulates infiltration of inflammatory cells into lesional skin and increases keratinocyte proliferation, acting synergistically with IL-17 in the induction of pro-inflammatory mediators.[1,12]

Other relevant cytokines in psoriasis are IL-12, acting mainly on Th1 lymphocytes; IFN-γ, characteristic of the Th1 response; and IL-22, associated with Th22 lymphocytes, contributing to epidermal hyperplasia and altered keratinocyte differentiation. This network positions psoriasis as a paradigm of mixed Th17/Th1 disease, with TNF-α and IL-17 as key effector mediators.

The interconnection among these circuits explains the heterogeneity of clinical phenotypes: IL-17 responses predominate in plaque psoriasis, interferon responses are prominent in early-stage plaque psoriasis and in anti-TNF-α antibody-mediated psoriasiform reactions, whereas the IL-36 circuit is hyperactivated in pustular forms.[12]

Keratinocytes do not merely function as responder cells but rather as active amplifiers of the immune response in psoriasis, producing antimicrobial peptides, growth factors, inflammatory cytokines (IL-1β, IL-6, TNF-α) and chemokines (CXCL1, CXCL2, CXCL8, CCL20) that promote angiogenesis, neutrophilic infiltration and recruitment of Th1 and Th17 lymphocytes, creating a self-sustaining inflammatory cycle.[11-13]

Nutrients can modulate these immune and oxidative mechanisms, so that certain fatty acids, antioxidants, vitamin D and dietary carbohydrate patterns influence systemic inflammation, oxidative stress and potentially the frequency and severity of psoriasis flares.[14] For example, keratinocytes respond to metabolic and nutritional mediators such as vitamin D and lipid derivatives, altering their proliferation and differentiation rates, thereby connecting immune pathways with the patient's nutritional environment.[13,15,16]

Although clinical evidence is heterogeneous, studies suggest a possible benefit of omega-3 fatty acids over omega-6 fatty acids, increased intake of dietary antioxidants and vitamin D, and reduced intake of simple sugars and control of insulin resistance, as adjunctive strategies to pharmacological treatment. This review summarises the immunological foundations of psoriasis and analyses the available evidence on the relationship between different nutrients and the immunopathogenesis and flares of the disease.[17]

Table 1. Key immune mediators in psoriasis pathogenesis and their principal factors.

Mediator	Principal cellular source	Key role in psoriasis
IL-23	Myeloid dendritic cells, macrophages	Maintains and expands pathogenic Th17 populations
IL-17A / IL-17F	Th17, Tc17, γδ T cells	Induces keratinocyte proliferation; stimulates chemokines and antimicrobial peptides
TNF-α	Macrophages, dendritic cells, keratinocytes	Promotes DC activation, Th17 survival; synergises with IL-17
IL-22	Th22 lymphocytes	Contributes to epidermal hyperplasia and altered differentiation
IFN-γ	Th1 lymphocytes	Characteristic of Th1 response; prominent in early-stage disease
IL-1β	Keratinocytes, macrophages	Pro-inflammatory; contributes to insulin resistance via p38 MAPK
IL-6	Keratinocytes, macrophages	Pro-inflammatory; shared pathway with metabolic syndrome

2. Polyunsaturated fatty acids: the ω-3 *versus* ω-6 balance

Polyunsaturated fatty acids (PUFAs) of the ω-3 and ω-6 series are precursors of eicosanoids and lipid mediators that modulate systemic inflammation.[18] ω-6 fatty acids, such as arachidonic acid, give rise to prostaglandins and leukotrienes — especially LTB4 — generally pro-inflammatory, whereas long-chain ω-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), give rise to resolvins and protectins with anti-inflammatory properties, modulating the Th17 response.[14,18-20]

Experimental evidence in three-dimensional skin models with psoriatic cells shows that α-linolenic acid (ALA, ω-3) decreases keratinocyte proliferation and improves epidermal differentiation, increasing filaggrin and loricrin expression.[21] Supplemented ALA is incorporated into epidermal phospholipids and metabolised into long-chain ω-3 PUFAs, mainly EPA and docosapentaenoic acid ω-3.[21] Supplementation also reduces ω-6 mediators such as 9-hydroxyoctadecadienoic acid, 12-hydroxyeicosatetraenoic acid and LTB4.[21]

In this context, ω-3 fatty acid intake has been shown to be the best dietary predictor of psoriasis severity measured by the PASI scale.[22]

EPA and DHA reduce epidermal hyperplasia in patients with psoriasis through interactions with the PPAR signalling pathway, increasing stratum corneum maturation via upregulation of filaggrin and keratin 10 expression; decreasing the expression of ω-6 PUFA-derived inflammatory mediators such as prostaglandin E2 (PGE2) and 12-HETE; and inhibiting the synthesis of TNF-α, IL-1β, IL-6 and IL-12.[14,19,23,24]

Clinical interventions with ω-3 supplements in patients with psoriasis have shown heterogeneous results. Among nine double-blind randomised clinical trials, only two reported a clinical benefit from supplementation.[18] However, a more recent meta-analysis including 10 studies and 560 participants indicated a significant reduction in PASI score of 1.58 points (95% CI: −2.24, −0.92; p = 0.001) in favour of the ω-3 group, with significant improvements in erythema, scaling and pruritus.[25,26]

Furthermore, fish oil rich in ω-3 (DHA and EPA) combined with conventional treatments has shown a reduction in PASI score (mean difference: −3.92; 95% CI: −6.15 to −1.69; p = 0.0006) and lesion area (mean difference: −30.00; 95% CI: −33.82 to −26.18; p = 0.0001).[19] Recent studies suggest that the effect of supplementation may vary by sex: in men, total ω-3 and/or EPA show nonlinear associations with PASI and BSA scores, whereas in women inverse associations have been described.[27]

Whilst some clinical studies have focused on ω-3 supplementation, fewer have evaluated the specific impact of reducing ω-6 intake or the ω-6/ω-3 ratio in psoriasis. A typical Western diet presents an ω-6/ω-3 ratio of 15-20/1, whereas an international expert panel recommends an ideal ratio of 1.8/1, similar to that observed throughout human history.[18] In psoriasis, it has been proposed that a relative excess of ω-6 over ω-3 favours a chronic inflammatory state, whereas increased ω-3 intake may have a protective effect.[3,14,19] Indeed, regions with higher relative ω-3 intake show a lower incidence of the disease.[18]

3. Antioxidants: vitamins E, C and polyphenols

Oxidative stress — defined as an imbalance between reactive oxygen species and the cell's capacity to repair damage — is involved in multiple skin diseases, including psoriasis.[28,29] Patients with psoriasis show increased superoxide release from granulocytes (10.0 ± 0.5 nmol/L per 10^6 cells/h in erythrodermic psoriasis *versus* 1.5 ± 0.1 in donors), altered copper/zinc superoxide dismutase and catalase activity in granulocytes and epidermis, along with increased plasma malondialdehyde (MDA) concentration and nitrite/nitrate ratio.[17,30] This contributes to damage of lipids, proteins and DNA, activates inflammatory pathways such as NF-κB and promotes the perpetuation of chronic inflammation.[17]

A cross-sectional analysis of 23,311 participants from the National Health and Nutrition Examination Survey (NHANES), including 621 diagnosed with psoriasis, showed that higher Composite Dietary Antioxidant Index (CDAI) scores were associated with a lower odds ratio of psoriasis (OR = 0.72, 95% CI: 0.56-0.92, p = 0.009).[31] Specifically, vitamin E intake showed an inverse correlation with psoriasis risk (OR = 0.76, 95% CI: 0.60–0.96, p = 0.039), whereas other CDAI components were not significantly associated.[31]

Vitamin C (ascorbic acid) is a water-soluble antioxidant that acts as an electron donor, neutralising ROS such as hydrogen peroxide and hydroxyl radicals, and regenerating other antioxidants such as vitamin E. Clinical studies have shown that vitamin C supplementation in patients with psoriasis reduces oxidative stress biomarkers such as MDA and increases antioxidant enzyme activity, with possible modulation of immune responses and reduction of inflammation, although evidence for supplementation benefit remains limited.[29]

Vitamin E (α-tocopherol) is a potent lipid-soluble antioxidant that protects cell membranes from lipid peroxidation. Reduced levels of vitamin E and other antioxidants have been described in psoriasis, and some studies suggest that supplementation may decrease ROS levels and be associated with clinical improvement.[17] For example, supplementation with coenzyme Q10 (ubiquinone acetate, 50 mg/day), vitamin E (natural α-tocopherol, 50 mg/day) and selenium (aspartate salt, 48 µg/day) for 30-35 days in patients with erythrodermic psoriasis and psoriatic arthropathy resulted in significant clinical improvement, corresponding to a faster normalisation of oxidative stress markers compared with placebo.[30] Nevertheless, evidence for the benefit of selenium supplementation is limited. In an intervention study based on one month of selenium-enriched yeast supplementation (600 µg/day), no increase in cutaneous selenium concentration or improvement in psoriasis severity was observed.[32] Likewise, selenium supplementation provided no additional clinical benefit in patients with psoriasis receiving narrowband UVB phototherapy.[33]

Polyphenols, found in fruits, vegetables, green tea, cocoa and olive oil, exhibit antioxidant and anti-inflammatory properties through neutralisation of ROS and modulation of signalling pathways such as NF-κB and Nrf2.[17] In particular, curcumin exerts clinical benefit through pleiotropic mechanisms of action: inhibition of cell proliferation, induction of apoptosis, suppression of pro-inflammatory cytokines (IL-17, IL-6, IL-8, IFN-γ, TNF-α) and improvement in cutaneous barrier protein expression.[34,35]

A meta-analysis including 26 studies (7 randomised clinical trials and 19 preclinical studies) showed that both curcumin monotherapy and combination therapy improved PASI scores compared with controls (standardised mean difference: −0.84; 95% CI: −1.53 to −0.14; p = 0.02).[35]

A 12-week randomised, double-blind, placebo-controlled clinical trial with oral curcumin (2 g/day) plus topical corticosteroids showed that 12% of the experimental group achieved 100% improvement *versus* 4% in the placebo plus topical steroid group, with significantly decreased IL-22 levels (p = 0.001).[36]

Topical curcumin formulations have also demonstrated efficacy. In a 9-week randomised, intra-individual, double-blind, placebo-controlled study, 34 patients treated with a turmeric extract gel showed statistically significant improvements in scaling, erythema and plaque thickness.[36]

Other polyphenols with therapeutic potential include resveratrol, quercetin and epigallocatechin-3-gallate, owing to their anti-inflammatory, antioxidant, immunomodulatory and antiproliferative properties, with the ability to suppress the aetiopathogenesis of psoriasis.[37]

4. Vitamin D: regulation of keratinocytes and immunity

Vitamin D plays fundamental roles in the pathogenesis and treatment of psoriasis through three main mechanisms: regulation of keratinocyte proliferation and maturation, immunomodulation and maintenance of skin barrier integrity.[38,39]

The active hormonal form, 1,25-dihydroxyvitamin D_3 (calcitriol), modulates immune homeostasis by enhancing innate immunity, downregulating pathological inflammatory cascades and controlling lymphocyte differentiation.[40] Specifically, vitamin D reduces IL-2 and IL-6 synthesis, blocks transcription of IFN-γ and GM-CSF, and inhibits the activity of NK cells and cytotoxic T lymphocytes. Therefore, supplementation may attenuate the pathological Th1/Th17 response in patients with psoriasis.[15,16] The immunomodulatory effect of vitamin D depends on maintaining serum 25(OH)D concentrations above 30 ng/mL.[41]

In human keratinocyte models, vitamin D has been shown to exert dose-dependent antiproliferative effects and promote cellular differentiation, increasing expression of tight-junction proteins and reinforcing skin barrier integrity.[15,16]

In addition, calcitriol regulates IL-1 family cytokine expression in keratinocytes, increasing IL-1α mRNA stability and transcription of the intracellular IL-1 receptor antagonist (icIL-1Ra), whilst decreasing IL-18 expression in a dose and time-dependent manner.[42] The magnitude of icIL-1Ra induction is much greater than that of IL-1α, so that the icIL-1Ra:IL-1α ratio increases markedly, leading to suppression of IL-1 activity.[42]

A significant association between vitamin D deficiency and psoriasis severity has recently been described.[13] As a modifiable risk factor, vitamin D_3 supplementation could play a relevant therapeutic role.[40] However, the results of randomised clinical trials on the role of oral vitamin D supplementation in psoriasis management have been contradictory.[13,43-47]

A randomised clinical trial conducted during winter in northern Norway in 70 patients with psoriasis and low 25(OH)D levels (24 ng/mL) evaluated the effect of vitamin D supplementation (cholecalciferol) on psoriasis severity measured by PASI, PGA, self-assessed PASI (SAPASI) and DLQI.[39] Participants in the control group received an induction dose of 100,000 IU, followed by a maintenance dose of 20,000 IU weekly for 4 months. Supplementation did not produce a statistically significant difference in PASI score (−0.34 *vs.* −0.42; p = 0.52), SAPASI (−0.5 *vs.* 0.25; p = 0.3) or DLQI (−0.59 *vs.* 0.1; p = 0.11).[39] No differences were detected in the amount of topical treatment (measured in grams) between groups during follow-up. Nevertheless, the results should be interpreted with caution, as only 41.1% of the experimental group reached the target serum 25(OH)D concentration ≥30 ng/mL and baseline severity was low, with a mean initial PASI score of 3.2.[39]

5. Simple carbohydrates, insulin and inflammation

Psoriasis is associated with an increased risk of metabolic syndrome and type 2 diabetes mellitus (T2DM), even after adjustment for body mass index (BMI), smoking, cardiovascular disease, hypertension and dyslipidaemia.[48]

Large prospective cohort studies have shown that the risk of T2DM correlates in a dose-dependent manner with body surface area affected and with the presence of psoriatic arthritis.[48] Recently, shared genetic loci between psoriasis and T2DM have been identified through signalling mechanisms mediated by the transcription factor NF-κB.[48]

The chronic inflammatory states of psoriasis, metabolic syndrome and T2DM share pathophysiological similarities, including predominance of Th1 and Th17 lymphocytes and the pro-inflammatory cytokines TNF-α and IL-6, increased leptin and resistin levels, and reduced adiponectin concentrations.[48,49]

TNF-α inhibits insulin receptor activity and reduces expression of the glucose transporter GLUT4, leading to insulin resistance.[48,49] On the other hand, IL-1β — present in high amounts in the interstitial space of patients with psoriasis — contributes to insulin resistance through p38 MAPK (mitogen-activated protein kinase).[50]

High intake of simple sugars is a typical feature of the Western diet and has been linked to increased systemic inflammation and exacerbation of autoimmune diseases. Experimental studies in murine models have shown that short-term exposure to a Western-type diet can exacerbate inflammation in psoriasis.[3]

A prospective cohort study based on the UK Biobank including 210,474 participants without psoriasis at baseline evaluated the association between carbohydrate intake and the risk of developing psoriasis. During follow-up (median = 13.25 years), 1,907 incident cases were recorded.[3] Compared with the lowest intake quartile (Q1), the highest quartile (Q4) of total carbohydrates [HR (95% CI) = 1.14 (1.01–1.29)], free sugars [1.22 (1.07–1.38)] and sucrose [1.14 (1.01–1.30)] was associated with increased psoriasis risk.[3] By contrast, the highest intake of starch [0.86 (0.76–0.98)] and fibre [0.84

(0.74–0.96)] showed a protective effect against psoriasis.[3] These findings support the hypothesis that high consumption of simple sugars may act as a nutritional risk factor for psoriasis, possibly through enhancement of systemic inflammation and insulin resistance.

On the other hand, hypoglycaemic drugs from different categories have been shown to improve psoriasis progression through different mechanisms. For example, liraglutide reduced psoriasiform inflammation in obese diabetic mice, with improvements in PASI, insulin resistance and glucose metabolism.[48]

Table 2. UK Biobank Prospective cohort: association between carbohydrate subtypes and psoriasis risk (Q4 *vs.* Q1)

Carbohydrate subtype	HR (95% CI)	Direction
Total carbohydrates	1.14 (1.01-1.29)	↑ Risk
Free sugars	1.22 (1.07-1.38)	↑ Risk
Sucrose	1.14 (1.01-1.30)	↑ Risk
Starch	0.86 (0.76-0.98)	↓ Risk (protective)
Fibre	0.84 (0.74-0.96)	↓ Risk (protective)

6. Advanced glycation end products (AGEs)

Advanced glycation end products (AGEs) are biologically active compounds formed physiologically through a sequence of non-enzymatic reactions generating highly oxidising reactive aldehydes that can covalently bind to proteins.[51] AGEs slowly accumulate in tissues during ageing, but also in certain metabolic and inflammatory disorders, with more rapid and intense accumulation in the skin and plasma of patients with type 2 diabetes, obesity, cardiovascular disease, chronic kidney failure, non-alcoholic fatty liver disease and psoriasis.[51,52]

Through activation of the STAT1/3 signalling pathway, AGEs promote keratinocyte proliferation by upregulating keratin 17 (K17) and downregulating p27KIP1.[53] In addition, AGEs increase interleukin-36α (IL-36α) production by keratinocytes, enhancing the Th17 immune response; they increase reactive oxygen species formation and activate the transcription factor NF-κB.[53]

Recent studies have detected abnormal AGE accumulation in epidermal keratinocytes of psoriatic plaques.[53] A cross-sectional case-control study involving 80 patients with psoriasis and 80 age-, sex- and BMI-matched controls (excluding smokers and patients with diabetes, dyslipidaemia, hypertension or systemic treatment) showed that AGE levels in skin ($p = 0.04$), plasma ($p = 0.03$) and pentosidine levels ($p = 0.05$) were higher in patients with severe psoriasis.[54] Cutaneous AGE concentrations showed a strong correlation with plasma AGE levels ($r = 0.93$, $p = 0.0001$) and PASI severity ($r = 0.91$, $p = 0.0001$).[54]

Another study evaluating skin autofluorescence (SAF) as a measure of AGE accumulation in 70 patients with psoriasis vulgaris without cardiovascular comorbidities and 59 healthy controls found SAF to be significantly increased in psoriasis patients with elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) compared with controls ($p = 0.00001$).[55] Similarly, increased SAF was observed in psoriatic patients with prediabetes (HbA1c = 5.7-6.4%) compared with controls ($p = 0.0012$, after adjustment for age).[55]

In addition, patients with psoriasis have increased concentrations of N-carboxymethyl-lysine (CML), N-carboxyethyl-lysine (CEL) and the soluble form of the receptor for advanced glycation end products (sRAGE), although these do not correlate with PASI severity.[56] Specifically, disease remission was followed by a significant decrease in the concentrations of these products compared with patients with active disease; however, levels remained significantly higher than in controls.[56]

7. Western diet and triggering of flares

Many patients with psoriasis report that certain foods trigger or worsen flares, although controlled scientific evidence on specific foods remains limited. Potential triggers include red meat and dairy products rich in saturated fat, as well as alcohol and ultra-processed foods, which have been associated with increased systemic inflammation.

The Western diet, characterised by a high content of fat and simple sugars, predisposes individuals to inflammatory dermatoses such as psoriasis, independently of the increased risk of overweight and obesity.[57,58] In fact, excessive consumption of pro-inflammatory foods such as alcohol, red meat, nightshades, dairy products and gluten may exacerbate the disease.[2,59,60]

Feeding mice a Western-type diet leads to a shift in cutaneous immune response towards a Th1/Th17 profile before any increase in body weight occurs, with a reduction in PPARγ$^+$ Treg lymphocytes.[57,61] This results in accumulation in the skin of IL-17A-producing γδ T lymphocytes, with increased IL-23R expression and elevated concentrations of inflammatory cytokines such as IL-6, IL-17, IL-23 and TNF-α.[57,61-63]

Table 3. Western *vs.* mediterranean dietary patterns: contrasting effects on psoriasis-related pathways

Dimension	Western dietary pattern	Mediterranean dietary pattern
ω-6/ω-3 ratio	High (15-20/1)	Low (closer to 1.8/1)
Predominant lipid mediators	Pro-inflammatory (PGE_2, LTB_4)	Anti-inflammatory (resolvins, protectins)
AGE exposure	High (dry-heat cooking, processed foods)	Lower (wet-heat methods, fresh foods)
Simple sugar intake	High	Low
Fibre and MAC intake	Low	High
Gut microbiota profile	Dysbiosis; ↑ pro-inflammatory taxa	↑ Diversity; ↑ *Faecalibacterium*, *Bifidobacterium*
Cutaneous immune profile	Th1/Th17 shift; ↓ PPARγ$^+$ Tregs	Anti-inflammatory milieu
Psoriasis severity association	↑ PASI, ↑ flare frequency	↓ Disease severity

MAC: microbiota accesible carbohydrates

Preclinical studies have also suggested an association between the Western diet and increased risk of psoriatic arthritis.[64] Specifically, when mice were returned to a standard diet, intestinal dysbiosis was corrected, and both skin and joint inflammation decreased.[64] These findings suggest that dietary intervention could have clinical benefit in patients with psoriasis and psoriatic arthritis.[64]

Diets rich in fruits, vegetables, olive oil, nuts and oily fish, characteristic of the Mediterranean pattern, are associated with lower systemic inflammation and reduced risk of cardiovascular and metabolic diseases. An observational study found that people with psoriasis were less likely to follow a Mediterranean-type diet than healthy controls, and that adherence to this pattern was associated with lower disease severity.[17] In fact, diets rich in fibre and plant compounds favour a microbiota that produces short-chain fatty acids with anti-inflammatory effects, whereas patterns rich in simple sugars, saturated fatty acids and processed foods tend to be associated with dysbiosis and systemic inflammation.[3,17]

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V. Actinic keratosis: solar damage, immunity and key nutritional factors

1. Clinical introduction and relevance of actinic keratosis

Actinic keratosis (AK), also termed solar keratosis, is an intraepithelial proliferation of atypical keratinocytes that develops as a consequence of chronic, cumulative exposure to ultraviolet (UV) radiation.[1,2] Clinically, it presents as scaly, rough-textured lesions of small size (typically between 2 and 6 mm), erythematous or skin-coloured, which on many occasions are more readily identified by palpation than by visual inspection.[3]

These lesions appear preferentially on sun-exposed areas such as the face, the scalp in individuals with alopecia, the ears, the neck, the dorsum of the hands and the forearms, where the majority of cases are located.[1] Their distribution directly reflects the cumulative effect of actinic damage over the course of a lifetime.

From an epidemiological standpoint, AK constitutes the most common premalignant cutaneous lesion in fair-skinned populations. Its prevalence may reach figures approaching 60% in individuals over 60 years of age, with a lifetime risk of development exceeding 50% in certain geographical settings, particularly in regions with high solar exposure such as the United States or Australia.[4,5] It affects males of advanced age more frequently, as well as individuals with low phototypes (Fitzpatrick I-II) and immunosuppressed patients, in whom the incidence and aggressiveness of the disease are greater.[7]

Histologically, AKs are characterised by epidermal proliferation with atypical keratinocytes displaying variable degrees of dysplasia, without reaching the full-thickness epidermal involvement characteristic of squamous cell carcinoma (SCC) *in situ*.[8] Nevertheless, the similarity between both entities has led to the consideration of AK as part of a biological continuum within cutaneous carcinogenesis, in which actinic lesions would represent early stages of neoplastic transformation.[8]

Importance as a precancerous lesion

The clinical relevance of AK lies in its role as the principal precursor lesion of squamous cell carcinoma (SCC), one of the skin tumours with metastatic potential. Each lesion may follow different evolutionary courses: persist in a stable state, undergo spontaneous regression or progress towards invasive carcinoma.[4]

The individual risk of progression is relatively low, with current estimates placing the annual rate between 0% and 0.075%, and spontaneous regression rates that may range from 15% to 63% within one year.[4] Large population-based studies have estimated an absolute risk of transformation to SCC of 0.6% per year.[9,10] However, this apparently low probability must be interpreted in the context of the total number of lesions, the patient's immune status and the long-term cumulative risk.[10]

Indeed, the overall risk of developing SCC in patients with AK increases significantly over time. Longitudinal studies have shown cumulative incidences approaching 17% at 10 years, substantially higher than those observed in populations without AK.[11] Likewise, the presence of multiple lesions increases the risk proportionally, reinforcing the notion that AK should not be assessed solely as an isolated lesion but rather as a marker of diffuse cutaneous damage over time.[10]

Beyond its relationship with SCC, AK acts as a clinical marker of increased risk of cutaneous cancer in general, including basal cell carcinoma and melanoma.[6] This finding underscores its value as an indicator of overall susceptibility to actinic damage.

A particularly relevant aspect from the clinical standpoint is the impossibility of predicting which individual lesions will progress to invasive carcinoma. No sufficiently reliable clinical or dermoscopic criteria exist to identify lesions with the greatest malignant potential.[12] This uncertainty forms the basis of current recommendations to treat all AKs early, even at initial stages.[8,13]

Table 1. Actinic keratosis: key epidemiological and clinical data

Parameter	Data
Prevalence in individuals >60 years	Up to ~60% in fair-skinned populations
Lifetime risk of development	>50% in high-exposure regions (USA, Australia)
Principal risk factors	Advanced age, male sex, Fitzpatrick I-II, immunosuppression, cumulative UV exposure
Most common locations	Face, scalp (alopecia), ears, neck, dorsum of hands, forearms
Annual risk of progression to SCC (per lesion)	0%-0.075% (individual lesion); 0.6% per year (population-based)
Spontaneous regression rate	15%-63% within one year
Cumulative SCC incidence in AK patients	~17% at 10 years
Key molecular alteration	*TP53* mutation (C→T UV signature)
Microbiome shift	↑ *S. aureus*, ↓ *C. acnes* (progressive from healthy skin → AK → SCC)

Cumulative solar damage and field cancerisation

Ultraviolet (UV) radiation constitutes the principal aetiological factor in the genesis of AK. UVB radiation (290-320 nm) induces direct DNA damage through the formation of pyrimidine dimers, particularly cyclobutane dimers, which, if not adequately repaired, generate mutations in key genes involved in cell cycle control.[14,15] UVA radiation, for its part, contributes to cellular damage through indirect mechanisms mediated by reactive oxygen species, affecting DNA, proteins and lipids.[16]

Among the most characteristic molecular alterations, mutation of the tumour suppressor gene *TP53* stands out, considered an early event in photocarcinogenesis. These mutations are detected in a significant proportion of AKs and in the majority of non-melanoma skin cancers.[1,17-19] UV radiation induces a characteristic mutational pattern, with cytosine-to-thymine substitutions at specific sequences, constituting a veritable «molecular signature» of actinic damage.[20] Keratinocytes harbouring these mutations acquire proliferative advantages and resistance to apoptosis, favouring their clonal expansion.[17,21]

To this mutagenic process is added a key immunological component: UV radiation-induced immunosuppression. Chronic exposure alters the function of antigen-presenting cells, reduces cellular immunity and promotes a tolerogenic immunological milieu, thereby hindering the elimination of transformed cells.[10,15]

This constellation of alterations gives rise to the concept of field cancerisation, in which the entire neighbourhood is affected, describing the presence of extensive areas of apparently normal skin harbouring genetic and epigenetic alterations induced by UV radiation.[22-24] Within these areas, visible lesions and subclinical changes coexist, which explains the high recurrence rate and the appearance of new lesions in previously treated zones.

Furthermore, chronic UV exposure alters the barrier function of the stratum corneum, increasing transepidermal water loss, modifying cutaneous pH and favouring epidermal hyperproliferation.[25] This milieu facilitates not only lesion progression but also the development of microbial dysbiosis.

In this regard, recent studies have described a progressive transition in the composition of the cutaneous microbiome from healthy skin towards AK and subsequently towards carcinoma, with a relative increase in *Staphylococcus aureus* and a decrease in commensals such as *Cutibacterium acnes*.[26,27] This imbalance could contribute to both chronic inflammation and carcinogenesis through the production of toxins and pro-inflammatory mediators.[26] Likewise, the persistence of certain bacteria following treatment has been associated with poorer therapeutic response, suggesting a possible role of the microbiome in the clinical evolution of the disease.[28].

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2. Nicotinamide: robust evidence in cutaneous chemoprevention

Nicotinamide (vitamin B_3 or niacinamide) is an active form of vitamin B_3 that acts as a precursor of NAD^+, a molecule essential for cellular energy metabolism.

Mechanism of action: cellular energy and DNA repair

Nicotinamide plays a key role in the cutaneous response to ultraviolet radiation-induced damage. At the cellular level, NAD^+ is a fundamental cofactor in ATP production, which is necessary to sustain energetically demanding processes such as DNA repair. Exposure to UV radiation causes ATP depletion in keratinocytes, thereby compromising the cell's capacity to repair genetic damage.[1-3]

The administration of nicotinamide prevents this energy crisis, favouring the maintenance of ATP levels and, consequently, potentiating nucleotide excision repair (NER) mechanisms. In this way, it facilitates the removal of characteristic UV-induced lesions such as cyclobutane dimers and oxidative DNA damage.[2,3] Furthermore, nicotinamide has been shown to partially reverse UV radiation-induced immunosuppression, improving the immunological surveillance of the skin without interfering with basal immunity, which renders it a particularly attractive intervention in the context of actinic keratosis carcinogenesis.[1,3]

From a practical standpoint, it is important to distinguish nicotinamide from nicotinic acid (niacin), since, unlike the latter, nicotinamide does not produce flushing or vasodilatory effects.[1]

Available clinical evidence

The ONTRAC trial constitutes the most relevant study in this field. This was a phase 3, randomised, double-blind clinical trial that included 386 immunocompetent patients with a history of at least two non-melanoma skin cancers. The administration of nicotinamide at a dose of 500 mg every 12 hours for 12 months was associated with a 23% reduction in the incidence of new non-melanoma skin cancers, a 30% reduction in squamous cell carcinomas and an approximately 13-20% reduction in the number of actinic keratoses.[1] A relevant finding was that the protective effect disappeared upon treatment discontinuation, suggesting that its benefit depends on continued administration.[1]

In immunosuppressed populations, the evidence is less consistent. The ONTRANS trial, conducted in solid organ transplant recipients, did not demonstrate a significant reduction in the incidence of skin cancer, although its sample size and statistical power have been the subject of debate.[4]

Recent observational data provide additional information. A large retrospective study in a US veterans population (n = 33,822) showed an overall 14% reduction in skin cancer and a 22% reduction in SCC. Notably, the greatest benefit was observed when nicotinamide was initiated after the first skin cancer, diminishing progressively in patients with multiple prior tumours.[5] Nevertheless, these results must be interpreted with caution. Recent critical analyses have highlighted possible methodological limitations, such as the presence of uncontrolled confounding factors or biases inherent to the observational design.[6]

Practical clinical applications

Current clinical guidelines, such as those of the NCCN, include nicotinamide as an option within prevention strategies for patients with field cancerisation, always in combination with fundamental measures such as daily photoprotection.[7]

From a practical standpoint, several key aspects may be summarised:[1,5]

- **Dose:** 500 mg orally every 12 hours (total 1,000 mg/day). Higher doses have not demonstrated greater efficacy.
- **Candidates:** immunocompetent patients at high risk of skin cancer, particularly those with a history of SCC. Early initiation, following the first tumour, may be associated with greater benefit.
- **Duration:** continued treatment, given that the effect is lost upon discontinuation.
- **Safety:** a very favourable safety profile, comparable to placebo, with no requirement for routine laboratory monitoring.
- **Availability:** accessible as a low-cost supplement.

In immunosuppressed patients, particularly transplant recipients, current evidence does not support a generalised recommendation for its use; other strategies such as systemic retinoids or optimisation of immunosuppressive therapy in selected cases are more appropriate.[4,8]

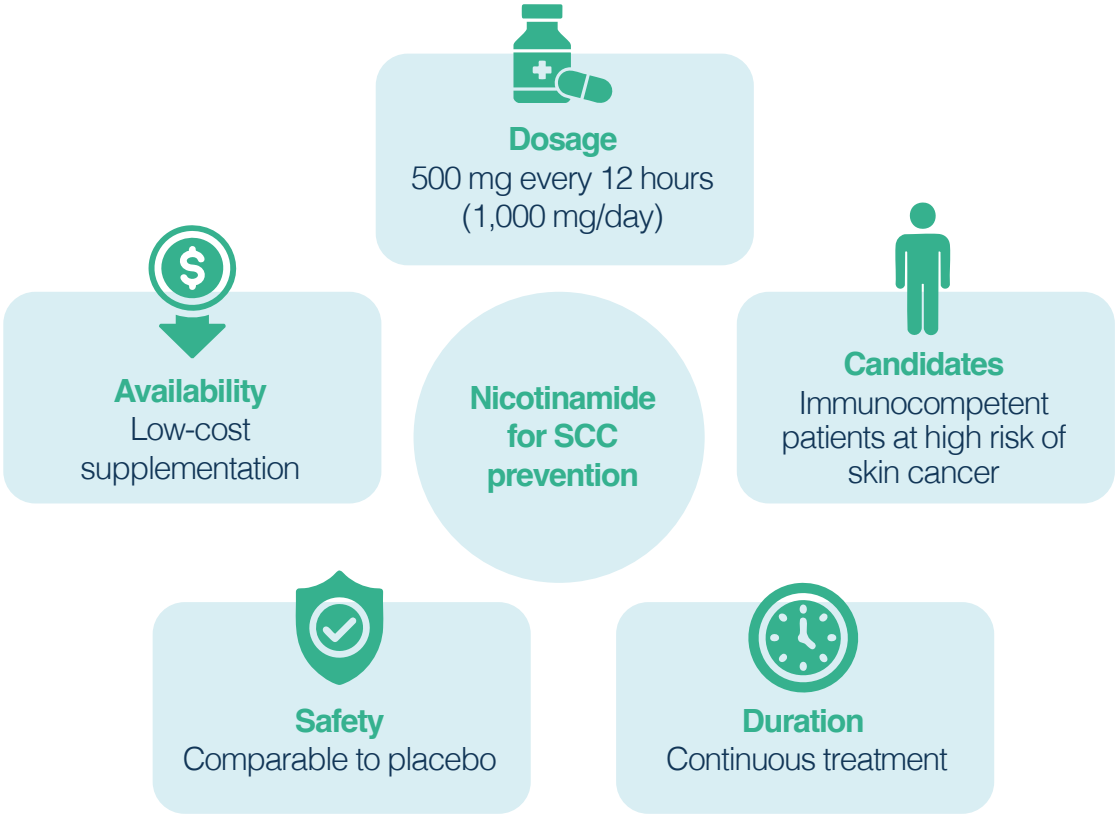

Figure 2. Summary of the use of nicotinamide in the prevention of squamous cell carcinoma.

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3. Antioxidant vitamins (A, C and E) in the prevention of actinic keratoses and squamous cell carcinoma

The available evidence on the role of vitamins A, C and E in the prevention of actinic keratoses (AK) and squamous cell carcinoma (SCC) is heterogeneous and, overall, limited. A key aspect is the distinction between dietary intake and pharmacological supplementation, as their effects are not equivalent. Whilst some epidemiological data suggest a possible benefit of dietary vitamin A, antioxidant supplementation has not demonstrated consistent efficacy and, in some instances, could even be harmful.[1,2]

Context: progression from AK to squamous cell carcinoma

AKs form part of a biological continuum towards squamous cell carcinoma. It is estimated that between 60% and 82% of SCCs derive from pre-existing AKs.[3,4] However, no studies have directly evaluated whether specific dietary factors modify the progression from AK to SCC.

Vitamin A (retinol and carotenoids)

Vitamin A presents the most consistent evidence when obtained through the diet. In the prospective NHS/HPFS study (n = 123,570), a higher intake of vitamin A was associated with a significant reduction in the risk of squamous cell carcinoma (HR 0.83; 95% CI 0.75-0.93).[5] This effect appears to derive from both retinol of animal origin and carotenoids present in fruit and vegetables, which act as antioxidants against UV radiation-induced damage and modulate keratinocyte differentiation.[6,7]

This possible protective effect appears to depend on prolonged exposures, as analyses with shorter follow-up did not show significant associations.[6] Furthermore, observational studies have found favourable associations between diets rich in carotenoids and a lower risk of non-melanoma skin cancer.[8]

By contrast, vitamin A supplementation yields inconsistent results. The SKICAP-AK trial showed that oral retinol (25,000 IU/day) reduced the risk of squamous cell carcinoma by 26% in patients with multiple AKs,[9] although this benefit is not reproduced in very high-risk populations.[10] Moreover, observational studies have even described an increased risk of SCC with supplementation.[11]

In clinical practice, guidelines reserve systemic retinoids (acitretin, isotretinoin) for selected high-risk patients, with an effect limited to the treatment period and a relevant adverse effect profile. Topical retinoids have not demonstrated preventive efficacy.[12,13]

Vitamin C

Vitamin C possesses a solid biological rationale as an antioxidant capable of neutralising reactive oxygen species induced by UV radiation. However, this property has not translated into consistent clinical benefits.

Prospective studies have not found a significant association between dietary vitamin C intake and the risk of SCC,[6] and systematic reviews have rated the evidence as weak.[14] In an Australian study, a higher intake was even associated with an increased risk of basal cell carcinoma in certain subgroups, with no effect on SCC.[15]

Although patients with skin cancer may present low vitamin C levels, it remains unclear whether this represents a causal factor or a consequence of the tumour process, and oral supplementation has not been shown to reduce the risk of skin cancer in clinical trials.[16-18]

Vitamin E

The evidence for vitamin E is equally inconsistent. No clear association has been demonstrated between its dietary intake and a reduction in the risk of squamous cell carcinoma.[6,14]

In published studies, topical vitamin E did not reduce the number of actinic keratoses, although it did modify some biomarkers of cellular proliferation.[19] Experimental data even suggest that its isolated use could favour carcinogenesis in sun-exposed skin, whereas its combination with other antioxidants may have protective effects.[20]

Overall synthesis and dietary approach

Taken together, the evidence does not support the use of antioxidant supplements as a strategy for skin cancer prevention. A meta-analysis of randomised controlled trials found no significant reduction in the risk of skin cancer with vitamin supplementation,[1] and both recent reviews and international organisations concur that these supplements offer no demonstrated preventive benefit and may be harmful at high doses.[2,21,22]

From a clinical standpoint, the data suggest that the possible benefits observed are more closely related to overall dietary patterns than to isolated nutrients. Vitamin A intake through foods, particularly fruit and vegetables rich in carotenoids, is associated with a lower risk of squamous cell carcinoma. By contrast, vitamins C and E, despite their biological interest, have not demonstrated preventive clinical utility.

This reinforces a practical message: in the context of AK and photocarcinogenesis, nutritional intervention should be directed towards a balanced diet rich in plant-based foods, rather than towards isolated supplementation.[14]

Table 3. Antioxidant vitamins A, C and E in the prevention of actinic keratosis and squamous cell carcinoma.

Vitamin	Dietary intake	Supplementation	Overall assessment
Vit. A (retinol, carotenoids)	Most consistent evidence: carotenoid-rich diet associated with ↓ SCC risk (HR 0.83)	Inconsistent results; systemic retinoids reserved for selected high-risk patients	Dietary intake: probable benefit. Supplementation: not routinely recommended
Vit. C (ascorbic acid)	No significant association with SCC risk; some ↑ BCC risk in certain subgroups	No demonstrated benefit in clinical trials	Not supported in any form for prevention
Vit. E (α-tocopherol)	No clear association with ↓ SCC risk	No benefit demonstrated; isolated use may promote carcinogenesis in sun-exposed skin	Not supported in any form for prevention
Overall synthesis	Dietary patterns rich in plant-based foods show the most favourable associations	RCT meta-analysis: no significant risk reduction; potentially harmful at high doses	Balanced diet rich in plant-based foods preferable to isolated supplementation

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4. Minerals: zinc and selenium

Trace elements play a relevant role in cutaneous homeostasis, particularly in the response to ultraviolet radiation-induced damage. Among them, zinc and selenium stand out for their involvement in DNA repair and antioxidant systems. However, the robustness of the clinical evidence in the prevention of actinic keratoses (AK) and squamous cell carcinoma (SCC) is limited and, in some cases, contradictory.

Zinc

Role in DNA repair

Zinc is an essential trace element with high concentration in the epidermis, where it reaches levels up to 5-6 times higher than those in the dermis.[1] It acts as a cofactor or structural component of multiple enzymes involved in genomic stability, including key DNA repair systems such as *OGG1, APE* and *PARP*, as well as antioxidant enzymes such as superoxide dismutase (SOD).[2]

Furthermore, zinc is fundamental for the structural and functional stability of p53, a central protein in the response to UV damage, regulating cell cycle arrest and apoptosis.[3,4] Zinc deficiency, even at mild degrees, has been associated in animal models with increased DNA damage, impaired p53 activity and deterioration of repair mechanisms — effects that are reversible upon repletion.[5]

Antioxidant function and photoprotection

Zinc exerts antioxidant effects through several mechanisms. On the one hand, it displaces redox-active metals such as iron and copper, reducing free radical formation. On the other, it induces the synthesis of metallothioneins, proteins with a high capacity for neutralising reactive oxygen species (ROS) implicated in the response to UV radiation-induced oxidative stress.[1,6]

In cellular models, zinc has been shown to reduce UV radiation-induced genomic damage and to favour the antioxidant response in keratinocytes and fibroblasts.[6,7] Likewise, in animal models, topical application of zinc diminishes sunburn cell formation and reduces the formation of UVB-induced pyrimidine dimers, lesions directly implicated in cutaneous carcinogenesis.[8,9]

Clinical evidence

Despite this solid biological basis, the evidence in humans is limited. No randomised clinical trials exist evaluating zinc, either oral or topical, in the prevention of AK or SCC.[10]

The available epidemiological studies, mostly of case-control design, show inconsistent results, with no clear association between zinc levels and skin cancer risk.[11] A recent Mendelian randomisation study has likewise failed to demonstrate a causal relationship between zinc levels and skin cancer.[12]

In preclinical animal models, zinc supplementation reduces tumour burden and inflammation in skin cancer, but these findings have not been confirmed in humans.[13,14]

Consequently, current clinical guidelines do not include zinc as a strategy for the prevention or chemoprevention of cutaneous carcinoma.[15]

Selenium

Role in DNA repair and antioxidant function

Selenium is an essential component of selenoproteins, among which the glutathione peroxidases (GPx) are particularly noteworthy, being fundamental in the neutralisation of peroxides and in protection against UV radiation-induced oxidative damage.[16]

In human keratinocytes, selenium has been shown to improve the repair of oxidative DNA lesions, such as 8-oxoguanine, although this effect is dependent on cellular age, being less efficient in senescent cells.[17]

Clinical evidence: the selenium paradox

The relationship between selenium and skin cancer is complex and paradoxical.

Observational studies have shown that elevated serum selenium levels are associated with a significant reduction in the risk of cutaneous carcinoma, including SCC.[18,19]

However, supplementation trials offer opposing results. The NPCT trial, designed specifically to prevent skin cancer, not only showed no benefit but revealed a significant increase in the risk of SCC (OR 1.25) in subjects receiving selenium.[20,21] This effect was more pronounced in individuals with adequate or high baseline levels.

These findings have been confirmed by systematic reviews and meta-analyses, which conclude that selenium supplementation does not reduce the risk of skin cancer and may increase it in certain populations.[19,22]

This phenomenon has led to the proposal of a biological threshold: above certain plasma levels (≈122 µg/L), selenium confers no additional benefit and may even prove harmful.[23]

Overall clinical synthesis

Zinc and selenium share a solid physiological basis as modulators of oxidative damage and UV radiation-induced DNA repair. However, the clinical translation of these mechanisms is limited.

Zinc lacks sufficient clinical evidence to recommend its use in the prevention of AK or SCC.

Selenium, for its part, paradigmatically illustrates the discrepancy between biology and clinical practice: although adequate levels are associated with lower risk, supplementation in well-nourished populations may increase the incidence of squamous cell carcinoma.

Neither of these minerals forms part of the strategies recommended in current clinical guidelines for the prevention or chemoprevention of field cancerisation.[10,15,24]

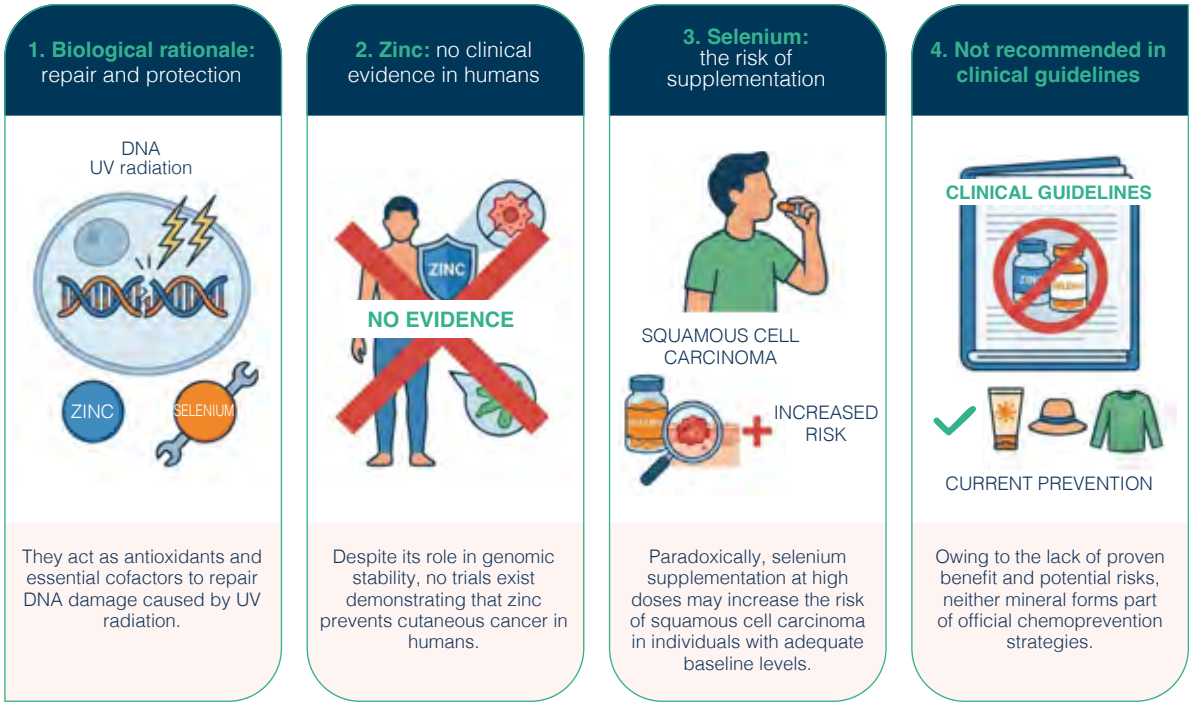

Figure 3. Selenium and zinc in the prevention of AK and SCC.

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5. Polyphenols and carotenoids

Polyphenols and carotenoids have attracted growing interest as agents of systemic photoprotection, owing to their capacity to modulate oxidative stress, inflammation and, in some cases, UV radiation-induced DNA repair. However, the available evidence varies considerably depending on the compound analysed, and there is generally a gap between preclinical results and their clinical translation in actinic keratoses (AK) and cutaneous squamous cell carcinoma (SCC).[1,2]

Green tea

Epigallocatechin-3-gallate (EGCG), the principal polyphenol of green tea, exerts antioxidant and anti-inflammatory effects by neutralising reactive oxygen species and inhibiting pathways such as NF-κB. It has also been linked to enhanced repair of UV-induced damage, particularly pyrimidine dimers, and to potentially antitumoral epigenetic effects.[3-5]

The preclinical evidence is robust. In murine models, both oral administration of green tea polyphenols and topical application of EGCG significantly reduce UVB-induced tumourigenesis, includingtumours with squamous differentiation.[4] In human skin, topical application of EGCG has been shown to diminish pyrimidine dimer formation following UVB irradiation.[5]

Nevertheless, this efficacy has not been clearly reproduced in humans. The only available randomised clinical trial with oral catechins showed no significant reduction in UV-induced erythema or other inflammatory markers, and the Cochrane review concluded that the clinical evidence for skin cancer prevention is currently insufficient and of low quality.[6,7] Accordingly, green tea does not form part of the recommended strategies for prevention or treatment of field cancerisation.[8]

Resveratrol

Resveratrol, present in grapes, red wine and berries, has also demonstrated antioxidant, anti-inflammatory and antiproliferative properties. In experimental models, it modulates NF-κB, COX-2, p53 and p21, and can induce selective apoptosis in UV-damaged tumour cells.[2,9]

In mice exposed to chronic UVB, topical application of resveratrol reduces tumour incidence and delays tumour onset, even when administered after irradiation, suggesting a biological effect beyond a simple physical sunscreen action.[9] However, no clinical trials in humans support its use in the prevention of AK or SCC. Its low oral bioavailability and instability currently limit its clinical applicability.[10]

Lycopene

Lycopene, the predominant carotenoid in tomatoes, is probably the compound with the best balance between biological and clinical evidence. It acts as a potent quencher of singlet oxygen and other free radicals and accumulates in the epidermis following prolonged intake.[11,12]

Unlike other compounds, consistent data in humans do exist. A recent meta-analysis showed that supplementation with tomato or lycopene increases the minimal erythemal dose and reduces molecular markers of UV-induced cutaneous damage, such as ICAM-1 and MMP-1.[11] These effects, however, require several weeks of continuous intake and are modest compared with a topical sunscreen.[12]

From an epidemiological standpoint, higher lycopene intake has been associated with a lower risk of SCC in large cohorts, reinforcing its interest within dietary patterns rich in plant-based foods.[13]

Beta-carotene

Beta-carotene reduces UV radiation-induced erythema, thereby confirming a certain biological photoprotective effect.[12,14] However, this finding has not translated into skin cancer prevention. Neither meta-analyses of clinical trials nor large cohort studies have demonstrated a reduction in SCC risk with beta-carotene supplementation or isolated dietary intake.[13,15]

Furthermore, some experimental data suggest that, under certain conditions of oxidative stress, beta-carotene may behave as a pro-oxidant, which warrants caution regarding its use as a supplement.[15]

Polypodium leucotomos

Although not a dietary polyphenol in the strict sense, *Polypodium leucotomos* deserves specific mention as the oral photoprotector with the most compelling clinical evidence in actinic damage. It is a plant extract rich in phenolic compounds with antioxidant, anti-inflammatory and DNA repair-modulating activity.[16]

In this case, clinical trials with promising results do exist. A multicentre study showed that the combination of oral and topical photoprotection with *Polypodium leucotomos* reduced the number of clinical AK and improved field cancerisation parameters.[17]

An improved response following photodynamic therapy for scalp AK has also been described.[18] Nonetheless, the overall quality of the evidence remains limited, and guidelines do not include it as a standard chemoprevention strategy.[8,19]

Mediterranean diet as an integrative framework

Rather than isolated compounds, the approach with the greatest clinical rationale is probably the overall dietary pattern. The Mediterranean diet naturally integrates polyphenols, carotenoids, unsaturated fatty acids and other bioactive compounds with potential synergistic effects.

In prospective cohorts, greater adherence to the Mediterranean diet has been associated with a lower risk of skin cancer overall, particularly basal cell carcinoma and melanoma, although the effect on SCC has not been consistent.[20]

In relation to actinic damage, dietary patterns rich in fruits, vegetables and fish have been associated with fewer AK and lower SCC risk, suggesting that the benefit may depend more on the combination of nutrients than on any single compound.[21,22]

Practical interpretation

In summary, the current evidence permits several conclusions. Green tea and resveratrol have well-defined photoprotective mechanisms and a robust preclinical basis but lack sufficient clinical support in AK or SCC. Lycopene is the compound with the strongest human evidence, both for its effect on the cutaneous response to UV and for its association with lower SCC risk. Beta-carotene reduces erythema from acute sunburn but has not been shown to prevent skin cancer. *Polypodium leucotomos* is the only agent with a direct clinical signal in AK, albeit with still limited evidence.

Therefore, the most reasonable clinical message is not to recommend isolated supplements as a chemoprevention strategy, but rather to favour a Mediterranean-type dietary pattern — rich in vegetables, tomatoes, fruits, olive oil and fish — as a complementary measure within a comprehensive approach whose pillars remain daily topical photoprotection, treatment of field cancerisation and, in selected patients, nicotinamide.[8,19]

Table 4. Polyphenols and carotenoids in the prevention of actinic keratosis and squamous cell carcinoma: comparative summary of evidence

Compound	Key mechanism	Preclinical evidence	Clinical evidence	Effect on AK/SCC	Included in guidelines?	Evidence level
Green tea (EGCG)	ROS neutralisation; NF-κB inhibition; pyrimidine dimer repair	Robust: ↓ UVB-induced tumorigenesis in mice (oral and topical); ↓ pyrimidine dimers in human skin (topical)	Only RCT: no significant ↓ in UV-induced erythema; Cochrane review: insufficient, low-quality evidence	No demonstrated effect	No	●● Insufficient
Resveratrol	NF-κB, COX-2 modulation; p53/p21 activation; selective apoptosis of UV-damaged cells	Promising: ↓ tumour incidence and delayed onset in UVB-exposed mice (topical)	No clinical trials in AK or SCC; low oral bioavailability limits applicability	No demonstrated effect	No	● Insufficient
Lycopene	Singlet oxygen quenching; epidermal accumulation after prolonged intake	Consistent biological rationale	Meta-analysis: ↑ minimal erythemal dose; ↓ ICAM-1 and MMP-1; epidemiological: ↑ intake associated with ↓ SCC risk	Strongest human evidence among compounds reviewed; requires weeks of continuous intake; modest effect	No	●●● Promising
Beta-carotene	Antioxidant; UV-induced erythema reduction	Established photoprotective effect	↓ UV-induced erythema confirmed; no ↓ SCC risk in meta-analyses potential pro-oxidant effect under oxidative stress	No demonstrated effect on AK/SCC prevention	No	●● Insufficient
Polypodium leucotomos	Antioxidant; anti-inflammatory; DNA repair modulation	Established biological rationale	Multicentre study: ↓ clinical AK count with oral + topical photoprotection; improved PDT response for scalp AK; evidence quality limited	Only agent with direct clinical signal in AK	No (not standard)	●●● Promising
Mediterranean diet	Synergistic integration of polyphenols, carotenoids, ω-3 fatty acids and other bioactive compounds	—	Prospective cohorts: ↓ skin cancer risk; effect on SCC not consistent; dietary patterns rich in fruits, vegetables and fish associated with ↓ AK and ↓ SCC risk	Most consistent overall dietary signal	Not as specific recommendation	●●●● Most consistent

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6. Practical integrative approach

The relationship between nutrition, actinic damage and cutaneous carcinogenesis is biologically plausible and, in some instances, clinically relevant. However, the practical message must be formulated with precision: no nutrient, supplement or nutraceutical has been shown to replace topical photoprotection, treatment of field cancerisation or dermatological follow-up.[1-3] Nutritional intervention should be understood as a complementary strategy, aimed at modulating oxidative stress, supporting DNA repair and reducing the chronic inflammation associated with cumulative ultraviolet damage.

From this perspective, the central measure remains daily photoprotection with broad-spectrum sunscreens, together with physical sun-avoidance measures and targeted treatment of actinic keratoses and field cancerisation.[2,3] In patients with chronic actinic damage, nutrition does not replace these interventions but may be integrated as part of a broader approach to cutaneous risk.

Which interventions hold the greatest practical interest

Among the agents reviewed, nicotinamide is the intervention with the strongest clinical support in high-risk immunocompetent patients, particularly those with a history of SCC. At a dose of 500 mg twice daily, it has been shown to reduce the incidence of new non-melanoma skin cancers and to decrease AK counts for as long as treatment is maintained.[4] Its safety profile is favourable, and guidelines include it as an option in the context of field cancerisation, always in conjunction with photoprotection.[3]

Systemic retinoids may be useful in selected patients with high risk and multiple lesions, but their use is limited by tolerability, the need for monitoring and the loss of effect upon discontinuation.[3,5] The same does not apply to conventional antioxidant supplements: the overall evidence does not support the use of supplemental vitamins A, C or E as a preventive strategy for AK or SCC, and in some scenarios they may even be associated with an adverse effect.[5,6]

In the dietary domain, the most consistent message derives not from isolated supplements but from the overall dietary pattern. A diet rich in fruits, vegetables, tomatoes, olive oil, fish and other foods characteristic of the Mediterranean pattern provides carotenoids, polyphenols and unsaturated fats

with potential antioxidant and anti-inflammatory effects.[7-9] Within this framework, lycopene stands out as the compound with the best combination of biological plausibility, evidence of human photoprotection and epidemiological association with lower SCC risk.[10,11] Even so, the effect is modest, cumulative and clearly inferior to that of a topical sunscreen.

Other compounds, such as green tea, resveratrol and *Polypodium leucotomos*, are of variable interest. In the case of green tea and resveratrol, the preclinical evidence is robust, but the clinical evidence for prevention of actinic keratoses or squamous cell carcinoma remains insufficient.[8,12] *Polypodium leucotomos* has shown promising results in reducing AK and improving field cancerisation, but the overall quality of the evidence does not yet place it on the same level as established preventive strategies.[13,14]

Which patient profile may benefit most

From a clinical standpoint, this complementary approach appears particularly reasonable in several patient profiles.

Firstly, in individuals with chronic actinic damage and multiple AK, in whom the concept of field cancerisation demands thinking beyond the individual lesion.[2,3] In these patients, optimising photoprotection, treating the field and reinforcing healthy dietary habits may represent a more coherent strategy than focusing solely on lesion-directed treatments.

Secondly, in patients with a history of keratinocyte carcinoma, particularly immunocompetent individuals, in whom oral nicotinamide may confer an additional benefit as part of a secondary prevention strategy.[4]

Thirdly, in subjects with intense photodamage, advanced age or unhealthy lifestyles, in whom it is reasonable to advise a higher-quality diet — rich in plant-based foods and low in ultra-processed products, refined sugars and Western dietary patterns — given their association with systemic inflammation, dysbiosis and disruption of cutaneous homeostasis.[7,9,15]

Conversely, simplistic messages should be avoided in patients who seek to “replace” sunscreen with supplements or nutraceuticals. Caution should also be maintained in special populations, such as transplant recipients or immunosuppressed individuals, where the evidence for several of these interventions is insufficient and preventive decisions must be individualised.[4,5]

How to translate this into clinical practice

In the consultation, the useful message may be summarised as follows: nutrition can help, but it helps as context, not as the principal treatment. It makes more sense to recommend a sustainable and globally healthy dietary pattern than to prescribe isolated antioxidant supplements without a clear indication. The most reasonable strategy consists of:

- Maintaining rigorous daily photoprotection.
- Actively treating AK and field cancerisation.
- Considering nicotinamide in high-risk immunocompetent patients.
- Promoting a Mediterranean-type diet, rich in vegetables, tomatoes, fruits, legumes, fish and olive oil.
- Avoiding the false expectation that isolated vitamins or antioxidants can, by themselves, prevent skin cancer.

In this way, nutritional intervention is realistically integrated within dermatological prevention: not as an alternative, but as a complementary tool that may reinforce a truly multidisciplinary approach to the patient with actinic damage.

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VI. Medical-nutritional integration

1. Connecting the mechanisms

If anything has become clear throughout this work, it is that the skin is not an isolated organ. Actinic keratosis (AK) is not merely the local consequence of ultraviolet (UV) radiation, but the result of a complex interplay between cumulative damage, immune response, inflammatory status and the patient's metabolic milieu.

UV radiation acts as the initial trigger: it induces direct DNA damage, generates reactive oxygen species and disrupts barrier function. Yet this damage does not progress in isolation. The organism's capacity to repair DNA, control inflammation and maintain immune surveillance largely determines whether such damage translates into lesion formation, persistence or tumour progression.

This is where the nutrition–microbiota–skin axis comes into play.

The intestinal and cutaneous microbiota modulate the immune response and systemic inflammatory tone. Dysbiosis — common in Western dietary patterns — promotes a chronic pro-inflammatory state, impairs immunity and may contribute to the progression of cutaneous diseases, including those related to actinic damage. In turn, the cutaneous microbiota in photo-exposed areas exhibits specific shifts (such as an increase in *Staphylococcus aureus*) that have been associated with carcinogenesis.

Nutrition operates at multiple levels within this axis:

- it modulates oxidative stress (polyphenols, carotenoids)
- it influences DNA repair (nicotinamide, zinc)
- it regulates the inflammatory and immune response
- it shapes the composition and function of the microbiota

These are not isolated effects but rather an interconnected network in which small, sustained changes can modify the biological terrain upon which solar damage acts.

From this perspective, the skin partly reflects the metabolic and immunological status of the individual. The key concept is not a specific nutrient, but the overall biological context in which photocarcinogenesis occurs.

2. From pathophysiology to intervention

Having understood these mechanisms, the inevitable question arises: what can actually be done in clinical practice?

Tabla 1. Medical-nutritional integration in the patient with chronic actinic damage: what can be done and what cannot.

The answer has two parts, and both are equally important.

What can be done	What cannot (and should not) be promised
Optimise daily photoprotection Broad-spectrum sunscreen + physical sun-avoidance measures. Central intervention; no nutritional approach compensates for cumulative UV damage.	**Antioxidant supplements do not consistently prevent AK or skin cancer** Overall evidence does not support vitamins A, C or E as chemoprevention strategies.
Nicotinamide in selected patients 500 mg twice daily in immunocompetent individuals with a history of skin cancer. Reduces new NMSC and AK counts whilst treatment is maintained. Favourable safety profile.	**No evidence that nutrition halts individual AK → SCC progression** No nutrient, supplement or dietary pattern has been shown to prevent the malignant transformation of a specific lesion.
Promote a Mediterranean-type dietary pattern Rich in fruits, vegetables, tomatoes (carotenoids), olive oil and nuts (polyphenols), oily fish (ω-3 fatty acids). Low in refined sugars and ultra-processed foods. Acts as a modulator of the inflammatory and oxidative milieu.	**No nutrient replaces sunscreen, field-directed treatment or dermatological follow-up** Nutritional intervention is complementary, never a substitute for established prevention and treatment strategies.
Avoid nutritional deficiencies Maintaining adequate micronutrient levels (zinc, selenium, vitamins) involved in DNA repair and antioxidant defence is reasonable, without systematic supplementation.	**More is not better** In some cases (selenium, fat-soluble vitamins), supplementation may be harmful. Risk of generating a false sense of security or medicalising the diet without clear indication.
Nutraceuticals as adjuncts in selected contexts *Polypodium leucotomos* and specific polyphenols may have a complementary role; evidence remains limited.	**Simplistic messages should be avoided** Patients should not be led to believe that supplements or nutraceuticals can “replace” photoprotection or conventional treatment.

3. Value of the multidisciplinary approach

All of this fits together better when the perspective shifts: the aim is not merely to treat lesions, but to manage risk.

The patient with chronic actinic damage is a complex patient, in whom environmental, genetic, immunological and behavioural factors converge. For this reason, the most coherent approach is necessarily multidisciplinary:

- Dermatology, for diagnosis, lesion treatment and control of field cancerisation.
- Nutrition, to intervene on dietary patterns, systemic inflammation and metabolic health.
- Immunology and internal medicine, in patients with comorbidities, immunosuppression or systemic disease.

And at the centre of it all, the patient.

Not as a passive recipient of treatments, but as an active participant in modifying habits: sun exposure, diet, therapeutic adherence. This point is crucial, because many of the interventions with the greatest impact — photoprotection, diet, lifestyle — depend directly on the patient.

Ultimately, medical-nutritional integration does not consist of adding more treatments, but of lending coherence to the whole. Understanding that solar damage occurs upon a modifiable biological terrain — and that acting upon that terrain, although it does not replace conventional therapies, may make a difference in the long term.

B

NUTRITION and CULINARY

DERMATOLOGY

I. Nutrition and cooking: a scientific context in dermatology

1. Nutrition as a variable in health studies: from nutrients to dietary patterns

Nutrition in health research. Methodological approaches from a scientific point of view

Nutrition science has been widely criticised for its apparently contradictory findings generated over time.[1] This perception is affected by many factors, such as public messaging often simplifying nuance into slogans, but many other technical aspects, mainly methodological, also play an important role. In this regard, it is important to acknowledge that nutrition is a hard science.[2] Therefore, in case of being interested in this field it is important to be aware of the unique methodological and epistemic considerations of this discipline. The objective of the following lines is to explore some of the major facets of this science's methodology that make it so complicated by mapping what is being measured and how this is measured.

What is being measured?

The term "diet" is the usual exposure construct related to nutrition science. Its definition, according to the Oxford English Dictionary, is "the sum of food consumed by a person or other organism". But when researchers state they are studying "diet" they usually refer to a concept that can be operationalised at different levels, from nutrients to dietary patterns and from a specific moment to a wider window frame.

A clear example of the existence of these different levels is reflected in how modern nutritional science has evolved during the last century, and the article of Mozaffarian *et al.*, "History of modern nutrition science — implications for current research, dietary guidelines and food policy", clearly exposes this idea.[3] In this article the authors describe the transition from the study of single nutrients, which happened due to the discovery of vitamins in the first half of the 20th century, to the reflection on the importance of general dietary patterns rather than single nutrients in the 1990s.

Regarding the second dimension previously mentioned, the time window frame, recent *vs.* usual intake is the main question. The construct recent intake is appropriate when the hypothesised biological mechanism is short-term, or the researcher's interest relies on a genuine need for a snapshot of a current behaviour. On the other hand, usual intake reflects an individual's long-run average intake over a specific period of time, usually from months to a year. It is important to keep in mind that the "usual intake" is not fixed forever — people can change their diet meaningfully, thus this should not be considered as a lifetime trait. These concepts are clearly exposed in the *Dietary Assessment Primer* published by the National Institutes of Health, a valuable guideline developed "to help researchers determine the best way to assess diet for any study in which estimates of group intakes are required".[4]

These two dimensions mentioned above are major, and perhaps evident, but other constructs must be considered. This is the case, for example, of interpretation target, because regarding diet, we can talk about addition *vs.* substitution, an important concept to keep in mind mainly in epidemiological studies, that can lead to important misconceptions. In this regard, Willett *et al.* discussed the importance of the concept of isocaloric substitution, a fundamental principle in modern nutrition that means modifying the intake of a specific nutrient by exchanging it for an equivalent amount of energy from other sources, whilst keeping the total caloric intake constant.[5]

How is this measured?

Assessing what people eat is inherently difficult, and the most appropriate dietary assessment method depends on the specific research question, study design, target population, and sample size.[2,4,6] In nutrition science, problems often arise when the dietary exposure of interest is not clearly defined or when the assessment method does not adequately capture the relevant exposure. This kind of mismatch, often discussed in the literature as exposure assessment error, measurement error, or misclassification, can attenuate diet-disease associations and contribute to apparently null findings.[6-10]

In the following lines, an effort has been made to summarise all this valuable information available in the *Dietary Assessment Primer* into a short guideline.[11]

1) Define your measurement target: recent or usual intake?

This reflection must be done because according to the answer very different methods will be applied.

Recent intake refers to what was consumed in a short and clearly bounded window, usually the past day. Choose recent intake when:

- The hypothesis is acute/short-term
- You care about immediate compliance
- You are studying behaviours like timing or within-day patterning where timestamps matter

Usual intake refers to the person's long-run average intake over a longer period, usually weeks, months or a year. Still keep in mind that diet can change over time and thus this can only be estimated for the period for which data were captured. Choose usual intake when:

- The hypothesis concerns chronic disease risk or long-term nutritional adequacy
- You want to compare intake with habitual recommendations
- You need population distributions of "typical" intake over time, rather than single-day snapshots

2) Decide on an instrument: dietary assessment methods

Dietary assessment methods are usually self-reported instruments designed to capture food and beverage intake in free-living individuals. The selection of the most appropriate instrument should align with the exposure window and the level of precision required for the intended health inference. The different instruments differ fundamentally in the reference period they target (recent *vs.* habitual intake) and in their typical error structure (random day-to-day variability *vs.* systematic reporting bias). For this reason, selecting among recalls, records, and questionnaires should be driven by the answer to the point described above. Bailey (2021) reviewed the strengths and limitations of the different methods; a brief overview is presented in the following lines.[12]

24-hour dietary recalls (24HDR)

A 24HDR is a structured interview (with an interviewer or self-administered) intended to collect detailed information on all foods and beverages consumed in the prior 24 hours. To account for large day-to-day variation in dietary intakes, it is necessary to conduct multiple 24HDR.

Benefits:

- Literacy of the subject is not required
- Allows for data collection of individuals with physical disability
- Interpretation problems are minimised because subjects can clarify directly to the interviewer
- Eliminates errors in response and missing data
- Has the potential to capture a wider variety of foods and dietary supplements
- Reduces reactivity because this must be administered on random days and after foods and beverages are consumed before the interview

Weaknesses:

- Is an expensive technique; the interviewers must be trained, and software is required to collect the information within the 24HDRs
- Difficult to apply in large epidemiological studies
- Relies on memory
- Is a tool with high within-person variation. This could be mitigated by conducting multiple 24HDRs

Food records/diaries (estimated or weighed)

Food records are prospective; participants record foods, beverages, and dietary supplements at the time of eating (or soon after). Its critical measurement issue is reactivity, because respondents know their intake is being measured on specific days, they may alter behaviour. Moreover, the use of this method requires highly motivated subjects.

Food frequency questionnaires (FFQ)

FFQ aim to measure "usual diet" over a specified longer period. These are usually self-administered, thus require cognitively demanding averaging and are typically dominated by systematic error.

Benefits:

- More cost-effective alternative to 24HDR
- Adaptable to different research needs: nutrient-specific, food-specific, or population-specific
- Useful for ranking individuals, important for studying diet-health relationships

Weaknesses:

- Not suitable for absolute intakes
- Requires literacy and physical ability
- Cognitively demanding

To improve accuracy, modern researchers often combine FFQ with 24-hour recalls, providing a more precise estimate of habitual intake.[13]

Screening tools

Capturing total diet with FFQ can be tedious for the participants, and moreover, sometimes researchers rather need a more narrowly focused area. Screening tools are designed to provide cost-effective and rapid estimates with minimal burden on the participants.

They share many limitations with the FFQ and are also dominated by systematic errors but are characterised by the low cognitive difficulty and the speed, usually less than 15 minutes. To be effective these tools should be validated and population specific.

Digital tools

In recent years many app- and image-based tools have been developed. These new methods reduce bias but are still prone to errors like the ones described for the traditional ones, since these are partly self-reported. On the other hand, omics-based biomarkers of food intake (metabolites, food-related DNA or food proteins) are objective measures derived from biological samples, but these mostly reflect recent intake and require careful sampling alignment to estimate usual intake.[14]

3) Be aware of these two concepts: measurement error and validation

These two concepts are closely related in self-reported dietary assessment methods and are equally important. On the one hand, measurement error for dietary data refers to the difference between reported dietary intake over a specified time period and the true usual dietary intake. It is important for the researcher to be aware of this type of error regarding the dietary assessment instrument they decide to use; otherwise, if this error is ignored, the results may be misleading.[15]

On the other hand, validation in dietary assessment is conducted to determine how accurately the self-reported instruments measure true intake. A key goal of validation would be to use an unbiased reference measure or instrument able to capture true intake without systematic error, but unfortunately, there are few of these types of methods and those are not too feasible. Dietary assessment methods are often evaluated using as a reference another self-report instrument to capture diet with systematic bias, but with less bias than the instrument being evaluated (the main instrument). These instruments are known as imperfect references.[16]

Beyond individual nutrients: foods, meals and dietary context

As previously mentioned, Mozaffarian *et al*. perfectly described the progression of modern nutritional science during the 20th century.[3] As stated in that paper, the first half of the 20th century (1910s-1950s), the era of discovery of vitamins, was a time of a reductionist approach focused on individual nutrients where research was centred on the identification of essential nutrients to prevent deficiency-related diseases such as scurvy, rickets and beriberi.[17-19] During this time the first Recommended Daily Allowances (RDAs) were established, focusing on calories and specific nutrients.

From the 1950s onwards, a reductionist approach on single nutrients was still dominating this science. First (1950s-1970s), the debate was on whether fat or sugar was the main cause of heart disease [20,23] and ultimately, the focus on reducing fat and cholesterol gained political acceptance, which shaped dietary recommendations for decades.[24] Later (1970s-1990s) a reductionist approach on single nutrients was still dominating and the first national nutritional guidelines were developed, focused on individual nutrients and urging people to avoid excessive amounts of fat, sodium and sugar.[25]

The reflection on the importance of general dietary patterns rather than single nutrients did not start until the 1990s.[26,27] This happened due to the observation of contradictory results among studies. It was found that, whilst supplements containing isolated vitamins often failed to demonstrate any benefits for chronic conditions in clinical trials, consuming foods rich in those same nutrients as part of a normal diet did.[28,29] The main questions changed. Nutrient science was highly effective for deficiency diseases, but it proved to be less adequate for chronic disease prevention.[30,31] Nowadays, the literature supports a clear move away from treating nutrition as the sum of isolated nutrients and towards treating it as foods, meals, and eating practices embedded in time, place, and social life, mainly in relation to chronic diseases.[31-33]

In the article “Foods, nutrients, and dietary patterns: Interconnections and implications for dietary guidelines”, Tapsell *et al*.[30] strongly defend the change of paradigm at the time of developing dietary guidelines, from the reductionist approach of nutrients to the more holistic vision of food synergies and dietary patterns. The rationale behind lies in the shift of the burden of nutrition-related diseases from undernutrition and nutrient deficiencies to chronic diseases like cardiovascular disease, cancer, and diabetes. As a result, nutritional epidemiology has moved beyond studying single nutrients to emphasise foods, food groups, and overall diet. Still, the experts declare that the study of foods, food patterns, and individual nutrients or food components must be seen as complementary. Epidemiological studies, clinical trials, and approaches are all needed.[30,32]

But apart from nutrients, foods, and dietary patterns, other types of dietary components such as meal timing, frequency, and regularity to circadian biology and cardiometabolic risk, could play an important role in relation to health. Under this idea that different eating styles like skipping meals and snacking could have an effect on cardiometabolic health markers such as obesity, lipid profile, insulin resistance, and blood pressure, St-Onge *et al*. reviewed the evidence.[34] The revision concluded that, even if there was a wide range of definitions regarding meals and snacks, irregular patterns seem to be less favourable for the maintenance of body weight and optimal cardiometabolic health.

And an ultimate construct regarding diet should be mentioned: the social and cultural context also matters. As described by Rozin, "in most, if not all cultures, food is laden with meaning and constitutes a major form of social exchange".[35] The act of eating together has been hypothesised to have positive effects. In this regard, Glanz *et al*. examined the literature researching the influence of in-home eating on diet quality, health outcomes and family relationships. The authors concluded that, even if most of the evidence was cross-sectional, thus there is a limit for attribution of causality, there is an association of shared family meals with favourable dietary patterns in children and adolescents, including consumption of fruits, vegetables, and healthful nutrients. It is also interesting to mention that the authors also conclude that the evidence links shared meals with health and psychosocial outcomes in youth, including less obesity and decreased risk for eating disorders.[36]

That said, again, it is important to keep in mind that diet is a complex construct encompassing multiple dimensions, from nutrients and foods to overall diet, dietary patterns, and eating habits.

From mechanistic studies to population-level evidence: keys to interpretation

As previously mentioned, nutritional science is a hard discipline with its unique methodological considerations and, as has been explained, this cannot be read with the habits of drug evidence.[2] Over the last century, a wealth of nutritional evidence has fed the databases and sometimes this has been stigmatised as contradictory, but experts conclude that this apparent conflict often reflects mismatched questions more than genuine contradiction, and it is important to keep in mind that nutrition science improves when researchers define more clearly what exposure, comparator, timing, and background diet they are actually studying.[37-39] In this regard, the different approaches (mechanistic studies, trials and cohorts) have different key sources of potential bias that are unrelated to each other, and if the results of different approaches all point to the same conclusion, this strengthens confidence in the finding. When there is a mismatch, the task is to ask whether they differ in population, timescale, exposure definition, or outcome rather than declare one design the winner.[40]

About mechanistic studies, in nutrition, these usually include cell studies, animal models, and short-term metabolic human studies. The aim of these is to show how a nutrient or food component might act, under what conditions a pathway is plausible, and why an observed association may be worth taking seriously.[41,42] These are important but rarely decisive on their own. As exposed before, diet is complex and we do not consume nutrients, but foods containing those nutrients within dietary patterns comprising these foods, without forgetting the context of consumption, *e.g.* timing.[34] Moreover, the same mechanistic studies have proven that isolated nutrients may behave differently from foods that contain those nutrients, and pointing at this it needs to be mentioned that nutrient synergies exist, and their combined consumption can lead to additive or detrimental effects.[43]

Within the mechanistic studies, randomised trials are a relevant source of knowledge, but neither are these free of limitations. Researchers are clear: these are powerful when the question is tightly specified, the intervention is feasible, and the outcome lies close enough in time to be affected within the trial window.[44,45] Traditionally, within this science, large randomised controlled trials with hard endpoints have occupied the highest position in this hierarchy of evidence, but as mentioned above, these may not be the best option when the question refers to long-term effects of specific foods or

nutrients, unless they can be packaged in a pill, as Satija *et al*. state, because blinding is often weak, adherence drifts, background diet matters, and many diseases of interest develop over decades rather than months.[44,45] Said all this, the point is not that trials are unimportant, but again, their authority depends on how well the trial question matches the nutrition question and how accurately the assessment methods are applied.

Another important component in the generation of evidence in nutrition science are cohort studies. This type of study is a major source of evidence behind the now familiar shift from nutrients towards foods and dietary patterns in dietary guidelines.[30,46] Cohort studies can observe long-term dietary exposures, diverse populations, and hard clinical outcomes on a scale that trials usually cannot.[45] But again, this evidence comes with its own hazards: measurement error, residual confounding, reverse causation (the situation in which the outcome affects the exposure, rather than the other way around), and selective emphasis on weak associations.[45,47] Within cohort studies, prospective cohort studies represent the strongest observational study design in terms of minimising bias and inferring causality. This type of study is less affected by several biases, such as reverse causation, recall bias, and selection bias, which are common types of bias in retrospective or cross-sectional study designs. Still, due to its observational nature this field has some detractors questioning the methodology and its results, demanding extreme rigour similar to that of a pharmacist to avoid false results,[48] whilst other researchers, aware that this level of control is often unfeasible in nutrition, claim that science must advance by integrating multiple types of evidence (observational and experimental) to guide public health.

Seen this way, the generation of evidence within the field of nutrition needs to feed from sources of different nature. Mechanistic work conducted in cells or animals tries to answer how an effect could happen, randomised controlled studies whether a bounded change can alter a proximate outcome under controlled conditions, and cohort studies analyse what happens when people live with dietary patterns over years in the real world. Guideline work then must combine these strands with judgement, usually giving greatest weight to pattern- and food-level evidence for chronic disease prevention, whilst using nutrient and mechanistic findings to refine, explain, and set limits.[49-51] The result is not a simple hierarchy. It is a layered model of inference in which good interpretation depends on matching each kind of evidence to the question it is actually able to answer. In any case, the methodology applied needs to be rigorous in order to compensate for the complicated nature of capturing diet.

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2. Dietary patterns and low-grade chronic inflammation: an overview of the evidence

In nutritional epidemiology, dietary pattern analysis was introduced as a complementary approach to nutrient-based models to better capture habitual dietary intake in free-living populations. Rather than examining isolated nutrients or single foods, this approach evaluates the overall diet — the combination of foods and nutrients consumed — providing a broader picture of habitual intake.[1]

This framework acknowledges that foods and nutrients are consumed in complex combinations and are highly interrelated, making it difficult to isolate independent effects of single dietary components in observational research.[2]

In the context of chronic immune-mediated conditions, including psoriasis and psoriatic arthritis, dietary exposure has been explored as one of several modifiable environmental factors potentially associated with systemic inflammatory profiles.[3,4]

It is important to note that most available data evaluating dietary patterns in inflammatory skin disease derive from observational research, in which associations between overall diet quality and disease-related outcomes have been described but do not establish causality.[5]

Conceptualising diet as a habitual exposure may therefore provide a structured framework for discussing long-term lifestyle factors in patients with chronic dermatoses, particularly when metabolic comorbidities coexist, situating diet within the broader cardiometabolic and inflammatory context of chronic skin disease.[6,7]

Dietary patterns as habitual dietary exposure

Patients with chronic inflammatory dermatoses frequently enquire whether dietary modifications may influence disease activity or long-term health outcomes. However, clinicians often encounter heterogeneous and predominantly observational evidence when addressing these questions.[5]

In this context, dietary patterns provide a structured approach to interpreting nutritional exposure. Rather than focusing on individual nutrients or short-term dietary modifications, this model considers habitual dietary intake and its potential association with inflammatory and metabolic processes.[1,7]

Such an approach may be particularly relevant in chronic immune-mediated skin diseases that often coexist with obesity, insulin resistance, or other cardiometabolic conditions.[7]

Conceptualising diet as a sustained exposure allows clinicians to integrate nutritional habits into the overall clinical assessment, without attributing direct causality.[6]

> ***Key concept:*** *In chronic inflammatory dermatoses, diet is best understood as a habitual long-term determinant associated with broader metabolic and inflammatory profiles, particularly in the presence of cardiometabolic comorbidities.*

Low-grade chronic inflammation: general concepts

Low-grade chronic inflammation refers to a persistent elevation of circulating inflammatory mediators that remains below the intensity of acute infection but has been implicated in the development and progression of several chronic non-communicable diseases.[8]

Unlike acute inflammation, which is rapid and self-limited, this form of inflammation is sustained over time and may coexist with metabolic alterations, including insulin resistance and adiposity-related changes.[8]

Psoriasis is recognised as a chronic immune-mediated inflammatory disease (IMID) characterised by sustained activation of the tumour necrosis factor alpha (TNF-α)/interleukin-23 (IL-23)/interleukin-17 (IL-17) axis.[9] Elevated systemic inflammatory markers, including C-reactive protein (CRP), have been reported in moderate-to-severe disease,[10] supporting the concept that inflammatory activity may extend beyond the skin.[4]

Epidemiological data have described associations between psoriasis, obesity, and increased cardiometabolic risk, a relationship sometimes conceptualised as the “psoriatic march”.[4]

Among modifiable environmental factors, habitual dietary patterns have been investigated in relation to systemic inflammatory markers in general populations.[11] Higher overall dietary inflammatory profiles have been associated with elevated levels of biomarkers such as CRP. However, when evaluated in relation to specific inflammatory skin diseases such as psoriasis, findings remain inconsistent, and much of the available evidence derives from cross-sectional analyses that cannot determine temporality.[12]

Dietary patterns characterised by higher intake of refined carbohydrates, saturated fats, and ultra-processed foods have been associated with elevated inflammatory markers in observational studies.[13] Conversely, dietary patterns rich in plant-derived foods have been associated with improvements in inflammatory biomarker profiles in some intervention studies, although effect sizes vary and heterogeneity is considerable.[14]

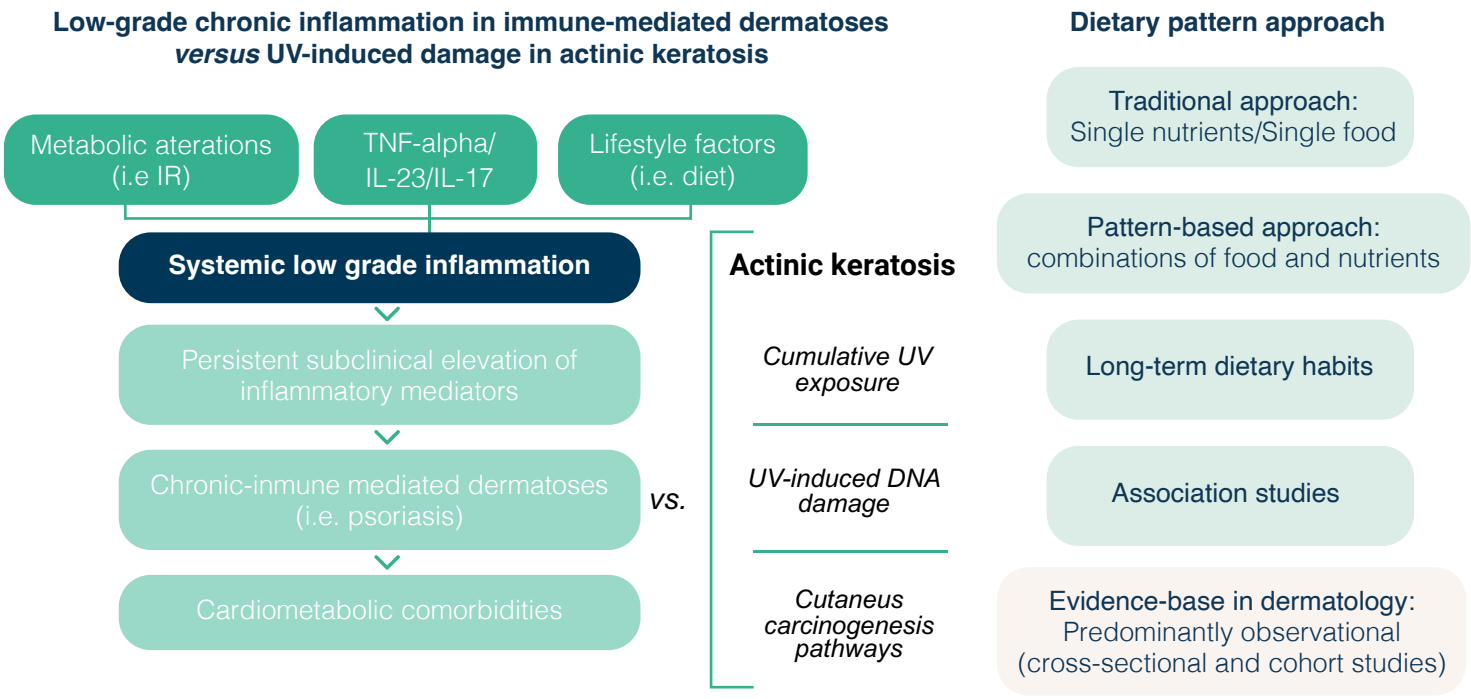
Whilst psoriasis exemplifies a chronic IMID in which systemic inflammation is central, other dermatological conditions, such as actinic keratosis (AK), arise through distinct pathogenic mechanisms. AK is widely regarded as a consequence of chronic ultraviolet exposure following cumulative sun damage. Its development is consistent with a multistep process of cutaneous

carcinogenesis, beginning with ultraviolet-induced DNA damage and followed by a promotion phase during which precursor lesions may emerge.[15]

In contrast to psoriasis, where metabolic and inflammatory comorbidities are well documented, evidence linking habitual diet or dietary patterns to AK remains limited. A small number of observational and experimental studies have explored whether specific dietary components, including omega-3 fatty acids typically derived from oily fish, may influence ultraviolet-induced skin damage or the development of AK. Although moderate intake of oily fish has been associated with reduced AK acquisition in longitudinal analyses, and experimental data suggest anti-inflammatory effects of omega-3 fatty acids on UV-induced pathways, findings remain heterogeneous and insufficient to support dietary recommendations for prevention or management.[16,17] Interventional studies conducted in high-risk populations have reported that reducing dietary fat intake may decrease the incidence of AK and non-melanoma skin cancer over short- to medium-term follow-up. However, these studies are limited in number, were conducted several decades ago, and have not been consistently replicated in contemporary cohorts.[15]

From a clinical perspective, these distinctions are relevant. Chronic inflammatory dermatoses such as psoriasis may coexist with systemic metabolic alterations, whereas AK primarily reflects cumulative photodamage. Nevertheless, in routine dermatological practice, patients frequently present with overlapping risk factors, including obesity and cardiometabolic comorbidity. In such contexts, consideration of overall health status, including metabolic profile and lifestyle factors, may be appropriate as part of a comprehensive clinical assessment.

Two pathogenic contexts in dermatology: immune-mediated inflammation *vs.* UV-driven keratinocytic damage



IR, insulin resistance; TNF-α, tumour necrosis factor alpha; IL, interleukin; UV, ultraviolet. Based on Furman *et al.*, Hu, and Jeffes Tang.[8,1,15]

Figure 1. Conceptual framework summarising the systemic inflammatory context in chronic dermatoses and the methodological evolution from single-nutrient analyses to dietary pattern research.

Dietary indices in context: measuring diet quality and inflammatory potential

Dietary exposure is multidimensional and cannot be fully captured through single nutrients or isolated food items. To quantify habitual dietary intake in epidemiological and clinical research, numerous dietary indices have been developed.[18,19] These tools assess different aspects of diet quality, including guideline-based quality scores,[20] pattern-adherence scores,[21] nutrient-density indices,[22] and inflammation-oriented tools.[23]

No single index comprehensively encompasses all relevant dimensions of diet. The selection of a dietary index should therefore be aligned with the specific research objective, the population under study, and the biological construct of interest. Whilst these instruments differ in construction and intended application, they share the objective of summarising complex dietary information into interpretable metrics.[18]

The following indices are presented as representative and widely applied examples within each category.[24]

Table 1. Conceptual categories of dietary indices used in epidemiological research

Primary dimension assessed	What It evaluates	Representative example(s)
Guideline-based diet quality	Adherence to national or international dietary recommendations	HEI-2020 · DGAI
Pattern adherence	Alignment with predefined dietary models	Mediterranean Diet Score (MDS / aMED) · DASH Score
Inflammatory potential	Estimated inflammatory profile based on associations with circulating biomarkers	DII · E-DII

HEI-2020, Healthy Eating Index–2020; DGAI, Dietary Guidelines for Americans Adherence Index; MDS, Mediterranean Diet Score; aMED, Alternate Mediterranean Diet Score; DASH, Dietary Approaches to Stop Hypertension; DII, Dietary Inflammatory Index; E-DII, Energy-adjusted Dietary Inflammatory Index. This table presents representative examples within each conceptual category and is not exhaustive.

Inflammation-oriented indices: operationalising dietary inflammatory exposure

Among the indices specifically designed to estimate the inflammatory potential of diet, the Dietary Inflammatory Index (DII) is the most widely applied in epidemiological research.[23]

The DII is a literature-derived instrument that assigns weighted scores to dietary components based on documented associations with inflammatory biomarkers, including CRP, interleukins (*e.g.*, IL-6, IL-1β, IL-4, IL-10), and TNF-α. Higher DII scores indicate dietary patterns previously associated with elevated inflammatory biomarker levels, whereas lower scores reflect patterns associated with lower inflammatory activity.[12]

Clinical relevance in dermatology

Dietary indices provide a structured method for interpreting habitual dietary intake within dermatological assessment. Depending on the construct evaluated, they may indicate whether a patient's dietary pattern:

- Aligns with established dietary recommendations
- Reflects adherence to defined dietary models (*e.g.*, Mediterranean-style patterns)

- Demonstrates adequate overall diet quality
- Is characterised by a profile previously associated with higher or lower systemic inflammatory biomarker levels

These tools do not establish causality nor predict individual therapeutic response. Their clinical utility lies in supporting structured, evidence-informed discussion within comprehensive patient evaluation.

Table 2. Conceptual differences between major inflammation-oriented dietary indices

Index	Development approach	Level of measurement	Interpretation of higher score
DII / E-DII	Literature-derived (*a priori*), based on published associations between dietary components and inflammatory biomarkers	Primarily nutrient and compound based (up to ~45 parameters)	Dietary profile previously associated with higher circulating inflammatory biomarker levels
EDIP	Empirically derived from observed diet-biomarker relationships in cohort studies	Food-group based	Food pattern empirically associated with higher inflammatory biomarker levels
DIS	Empirical, biomarker-driven; integrates dietary and selected lifestyle components	Food-group based	Dietary pattern associated with higher chronic low-grade inflammatory biomarker levels

DII, Dietary Inflammatory Index; E-DII, Energy-adjusted Dietary Inflammatory Index; EDIP, Empirical Dietary Inflammatory Pattern; DIS, Dietary Inflammation Score.[24] Indices differ in how they are developed and in the dietary components they include; interpretation should consider study design and population context.

Evidence linking dietary patterns to markers of low-grade chronic inflammation

Accumulating research has examined whether habitual dietary patterns are associated with circulating inflammatory biomarkers and clinical indicators of disease activity in dermatology. Most available evidence derives from observational cohort studies and a limited number of controlled dietary interventions.

Across conditions such as psoriasis, AK, acne vulgaris, and hidradenitis suppurativa, dietary patterns have been evaluated in relation to systemic inflammatory markers (*e.g.*, CRP, TNF-α) and measures of disease severity. However, findings remain heterogeneous, and the overall strength of evidence varies considerably between conditions.

Nutritional considerations in clinical practice

The following sections summarise condition-specific data, highlighting the type of evidence available, its consistency, and its clinical interpretability.

a. Psoriasis

Psoriasis is a chronic IMID frequently associated with obesity, metabolic syndrome, and increased cardiometabolic risk. Dietary factors have been examined in relation to both systemic inflammatory markers and clinical severity.[13,25]

Weight management in patients with overweight or obesity: psoriasis severity is positively associated with obesity. In patients with overweight or obesity,[26] hypocaloric dietary interventions

leading to weight loss have been associated with reductions in Psoriasis Area Severity Index (PASI) scores and improved response to systemic therapies in controlled studies.[27] Improvements have also been reported following bariatric surgery.[26]

Clinical implication: weight management should be considered an adjunctive component of psoriasis care in patients with excess body weight.

Dietary patterns

1. Mediterranean-style and plant-predominant dietary patterns

Observational studies have reported inverse associations between adherence to Mediterranean-style dietary patterns and psoriasis severity.[28] Other predominantly plant-based dietary models, including vegetarian and Dietary Approaches to Stop Hypertension (DASH)-type patterns, share common features such as higher intake of vegetables, fruits, legumes, nuts, whole grains, and unsaturated fats, alongside lower intake of saturated fat and arachidonic acid.[29] These characteristics are biologically consistent with anti-inflammatory and antioxidant effects, given their higher fibre, micronutrient, and omega-3 fatty acid content.[30] However, in psoriasis specifically, evidence remains largely observational, and no single dietary model can currently be recommended as disease-specific therapy.

Clinical implication: encouraging dietary patterns rich in plant-derived foods and unsaturated fats may support systemic metabolic health, particularly in patients with cardiometabolic comorbidities.

2. Ketogenic interventions

Very low-energy ketogenic interventions have been evaluated in small interventional studies involving patients with obesity and psoriasis. Reductions in PASI scores and inflammatory markers have been reported.[31]

However, these findings derive from limited cohorts, and it remains uncertain whether clinical improvements result from ketogenic composition *per se* or from weight loss.

Clinical implication: ketogenic dietary approaches may be considered in selected patients with obesity under medical supervision, primarily as part of weight management strategies rather than as disease-specific therapy.

3. Gluten restriction in selected patients

Given the shared genetic susceptibility between coeliac disease and psoriasis, gluten-free diets have been associated with improvement in patients with confirmed coeliac disease or positive gluten-related antibodies. No consistent benefit has been demonstrated in patients without these markers.[32]

Clinical implication: routine gluten elimination is not recommended. Screening for coeliac disease or gluten-related antibodies may be considered in selected patients with suggestive clinical features.

4. Alcohol intake

Alcohol consumption is a recognised trigger associated with increased psoriasis severity. Meta-analytic data suggest a dose–response relationship between alcohol intake and psoriasis risk.[33]

Clinical implication: assessment and moderation of alcohol intake should be part of routine lifestyle evaluation.

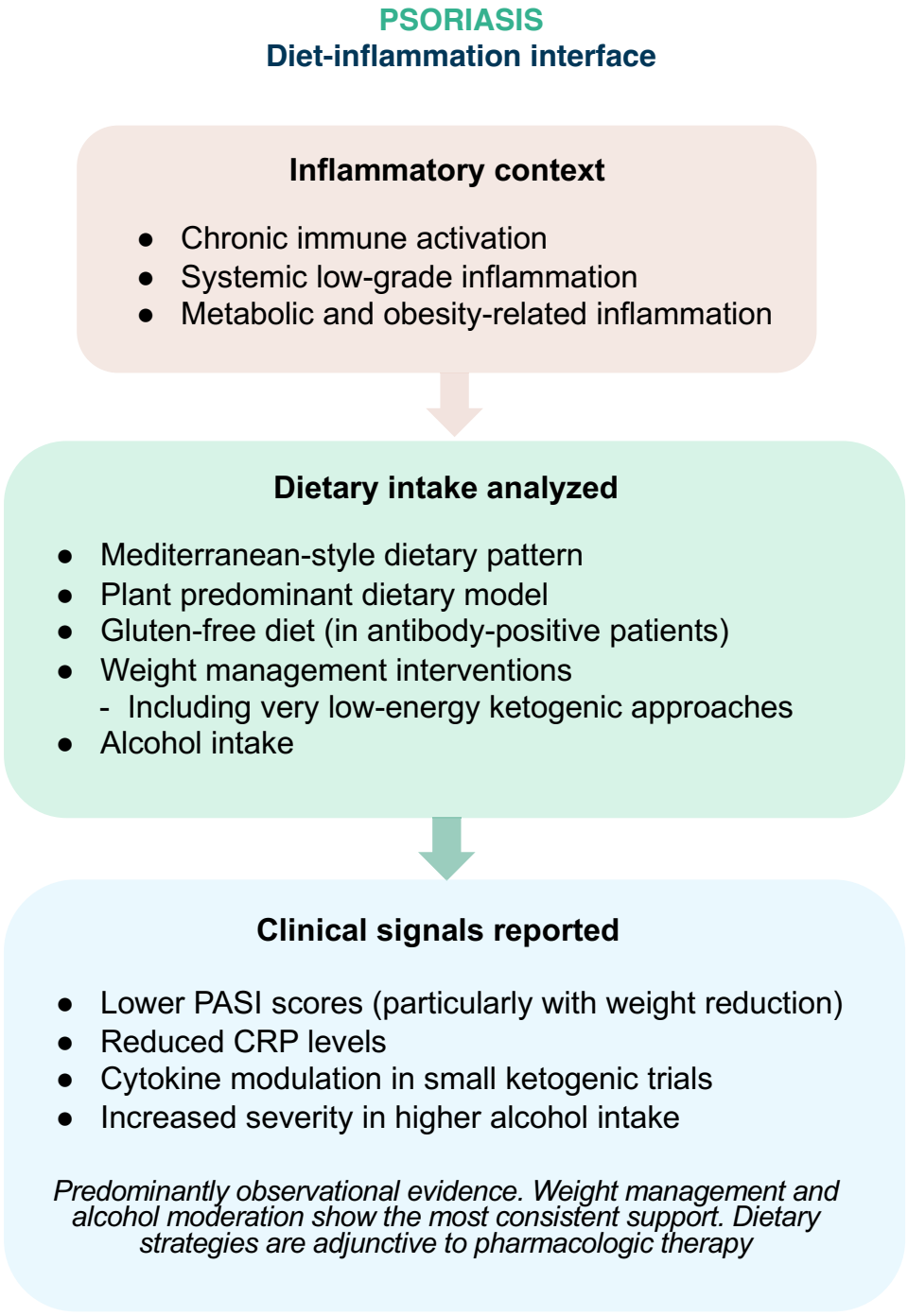


Figure 2. Diet-inflammation interface in psoriasis. Conceptual overview summarising the inflammatory context of psoriasis, the main dietary patterns and nutritional factors that have been studied, and the clinical signals reported in the literature.

Clinical interpretation box

Psoriasis: clinical considerations

- Evaluation of weight status and cardiometabolic context may be relevant in patients with psoriasis.
- In individuals with overweight or obesity, weight management strategies have been associated with clinical improvement.
- Mediterranean- or plant-predominant dietary patterns are observationally associated with lower inflammatory burden.
- Gluten restriction appears beneficial only in patients with confirmed coeliac disease or positive serology.
- Alcohol intake has been associated with increased disease severity and may warrant discussion in routine care.
- Dietary approaches should be regarded as adjunctive to standard dermatological therapy.

Clinical perspective

In patients with psoriasis and metabolic comorbidity, metabolic context and weight status may influence the inflammatory milieu. Nutritional strategies should be considered adjunctive to standard dermatological therapy and, when appropriate, implemented in collaboration with qualified healthcare professionals.

b. Actinic keratosis

AK is a premalignant lesion arising primarily from cumulative ultraviolet (UV) exposure and represents an early stage in cutaneous carcinogenesis. In contrast to chronic immune-mediated dermatoses, systemic metabolic inflammation is not considered a central pathogenic driver.

Limited research has explored whether dietary factors may influence UV-induced skin damage or lesion development. Interventional data from selected high-risk populations have suggested that reduced dietary fat intake may be associated with a lower incidence of new AK lesions over time.[34] Longitudinal cohort analyses have reported inverse associations between higher intake of oily fish and AK acquisition. Moderate wine consumption has also been associated with reduced lesion development in observational studies.[17] However, broader dietary pattern analyses have not demonstrated consistent associations with AK incidence.

Overall, available evidence remains limited, largely observational, and insufficient to support specific dietary prescriptions for prevention or management.

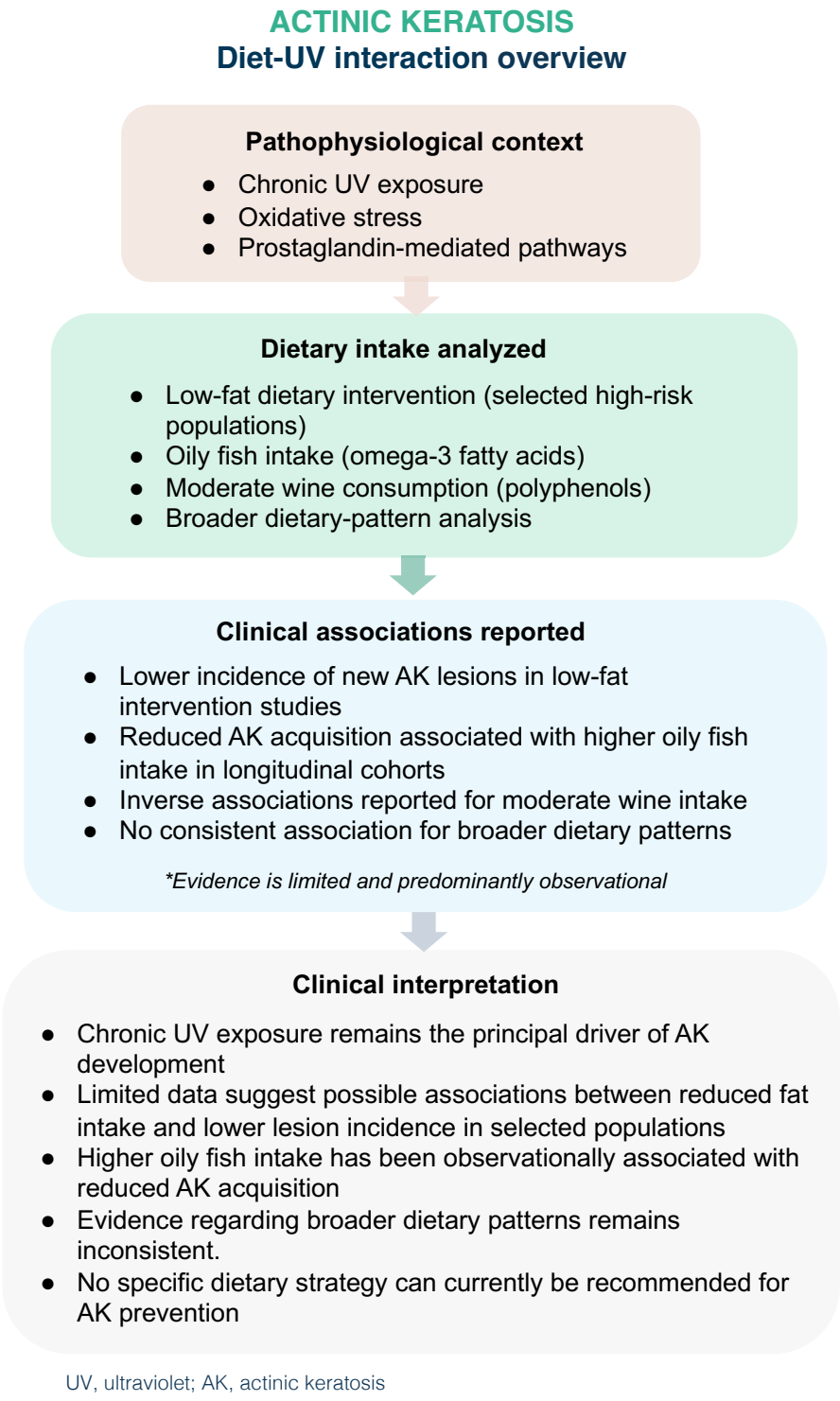


Figure 3. Dietary patterns and clinical associations in actinic keratosis. Conceptual overview summarising the pathophysiological context of AK, the dietary patterns investigated in clinical and epidemiological studies, and the clinical associations reported in the literature. Evidence remains limited and largely observational; photoprotection continues to be the cornerstone of AK prevention and management.

Clinical interpretation box

Actinic keratosis and dietary patterns: clinical perspective

- Chronic UV exposure remains the primary driver of AK.
- Limited evidence suggests possible associations between reduced dietary fat intake and lower lesion incidence in selected high-risk populations.
- Higher oily fish intake has been observationally associated with reduced AK acquisition in longitudinal cohorts.
- Broader dietary patterns have not demonstrated consistent associations with AK incidence.
- Current data do not support specific dietary recommendations for AK prevention. Photoprotection remains the cornerstone of management.

c. Other dermatoses

Beyond psoriasis and AK, dietary factors have also been explored in acne vulgaris and hidradenitis suppurativa (HS). Evidence regarding these conditions is largely synthesised in a recent multidisciplinary consensus statement,[25] from which the following considerations are derived.[25]

Acne vulgaris is characterised by chronic inflammation and oxidative stress, with dietary factors implicated in modulation of insulin and insulin-like growth factor-1 (IGF-1) signalling pathways. Observational data suggest that Western-style and high-glycaemic dietary patterns may be associated with increased disease activity, whereas adherence to Mediterranean-style dietary models has been associated with lower severity. However, most available data remain observational and do not establish causality.

HS is an inflammatory dermatosis frequently associated with obesity and metabolic comorbidity. Weight status appears clinically relevant, and weight reduction strategies may contribute to improvement in selected patients. Evidence supporting specific dietary compositions remains limited.

Across these dermatoses, available data remain predominantly observational. Nutritional strategies may be considered complementary and individualised, particularly in the presence of metabolic comorbidity, but should not replace standard dermatological management.

Interpretation of pattern-based evidence: strengths, limitations and applicability

Strengths of pattern-based research

- Reflects habitual dietary behaviours rather than isolated nutrients
- Captures cumulative and synergistic effects of foods consumed in combination
- Enables evaluation of dietary quality indices (*e.g.*, Mediterranean adherence, inflammatory indices)
- Has identified clinically relevant associations with inflammatory markers and disease severity scores

Limitations of the available evidence

- Predominantly observational in design
- Limited number of randomised controlled trials
- Small sample sizes in many interventional studies
- Potential residual confounding (*e.g.*, body mass index [BMI], lifestyle, socioeconomic factors)
- Heterogeneity in dietary assessment methodologies

Clinical applicability

- Evidence supports consideration of metabolic and lifestyle context in inflammatory dermatoses
- No dietary pattern can currently be recommended as stand-alone therapy
- Nutritional strategies should be regarded as adjunctive to standard dermatological care
- Multidisciplinary collaboration may enhance individualised patient management

Interpretation based on the studies cited in Sections:

Dietary patterns as habitual dietary exposure

Low-grade chronic inflammation: general concepts

Dietary indices in context: measuring diet quality and inflammatory potential

Evidence linking dietary patterns to markers of low-grade chronic inflammation

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3. Diet, microbiota and intestinal barrier functions: contextual considerations

Diet as a modulator of the intestinal microbial ecosystem

The human gastrointestinal tract represents a dynamic biological interface where dietary intake interacts with a complex microbial ecosystem.[1] The gut microbiota, composed of trillions of microorganisms, contributes to host metabolic, digestive, immune, and neurobiological processes and plays an important role in maintaining systemic physiological balance.[1]

Current evidence indicates that diet is a major environmental contributor to gut microbiome diversity, with both short-term and sustained dietary patterns influencing microbial composition and function.[2] Large population-based analyses further suggest that interindividual variation in gut microbiota composition appears to be more strongly associated with environmental factors, particularly diet, than with identifiable host genetic factors.[3]

Taken together, these findings support the concept that long-term dietary patterns represent a relevant and modifiable determinant of microbial ecology.

> ***Key concept:*** *Diet represents one of the most important modifiable determinants of gut microbiota composition and diversity. Long-term dietary patterns appear to influence microbial ecology more strongly than host genetic factors.*

Dietary patterns and microbial ecology

The impact of diet on the gut microbiota may be better understood at the level of whole foods and dietary patterns rather than isolated nutrients, given the complex interactions within the food matrix.[4]

Western-type dietary patterns, characterised by reduced amounts of fruits and vegetables and high intake of processed meat, fast food, refined carbohydrates, and sugar, have been associated with reduced microbial diversity and increased inflammatory markers in observational studies.[5] Large cross-cohort meta-analyses have further described enrichment of specific taxa such as *Clostridium bolteae, Ruminococcus obeum, Ruminococcus gnavus* and *Blautia hydrogenotrophica* in inflammatory processes.[4] These microbial profiles have been described in individuals with obesity and other low-grade inflammatory states and have also been reported across several IMIDs, where diet-related shifts in gut microbial homeostasis and intestinal inflammatory signalling are increasingly recognised as part of the broader inflammatory context.[4]

In contrast, Mediterranean-style dietary patterns, characterised by high intake of plant-based foods, legumes, whole grains, nuts and olive oil, are associated with greater gut microbial diversity and enrichment of genera such as *Faecalibacterium* and *Bifidobacterium* in human studies.[6] These taxa are commonly linked to beneficial metabolic functions within the intestinal ecosystem, including the production of short-chain fatty acids (SCFAs) such as butyrate, particularly by *Faecalibacterium*, and other host-supportive activities attributed to *Bifidobacterium*, which together have been associated with anti-inflammatory and metabolic health effects.[7,8]

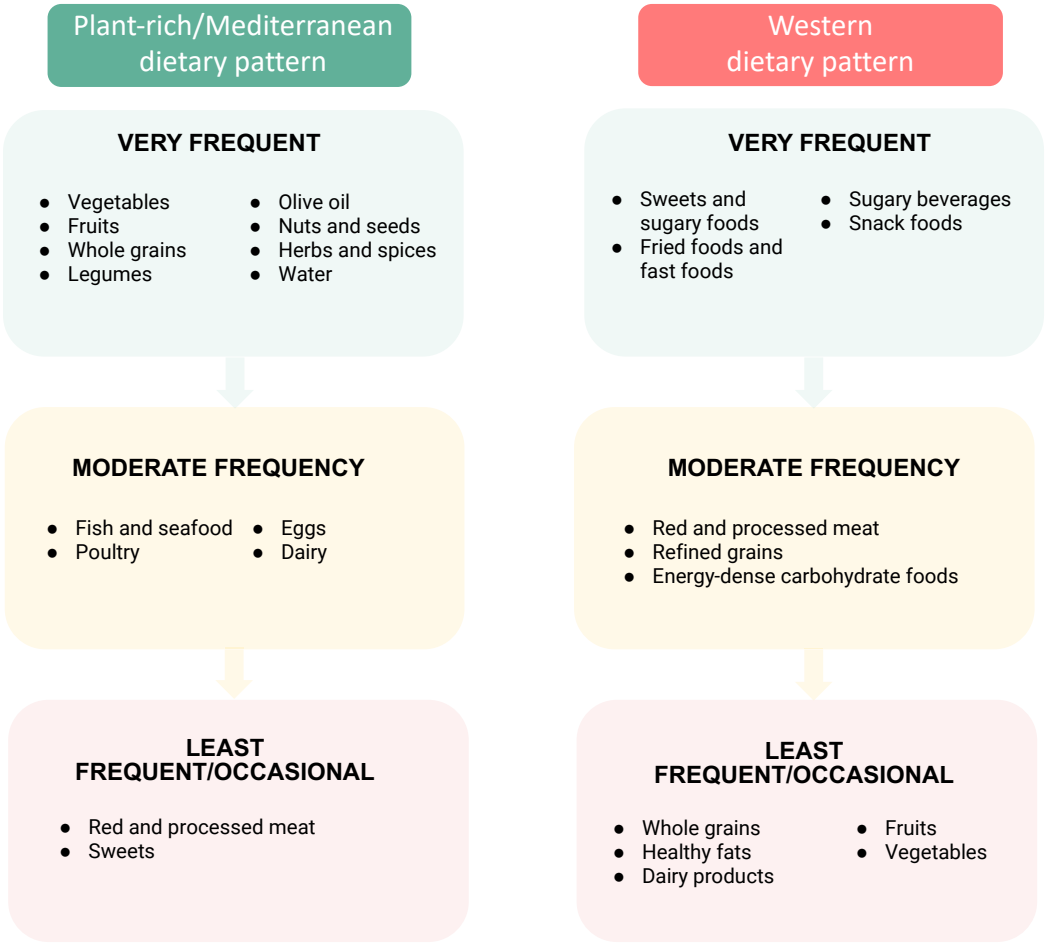

Figure 3. Schematic comparison of plant-rich/Mediterranean and Western dietary patterns based on frequency of food consumption. Adapted from Randeni *et al*.[5]

A defining feature of this dietary pattern is its high content of dietary fibre and microbiota-accessible carbohydrates (MACs), complex carbohydrates that reach the colon and serve as substrates for microbial fermentation.[9] MACs promote the production of SCFAs, contributing to a microbial configuration generally associated with metabolic and inflammatory homeostasis.[6] However, the extent to which SCFA changes directly mediate clinical outcomes remains under investigation.[6]

The influence of dietary patterns extends beyond shifts in bacterial taxa to the modulation of microbial metabolic activity. Differences in fat, sugar, and fermentable carbohydrate intake alter substrate availability and microbial-derived metabolites, with implications for epithelial integrity, tight junction regulation, and immune homeostasis at the intestinal interface.[10]

Furthermore, many nutrients associated with skin and metabolic health are naturally embedded within Mediterranean dietary foods that simultaneously modulate microbial ecology and metabolic output (Figure 4).

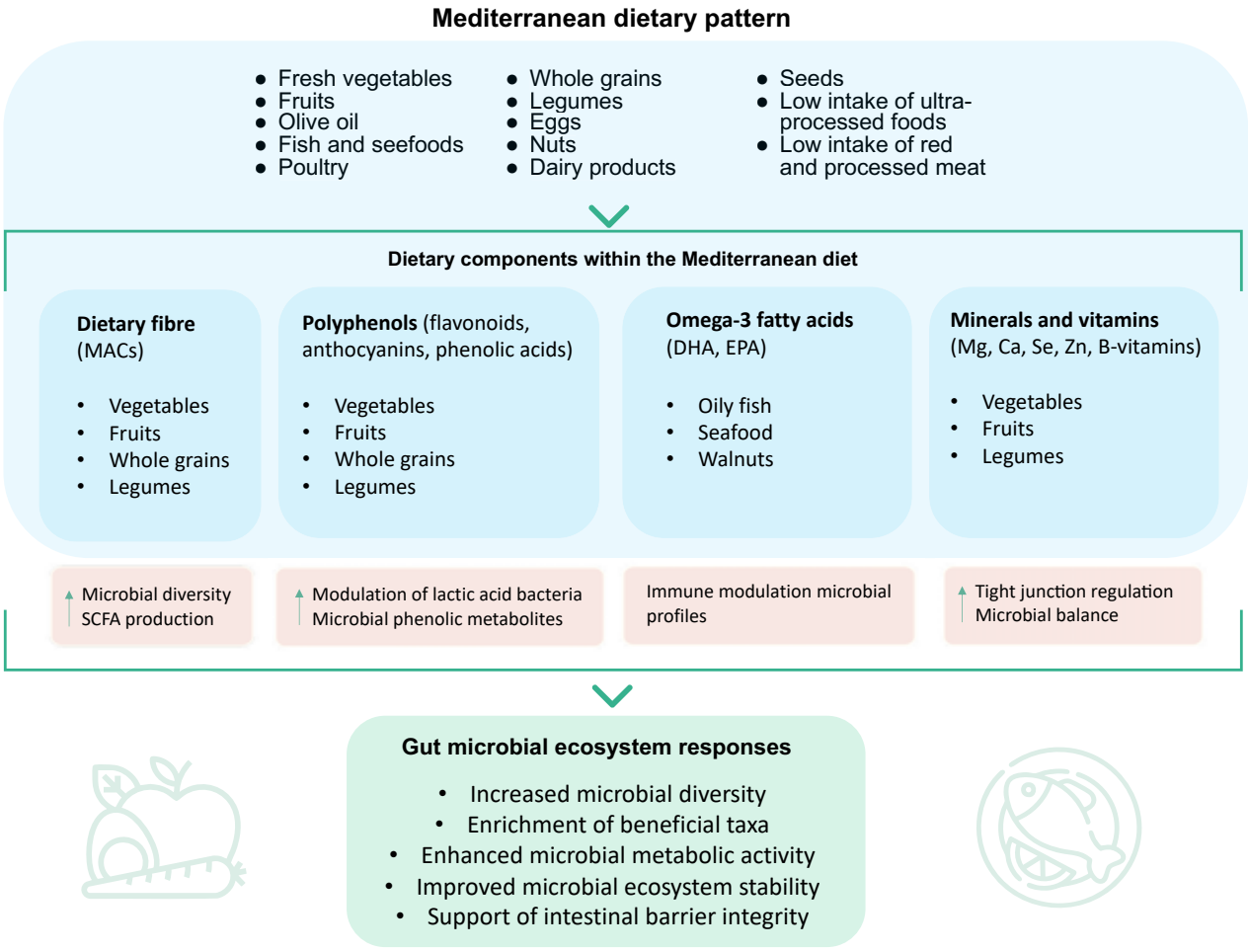

Figure 4. Key dietary components of the Mediterranean diet and their microbiota-related effects.

MAC, microbiota-accessible carbohydrates; SCFA, short-chain fatty acids; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; Mg, magnesium; Ca, calcium; Se, selenium; Zn, zinc.

Intestinal barrier function as an interface between diet, microbiota and systemic physiology

The intestinal barrier is a highly specialised, multilayered interface separating the luminal environment from the systemic circulation. It comprises a mucus layer, the intestinal epithelium sealed by tight junction complexes, and immune cells located within the *lamina propria.* Together, these elements regulate nutrient absorption whilst limiting the systemic translocation of luminal antigens and microbial components.[11]

Dietary influence on barrier integrity

Diet-microbiota interactions influence intestinal barrier function through both structural and metabolic mechanisms. Experimental and *in vivo* studies indicate that dietary patterns characterised by high fat, refined carbohydrates, and low fibre intake are associated with alterations in mucosal barrier integrity and increased intestinal permeability.[12] High-fat intake has further been linked to elevated circulating lipopolysaccharide (LPS) and serum endotoxin concentrations, reflecting markers of barrier dysfunction. This phenomenon has been described as metabolic endotoxaemia in the context of diet-induced intestinal permeability.[11]

When barrier integrity is altered, luminal antigens, microbial fragments, and metabolites may gain access to the underlying mucosa, triggering immune sensing and inflammatory signalling. Such interactions illustrate that the intestinal barrier functions not only as a physical defence but also as a dynamic regulatory interface between the intestinal environment and host immune responses.[13]

In this context, particular attention has been directed towards microbiota-derived metabolites as key mediators linking dietary patterns, microbial activity, and host physiology.[14]

Microbiota-derived metabolites as mediators between diet and host physiology

Dietary components that escape digestion in the upper gastrointestinal tract reach the colon, where they are metabolised by the intestinal microbiota into a wide range of bioactive molecules.[15] These microbiota-derived metabolites constitute a key functional interface between diet and host physiology, translating habitual dietary intakes into metabolic and immune signals that influence epithelial integrity, immune regulation, and systemic metabolism.[16]

Short-chain fatty acids (SCFAs)

Among the most extensively studied microbial metabolites are SCFAs, produced through the bacterial fermentation of dietary fibre and other microbiota-accessible carbohydrates.[14] The primary SCFAs — acetate, propionate, and butyrate — exert several beneficial physiological effects, acting as an energy substrate for colonocytes, promoting intestinal barrier function, and regulating anti-inflammatory signalling pathways.[17] Butyrate, in particular, serves as the main energy source for colonocytes and contributes to the maintenance of epithelial barrier integrity. In addition to their metabolic role, SCFAs exert immunomodulatory effects through several mechanisms, including activation of G-protein-coupled receptors (GPRs; such as GPR41, GPR43, and GPR109A), inhibition of histone deacetylases, and modulation of cellular metabolism in immune and epithelial cells. These signalling pathways influence cytokine production, regulatory T-cell differentiation, and inflammatory responses, highlighting the importance of dietary fibre intake in shaping host immune function through microbial metabolism.[14]

Secondary bile acids

Another important group of diet-dependent microbial metabolites arises from the transformation of bile acids. Primary bile acids synthesised in the liver are released into the intestine to facilitate lipid digestion. Once in the gut lumen, they undergo extensive modification by intestinal bacteria, which convert them into secondary bile acids with distinct biological properties. Beyond their role in fat absorption, bile acids function as signalling molecules interacting with host receptors such as the farnesoid X receptor (FXR) and the G-protein-coupled bile acid receptor (TGR5). Through these pathways, bile acids influence glucose and lipid metabolism, immune responses, and epithelial function. Alterations in dietary fat intake and gut microbial composition can therefore reshape bile acid pools and downstream signalling pathways, further linking dietary patterns with systemic metabolic and inflammatory regulation.[18,19]

Tryptophan-derived indole metabolites

Dietary amino acids can also serve as substrates for microbial metabolism, generating metabolites with relevant immunological effects. One well-characterised example involves tryptophan-derived indole metabolites, produced when intestinal bacteria metabolise dietary tryptophan. These microbial products can interact with host signalling pathways involved in immune regulation and epithelial barrier function.

Through these mechanisms, tryptophan-derived metabolites contribute to the maintenance of mucosal immune balance and epithelial integrity. Alterations in tryptophan metabolism have been associated

with several IMIDs, including psoriasis, suggesting that diet–microbiota interactions may influence inflammatory processes through microbial metabolic pathways.[14]

Polyphenol-derived microbial metabolites

Polyphenol-rich foods, including berries, fruits, vegetables, tea, cocoa, and olive oil, represent another important dietary source of microbiota-derived metabolites. Many dietary polyphenols exhibit limited absorption in the small intestine, allowing a substantial fraction to reach the colon where they undergo extensive microbial metabolism. Intestinal bacteria transform these compounds into low-molecular-weight phenolic metabolites, including various phenolic acids, which are often more readily absorbed and biologically active than the original polyphenol structures.[20]

Beyond their metabolic transformation, polyphenols also interact bidirectionally with the gut microbiota. Experimental and observational evidence suggests that polyphenol intake can influence microbial composition, frequently promoting the growth of beneficial taxa such as *Bifidobacterium* and *Lactobacillus*, whilst microbial activity simultaneously enhances the bioavailability and physiological activity of polyphenol-derived metabolites.[20] Through this reciprocal interaction, plant-rich dietary patterns may help modulate immune responses, support intestinal barrier function, and contribute to overall metabolic balance through microbiota-mediated pathways.

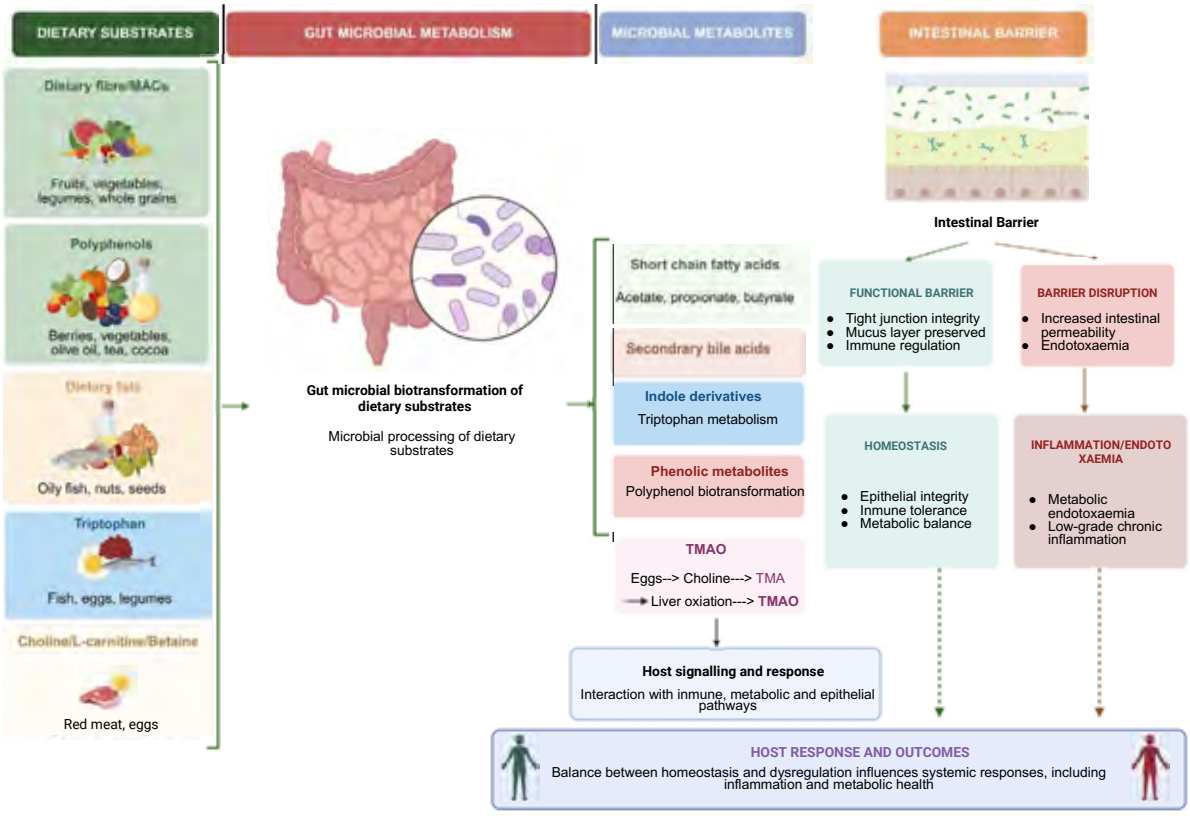

Figure 5. The diet-microbiota-barrier axis: microbial metabolites linking dietary patterns with intestinal barrier function and inflammatory responses.

MAC, microbiota-accessible carbohydrates; SCFA, short-chain fatty acids; TMAO, trimethylamine-N-oxide; TMA, trimethylamine.

Additional diet-derived microbial metabolites

In addition to these major metabolite classes, intestinal microorganisms generate a variety of compounds from dietary substrates that can influence host physiology. These include polyamines, produced both by gut microbiota and from dietary sources, and metabolites derived from amino acids, such as trimethylamine (TMA), which is further converted in the liver into trimethylamine-N-oxide

(TMAO). Polyamines are involved in multiple biological processes, including epithelial proliferation and immune modulation, and contribute to host-microbiota interactions relevant to intestinal function,[21] whereas TMAO has been associated with pro-inflammatory and metabolic disturbances.[22] Together, these findings highlight the complexity of diet-microbiota interactions in shaping host physiology.

Diet-microbiota interactions in the context of the gut–skin axis

The gut-skin axis represents a complex bidirectional communication network involving immune, metabolic and neuroendocrine pathways. Within this context, diet acts as a key upstream modulator by shaping gut microbiota composition and function.[23] Microbial metabolites, including SCFAs, play a central role in regulating immune responses, epithelial barrier integrity and inflammatory pathways.[23] Disruptions in this system, often driven by gut dysbiosis, may trigger immune activation and systemic inflammation, contributing to the pathogenesis and clinical exacerbation of inflammatory skin diseases such as psoriasis, atopic dermatitis and acne. In this context, diet emerges as a modifiable factor within the gut-skin axis, although current evidence does not support its use as a stand-alone therapeutic strategy.[24]

Key points for interpretation and clinical contextualisation

From a clinical standpoint, the diet-microbiota axis can be understood as a modulatory layer influencing the systemic inflammatory and metabolic milieu in which skin diseases develop and evolve. Habitual dietary patterns contribute to shaping gut microbial composition and, importantly, its metabolic output over time, with potential downstream effects on immune regulation and inflammatory signalling relevant to dermatological conditions.

In this context, dietary factors should be interpreted as part of a broader clinical framework, where they may contribute to the overall inflammatory burden alongside established medical treatments and other lifestyle-related determinants.

Accordingly, the integration of dietary considerations into dermatological evaluation may provide additional context for clinical interpretation and patient stratification. At present, their application remains complementary and non-prescriptive, requiring clinical judgement and alignment with the overall management strategy.

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4. Culinary medicine as a nutrition-culinary framework for dermatology practice

Culinary medicine: concept and clinical positioning

Definition and scope in healthcare

Culinary medicine (CM) has been described as an evidence-based field that blends the art of food and cooking with the science of medicine, aimed at helping individuals make informed decisions about diet in the context of health and disease.[1] As the field has expanded across professional and community settings, a multidisciplinary consensus process recently defined it, from the healthcare professional perspective, as a field bridging evidence-based nutrition science with culinary tradition, grounded in food-is-medicine principles.[2] A key operational distinction is that CM is health practitioner-led, differentiating it from broader culinary nutrition activities.[3]

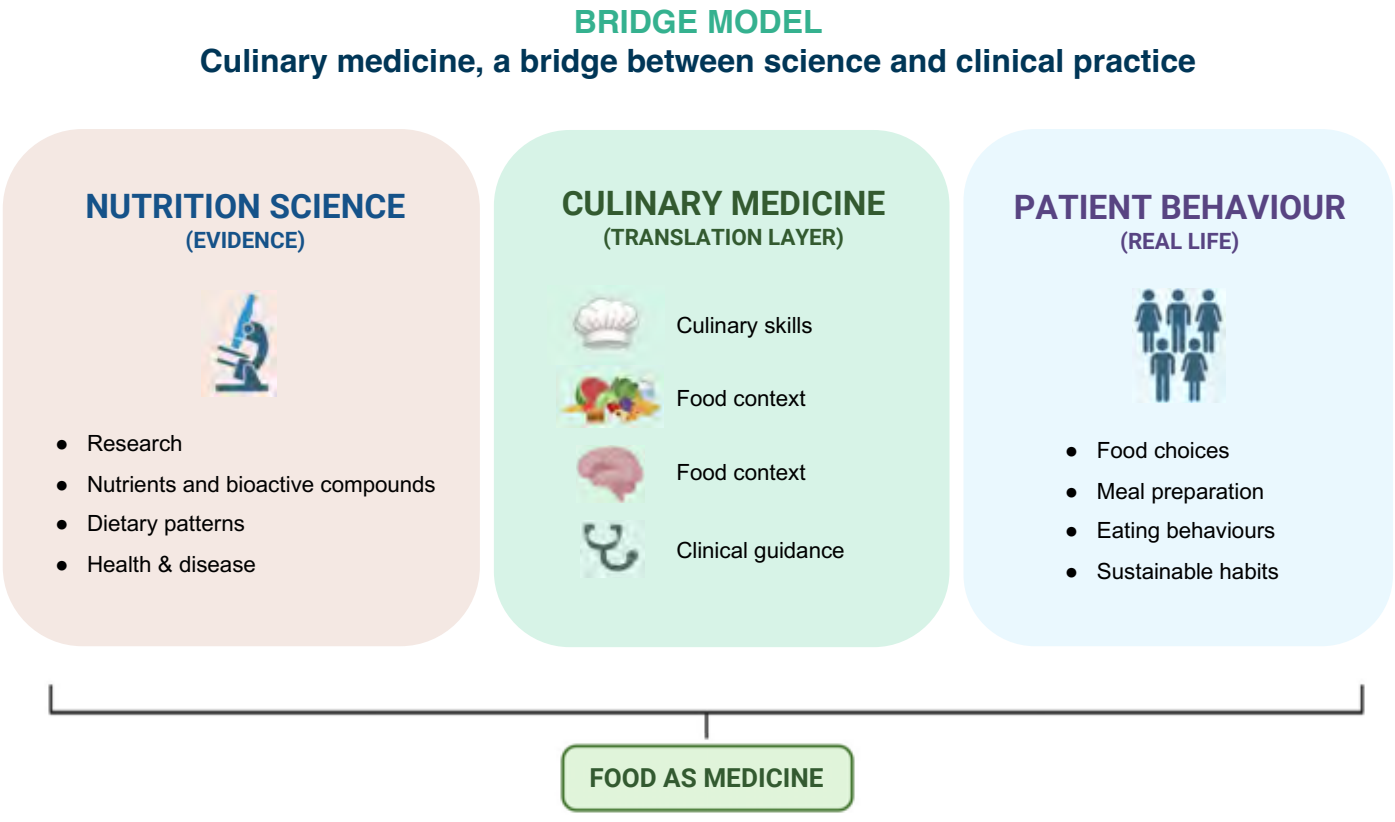

Figure 6. Positioning culinary medicine within the translation of evidence-based nutrition into clinical practice.

Relevance in Dermatology

Diet is a topic of considerable interest among patients with chronic inflammatory dermatoses, and dermatologists are increasingly expected to address nutritional questions within clinical practice.[4,5] Patients with psoriasis frequently seek dietary information independently, often without prior discussion with their healthcare professional, and the guidance they encounter is frequently unsubstantiated or misleading.[4,6]

Moreover, addressing nutrition in dermatology practice is subject to real constraints. Diet can be a sensitive subject, and the limited time available in routine consultations does not always allow for a detailed dietary discussion.[5] Additionally, socioeconomic and social barriers to dietary change are common and should be acknowledged when considering whether and how to introduce the topic.[5] This creates a practical need for clinicians to be equipped with a structured, evidence-informed approach to the topic.[6]

The kitchen as a determinant of dietary exposure

The implementation gap: from dietary patterns to real-life eating

Nutritional research has consistently linked habitual dietary patterns with systemic inflammation and metabolic health.[7] Despite the strength of this evidence, a gap persists between scientific knowledge and its implementation in clinical practice and community settings.[8]

This gap is also reflected at the patient level, where recommended dietary patterns are not always translated into daily behaviours. Importantly, this cannot be explained by nutritional knowledge alone. Rather, dietary behaviour appears to be influenced by a range of practical and contextual determinants, including cooking skills, time constraints, perceived cost, access to fresh foods, cultural habits, and the home food environment.[9-11]

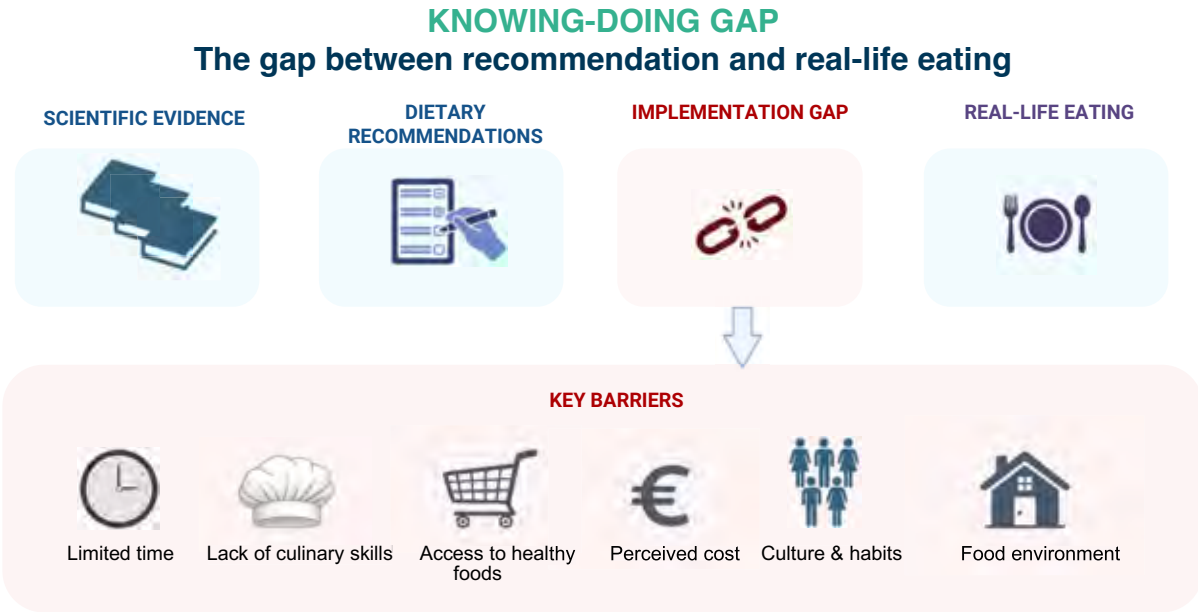

Figure 7. Barriers to the translation of dietary recommendations into daily practice.

From a clinical perspective, this distinction is critical. Recommendations framed at the level of food groups — for example, increasing vegetable, legume, or oily fish intake, or reducing ultra-processed foods — are scientifically well supported.[12] However, their implementation requires practical skills and contextual conditions that may not always be present. As a result, a disconnect may emerge between knowing what to eat and being able to act accordingly, partly due to limitations in cooking skills and contextual barriers. This may contribute to the challenges in translating evidence-based dietary recommendations into routine clinical practice.[11,13]

CM directly addresses this gap by shifting the focus from dietary prescription to dietary implementation.[14] It expands the clinical conversation to include the context in which food is selected, prepared, and consumed, recognising that dietary behaviour is shaped at this practical level, and that recommendations that do not account for it may be difficult to sustain in everyday life.[8,9]

This implementation gap is further reinforced by both structural and individual-level barriers. Declining culinary skills, reduced home cooking, and the increasing availability of convenience foods have been identified as key upstream drivers of current dietary patterns.[15] At the same time, limited health literacy, time constraints, and competing social or caregiving demands may restrict patients' capacity to act on dietary advice, particularly in urban and lower-income settings.[10]

At the healthcare level, additional constraints exist. The provision of nutritional counselling in primary care remains inconsistent, and general practitioners frequently report barriers that hinder its delivery, including time constraints, insufficient nutrition training, and limited structural support.[16] Together, these factors highlight the need for approaches that are not only evidence-based, but also feasible, scalable, and adaptable to diverse clinical and social contexts.

Cooking as a determinant of dietary exposure

Cooking is not only a process that modifies flavour and texture, but also a key determinant of dietary exposure.[17] It influences the compounds to which individuals are exposed by promoting both the transformation of food constituents and the formation of new molecules during thermal processing. As a result, similar foods may lead to different biological effects depending on how they are prepared.[18] Whilst the impact of cooking on nutrient bioavailability has been widely described,[19] its clinical relevance is more consistently linked to the formation of compounds associated with oxidative stress and inflammation.[20]

Thermally generated compounds: advanced glycation end products (AGEs) and oxidised lipids

High-temperature, dry-heat cooking methods favour the formation of advanced glycation end products (AGEs) and lipid oxidation products, particularly in foods rich in protein and fat. These compounds have been associated with increased oxidative stress and activation of inflammatory pathways in human studies, and dietary patterns characterised by lower exposure have been linked to improvements in metabolic and inflammatory markers.[20]

From a mechanistic perspective, AGEs may interact with pathways involved in inflammation and oxidative stress, including the AGE-receptor for advanced glycation end products (RAGE) axis, which has been implicated in inflammatory conditions.[21]

The mechanisms through which culinary techniques influence the nutritional composition and biological activity of foods are explored in the following section.

Culinary techniques as modifiers of nutritional composition and biological activity

Culinary techniques play a central role in determining the nutritional composition and biological activity of foods. Through processes such as heating, hydration, and mechanical disruption, cooking

modifies the food matrix and influences both the retention and the bioaccessibility of nutrients and bioactive compounds.[22] These effects are not uniform and depend on the interaction between the cooking method, the food matrix, and the specific compound considered.[23]

Whilst water-soluble vitamins are generally more susceptible to losses with prolonged heat and water exposure,[17] other compounds such as carotenoids may become more bioaccessible following cooking, particularly when combined with fat and matrix disruption.[19] For phytochemicals such as polyphenols, the effects of cooking are more variable and not always straightforward to interpret, as both decreases and apparent increases have been reported depending on the cooking and processing conditions involved.[17]

Overall, cooking should be understood not only as a source of nutrient loss, but as a process that reshapes the biological profile of foods.[22]

Table 3. Impact of culinary techniques on nutrient bioaccessibility and biological activity

Technique	Dominant effect	Typically enhances	Main risk
Boiling[17,24]	Leaching into cooking water (mass transfer of water-soluble compounds)	Tissue softening, increased digestibility of starch and proteins	Loss of vitamin C, folate, glucosinolates and some polyphenols
Steaming[17,23]	Reduced water contact, moderate temperatures	Better retention of water-soluble vitamins and glucosinolates	Limited flavour development, but minimal nutrient loss
Microwave cooking[17]	Rapid heating, low water use	Preservation of micronutrients in vegetables (short exposure time)	High variability depending on time, power and water content
Sautéing (low-fat)[19,25]	Matrix disruption + lipid-mediated micellisation	Increased bioaccessibility of carotenoids and some polyphenols	Thermal degradation if temperature is excessive or prolonged
Cooking with oil[19,26,27]	Enhanced solubilisation of lipophilic compounds	Lycopene, β-carotene and phenolic transfer into lipid fraction	Increased energy density; lipid oxidation if overheating occurs
Grilling / roasting / baking[20,28,29]	Dry heat, high temperature, Maillard reactions	Palatability and sensory acceptance	Formation of AGEs, lipid oxidation products and potentially pro-inflammatory compounds
Deep frying[30,31]	High temperature in lipid medium	Increased extractability of some carotenoids	Lipid oxidation, formation of thermal degradation compounds
Pressure cooking [25]	High temperature, reduced cooking time	Improved softening and potential carotenoid bioaccessibility	Loss of heat-sensitive compounds depending on matrix and duration
Blending / puréeing[27,32]	Particle size reduction, matrix disruption	Increased release and bioaccessibility of carotenoids and phenolics	Limited effect on water-soluble vitamins; potential oxidation if prolonged exposure

AGEs, advanced glycation end products.

Beyond the biochemical effects of cooking, the ability to apply these techniques in daily life depends on individual culinary skills and contextual factors, reinforcing the importance of approaches that integrate both knowledge and practical implementation.

Clinical relevance in dermatology practice

Role of the dermatologist

Dermatologists are increasingly exposed to questions related to lifestyle and dietary factors in the context of chronic inflammatory skin diseases. Whilst emerging evidence suggests that modifiable lifestyle factors, including diet, physical activity, sleep, stress, and substance use, may influence disease pathways through mechanisms such as inflammation, immune regulation, and oxidative stress, their integration into routine clinical practice remains limited and highlights the growing interest in considering these factors as part of a more comprehensive and patient-centred model of care.[33]

In this context, the role of the dermatologist is not to provide detailed lifestyle or nutritional counselling, but to recognise when these factors may be clinically relevant. This includes identifying situations in which disease expression, persistence, or treatment response may be influenced by broader metabolic or behavioural contexts, within the practical constraints of routine clinical care.[16] Brief, targeted questions may help explore this dimension within routine consultations, without requiring detailed assessment. Recognising these elements does not imply causality, but supports a more comprehensive interpretation of the clinical picture and a patient-centred approach to care.

Culinary medicine as a structured approach

Rather than introducing new dietary concepts, CM builds on existing nutritional evidence by providing a structured way to operationalise this knowledge within real-life contexts. In dermatology, where time constraints and the complexity of lifestyle-related factors may limit the feasibility of detailed counselling, this approach may offer a practical lens through which dietary behaviours can be considered without requiring extensive intervention.

Its relevance lies in shifting the clinical focus from isolated dietary advice towards the context in which food-related behaviours occur, including food selection, preparation, and habitual routines.[10] These elements may be particularly relevant in chronic inflammatory skin diseases, where adherence to dietary patterns has been associated with pathways such as inflammation, oxidative stress, and metabolic regulation.[34]

From a clinical perspective, this approach does not position the dermatologist as responsible for delivering comprehensive nutritional counselling. Instead, it can support the identification of patients who may benefit from a more structured, behaviour-oriented intervention, and may facilitate the integration of dietary considerations into a broader, patient-centred model of care.[35]

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II. Practical guidance for the clinical application of nutrition and culinary approaches in dermatology

1. Objective and scope

The aim of this section is to support dermatologists in identifying situations where lifestyle factors, including diet, may be relevant in the context of skin disease.

It is not intended to promote the systematic integration of nutritional counselling into routine dermatology practice, nor to replace standard treatment approaches. Rather, it provides practical guidance to help clinicians recognise when a broader, lifestyle-related context could be contributing to disease expression or persistence, and how to address this appropriately within the constraints of a routine consultation.

The content is designed to be pragmatic and applicable in everyday clinical settings, acknowledging the limited time available in dermatology visits. It focuses on supporting clinical judgement and facilitating simple, patient-centred conversations, rather than on conducting detailed nutritional assessments.

This section should be interpreted in the context of the scientific evidence presented previously. It does not aim to extend beyond the current level of evidence, but to offer a structured way to approach its clinical interpretation.

2. Interpreting current evidence on nutrition and lifestyle dermatology: what can be considered — and what cannot

The growing interest in the role of nutrition in dermatology has been accompanied by an increasing body of scientific evidence.[1] However, interpreting this evidence in a clinical context requires caution.

Current research supports the existence of associations between dietary patterns, systemic inflammation, and certain inflammatory skin conditions. In particular, dietary patterns have been linked to metabolic status and inflammatory markers, which may be relevant in diseases such as psoriasis.

At the same time, it is important to recognise that most of the available evidence is observational, and therefore does not allow causal relationships to be established. Findings are often heterogeneous, and may be influenced by factors such as study design, population characteristics, and methods used to assess dietary intake.

In this context, nutrition should not be considered a stand-alone therapeutic strategy in dermatology. Rather, it may be understood as a complementary component within a broader clinical approach, particularly in patients with an underlying metabolic or inflammatory profile.

It is also important to move away from a nutrient-focused perspective and consider diet at the level of overall patterns. This approach better reflects real-life eating behaviours and captures the combined and cumulative effects of foods, rather than isolated components.

Finally, individual variability should be taken into account. Patients may differ in their clinical presentation, lifestyle context, and response to interventions, which reinforces the need for a cautious and personalised interpretation of nutritional aspects in dermatology.

3. From evidence to practice: supporting clinical reasoning in consultation

Bringing current evidence on nutrition and lifestyle into dermatology practice requires a pragmatic and realistic approach.

Dermatologists are not expected to carry out detailed nutritional assessments or to provide specific dietary recommendations. However, they are in a good position to recognise when lifestyle factors, including diet, may be relevant in the context of a patient's condition.

This section aims to support clinical judgement in those situations, helping to approach the topic in a simple and practical way, without adding unnecessary complexity to the consultation.

Identifying patients for whom lifestyle factors may be relevant

In daily practice, certain patient profiles may suggest that lifestyle factors could be playing a role.

These may include:

- Recurrent or persistent inflammatory dermatoses
- Moderate disease burden or suboptimal response to treatment
- Presence of metabolic comorbidities (*e.g.* obesity, insulin resistance, dyslipidaemia)
- Clinical or laboratory signs suggesting a broader inflammatory context
- Patient-reported habits that may reflect lower overall diet quality

The presence of these elements does not establish a causal relationship, but it may help identify patients for whom it makes sense to consider a wider clinical perspective.

Practical questions to explore lifestyle context

When appropriate, a few simple questions can help explore whether lifestyle factors may be relevant in a given case.

For example:

- "How would you describe your usual diet?"
- "Do you mostly eat home-cooked meals or ready-to-eat foods?"
- "How often do you include fruits, vegetables or fish in your meals?"
- "Have you noticed any link between your lifestyle and your skin condition?"

These questions are not intended to assess diet in detail, but to give a general sense of the patient's context and to help decide whether it is worth exploring this area further.

A simple pathway to support patient identification

A simple clinical pathway can help bring these elements together and support decision-making in a consistent and practical way. This pathway is illustrated in Figure 7.

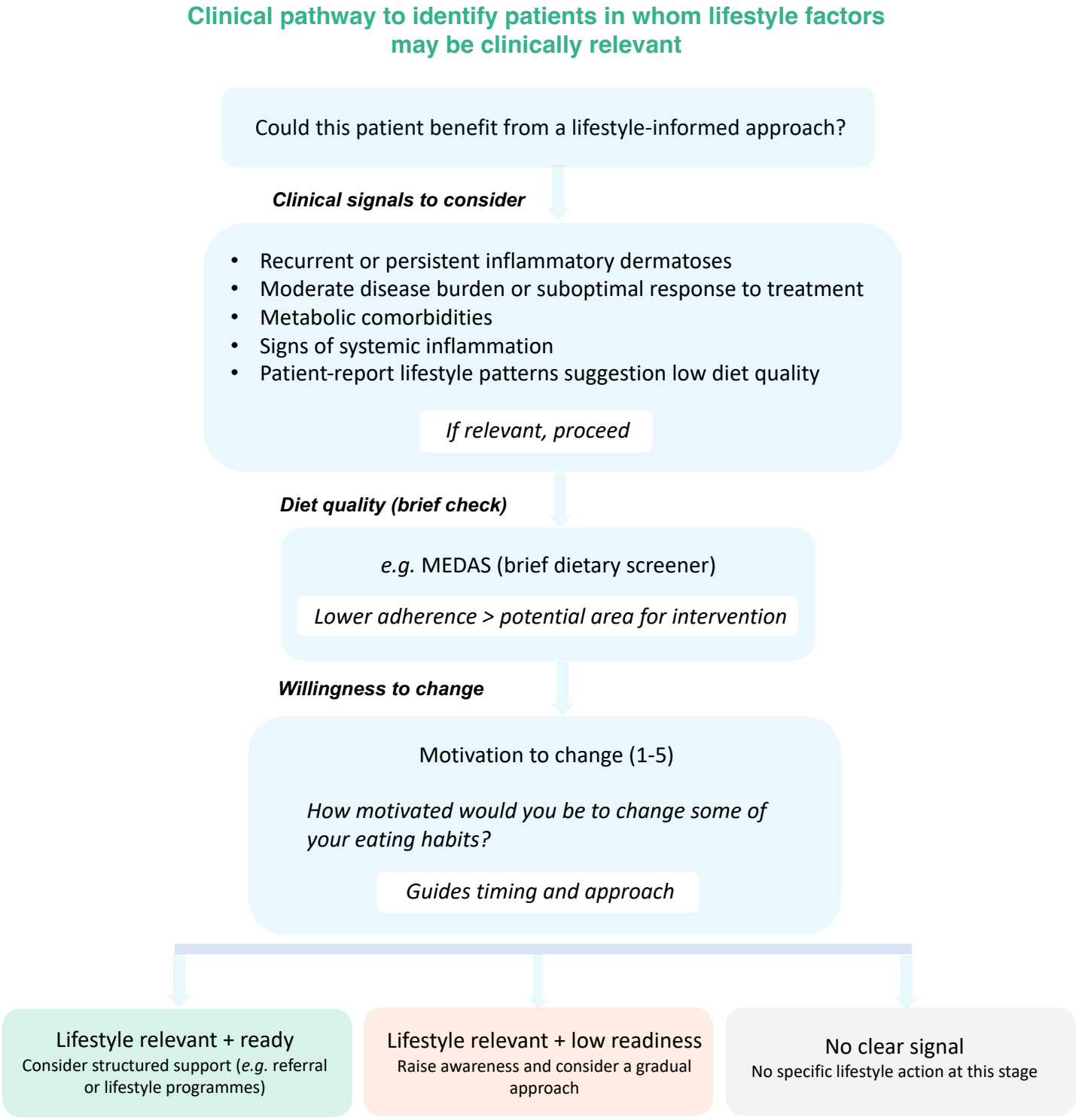

Figure 8. Clinical pathway to support patient identification in dermatology.

MEDAS, Mediterranean Diet Adherence Screener.

It starts with a basic clinical consideration:

Could lifestyle factors be relevant in this patient?

This may be considered in patients presenting with one or more of the following:

- Recurrent or persistent inflammatory dermatoses
- Moderate disease burden or suboptimal response to treatment
- Presence of metabolic comorbidities (*e.g.* obesity, insulin resistance)
- Clinical or laboratory signs suggesting a broader inflammatory context
- Patient-reported lifestyle patterns that may reflect lower overall diet quality

The presence of these elements does not establish a causal relationship, but may indicate that lifestyle factors could be contributing to the overall clinical picture.

If considered relevant, a brief and targeted exploration of lifestyle factors may be appropriate within the consultation.

Exploring diet quality and readiness to change

When lifestyle factors are considered potentially relevant, two aspects may help guide the next step: overall diet quality and the patient's readiness to engage in changes.

A brief approximation of diet quality can be obtained through simple questioning or by using short, validated tools such as the Mediterranean Diet Adherence Screener (MEDAS).[2] (see Appendix 1, page. 103). This type of tool provides a quick overview of dietary patterns and may help identify areas that could be improved.

MEDAS results should be interpreted as an indication of overall dietary pattern quality, rather than as a diagnostic tool. Lower adherence to a Mediterranean dietary pattern may suggest a potential area for intervention, but should always be considered in the context of the broader clinical picture.

In parallel, it is useful to explore the patient's willingness to engage in lifestyle changes. A simple question can be used in clinical practice:

"On a scale from 1 to 5, how motivated would you be to change some of your eating or lifestyle habits if this could potentially support your skin condition?"

Rather than applying strict thresholds, this information can help guide the type and timing of the approach. Higher readiness may support more active or structured interventions, whereas lower readiness may call for a more gradual approach focused on awareness and engagement.

Taken together, these elements allow the clinician to orient the next step in a pragmatic way. In practice, this may range from simply raising awareness, to considering referral to a qualified professional, or suggesting participation in structured lifestyle-oriented programmes where available.

This approach is intended to support clinical judgement, not to replace it, and should be adapted to each patient and clinical context.

Box 1. Example of a brief dietary assessment tool: Mediterranean Diet Adherence Screener (MEDAS)

The MEDAS is a validated 14-item questionnaire originally developed within the PREDIMED study to assess adherence to the Mediterranean dietary pattern.[3] (see Appendix 1, page. 103).

The questionnaire includes items covering key aspects of dietary intake, such as:

- Use of olive oil as the main culinary fat
- Consumption of vegetables, fruits, legumes, and nuts
- Intake of fish and seafood
- Consumption of red and processed meat
- Intake of sugar-sweetened beverages and commercial pastries

Each item is scored as 0 or 1, resulting in a total score ranging from 0 to 14, with higher scores indicating greater adherence to a Mediterranean dietary pattern.

In the context of this guide, MEDAS may be used as a practical tool to support a brief estimation of overall diet quality during clinical encounters.

Results should be interpreted as an approximation of dietary pattern rather than as a diagnostic or prescriptive measure, and should be considered alongside the broader clinical context.[2]

> ***Note:*** *Some studies have used cut-off values (e.g. <10 points) to indicate lower adherence.*[4] *However, in this context, results are interpreted as a continuous indication of dietary pattern.*

Box 2. Example of a brief question to assess readiness to change

Assessing the patient's willingness to engage in lifestyle changes may help guide the type and timing of the clinical approach.

A simple question can be used in practice:

"On a scale from 1 to 5, how motivated would you be to change some of your eating or lifestyle habits if this could potentially support your skin condition?"

As a general reference:

- 1 indicates low readiness to change
- 5 indicates high readiness to change

This question provides a quick indication of the patient's level of engagement without requiring a formal behavioural assessment.

Rather than applying strict thresholds, responses should be interpreted in a flexible way:

- Lower scores may suggest the need for a more gradual approach focused on awareness and engagement

- Higher scores may support a more active or structured intervention

This information should always be considered alongside the broader clinical context.

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4. Clinical cases

Case 1

Psoriasis in a patient with metabolic comorbidities

Clinical description

A 52-year-old male presents with chronic plaque psoriasis diagnosed 8 years ago. The current disease activity is moderate (PASI ~10), with lesions affecting the elbows, scalp, and lower back.

Over the past year, the patient reports an increase in the frequency of flare-ups.

His medical history includes obesity (BMI 31 kg/m^2), hypertension, and impaired glucose regulation (glycated haemoglobin [HbA1c] 6.1%). He describes a sedentary lifestyle and reports poor sleep quality.

The patient is currently managed with topical treatments and has not received systemic or biologic therapy.

Lifestyle context

Based on brief clinical questioning, the patient reports a dietary pattern characterised by:

- Frequent consumption of processed and ready-to-eat foods
- Regular intake of red and processed meat
- Low consumption of vegetables, legumes, whole grains, and nuts
- Limited use of fresh ingredients and minimal involvement in cooking

This pattern is consistent with low adherence to a Mediterranean dietary pattern, which, if formally assessed using tools such as MEDAS, would likely correspond to a low or moderate adherence score.

Interpretation

The coexistence of psoriasis and metabolic comorbidities suggests a broader systemic context, potentially characterised by low-grade systemic inflammation.

In this context, the patient's dietary pattern, characterised by low intake of plant-based foods and high consumption of processed and ultra-processed products, is consistent with patterns that have been associated with a more pro-inflammatory metabolic profile.

From a mechanistic perspective, such dietary patterns may be associated with:

- Reduced intake of fibre and bioactive compounds (*e.g.* polyphenols), which are relevant for gut microbiota composition and short-chain fatty acid production
- Increased intake of ultra-processed foods and saturated fats, which have been linked to inflammatory pathways
- Lower overall dietary diversity, which may impact metabolic and immune regulation

These mechanisms may contribute to a broader inflammatory milieu and provide biological plausibility for a potential link between dietary patterns and the patient's overall clinical context.

However, it is important to emphasise that these associations do not establish a direct causal relationship with psoriasis activity or flare-ups.

Taken together, the clinical profile and lifestyle context suggest that lifestyle factors may be relevant in this patient. The patient's reported symptoms (fatigue, recurrent flares) and moderate motivation indicate that this may be an appropriate moment to introduce the topic and explore potential next steps.

The interpretation presented in this case is based on the evidence discussed in previous sections, particularly in relation to dietary patterns, systemic inflammation, and metabolic context.

Points to consider

- The combination of psoriasis and metabolic comorbidities may be consistent with a broader systemic context characterised by low-grade inflammation
- The patient's dietary pattern, characterised by low intake of plant-based foods, may be associated with reduced intake of fibre and bioactive compounds relevant for gut microbiota composition and metabolic regulation
- From a mechanistic perspective, such patterns have been linked to alterations in gut microbiota and intestinal barrier function, which may be relevant in the context of the gut-skin axis
- These mechanisms provide biological plausibility, but do not establish a direct causal relationship with psoriasis activity or flare-ups
- The relevance of dietary factors should be interpreted within the overall clinical context, rather than as isolated drivers of disease

Case 2

Actinic keratosis in a patient with high cumulative sun exposure

Clinical description

A 68-year-old male presents with multiple AK located on the scalp and dorsal aspects of the hands. He reports a long history of occupational sun exposure (construction worker) and inconsistent use of photoprotection.

Over the past two years, he has noticed an increase in the number of lesions.

His medical history is otherwise unremarkable, with no major metabolic comorbidities. He is not receiving systemic treatments.

Lifestyle context

Based on brief clinical questioning, the patient reports a dietary pattern characterised by:

- Low consumption of fruits, vegetables, legumes, and nuts
- Limited intake of fish
- Frequent consumption of refined carbohydrates and processed foods
- Minimal involvement in cooking and reliance on convenience meals

When asked about lifestyle, the patient expresses low interest in dietary changes and believes that sun exposure is the only relevant factor in his condition.

Interpretation

From a mechanistic perspective, such patterns may be associated with:

- Lower intake of antioxidants (*e.g.* carotenoids, vitamins C and E, and polyphenols), which are involved in protection against oxidative stress and UV-induced damage
- Reduced availability of nutrients relevant for skin barrier function and repair, including essential fatty acids, certain vitamins (*e.g.* vitamin A derivatives), and trace elements involved in epidermal turnover
- A dietary profile that may not optimally support cellular protection, immune response, and maintenance of skin integrity under conditions of chronic UV exposure

These mechanisms may influence how the skin responds to chronic UV exposure and contribute to a less favourable environment for cellular protection and repair.

However, it is important to emphasise that current evidence does not support a direct causal role of diet in the development or progression of AK.

Rather, dietary patterns may be considered within a broader prevention-oriented context, as a factor that may modulate the skin's response to environmental stressors.

Given the patient's low readiness to change, any discussion around lifestyle should be introduced gradually, focusing on awareness rather than immediate intervention.

The interpretation presented in this case is based on the evidence discussed in previous sections, particularly in relation to dietary patterns, oxidative stress, and skin response to environmental factors.

Points to consider

- UV exposure remains the primary driver of AK and should be prioritised in clinical management
- Dietary patterns may influence the skin's response to oxidative stress, but do not replace established preventive strategies such as photoprotection
- Low intake of plant-based foods may be associated with reduced antioxidant capacity, which could be relevant in the context of chronic UV exposure
- The role of diet should be interpreted within a broader prevention framework, rather than as a treatment for actinic keratosis
- Patient beliefs (*e.g.* attributing the condition exclusively to sun exposure) may influence engagement and should be addressed carefully

Appendix 1. Mediterranean Diet Adherence Screener (MEDAS)

The MEDAS questionnaire (Schröder et al., 2011) is a 14-item tool developed within the PREDIMED study to assess adherence to the Mediterranean dietary pattern (Estruch et al., 2018).

It is included here as a reference for optional use in clinical practice.

1. Do you use olive oil as main cooking fat?

◯ Yes
◯ No

2. How much olive oil do you consume in a day (including oil for frying, on salads, among others)?

◯ ≥ 4 tablespoons
◯ < 4 tablespoons

3. How many servings of vegetables do you eat per day? (1 serving = 200g)

◯ ≥ 2 servings
◯ < 2 servings

4. How many fruit portions do you eat per day? (Including fresh juice)

◯ ≥ 3 servings
◯ < 3 servings

5. How many servings of red meat, hamburger, or processed meat do you eat per day? (1 portion = 100-150g)

◯ ≥ 1 portion
◯ < 1 portion

6. How many servings of butter, margarine, or cream do you eat per day? (1 serving = 12g)

- ◯ ≥ 1 serving
- ◯ < 1 serving

7. How many sweet beverages do you drink per day? (1 serving = 12g)

- ◯ ≥ 1 serving
- ◯ < 1 serving

8. How many glasses of wine do you drink per week?

- ◯ ≥ 7 glasses/week
- ◯ < 7 glasses/week

9. How many servings of legumes do you eat per week? (1 portion = 150g)

- ◯ ≥ 3 servings
- ◯ < 3 servings

10. How many servings of fish or shellfish do you eat per week? (1 portion = 150/200g)

- ◯ ≥ 3 servings
- ◯ < 3 servings

11. How many times per week do you eat commercial sweets or pastries (not homemade)?

- ◯ ≥ 2 servings
- ◯ < 2 servings

12. How many servings of nuts do you eat per week? (1 serving = 30g)

- ◯ ≥ 3 servings
- ◯ < 3 servings

13. Do you preferably eat chicken, turkey, or rabbit meat instead of beef, pork, hamburger, or sausage?

- ◯ Yes
- ◯ No

14. How many times per week do you eat vegetables, pasta, rice or other dishes seasoned with tomato, garlic, onion or leek sauce cooked in olive oil (sofrito)?

- ◯ ≥ 2 times per week
- ◯ < 2 times per week

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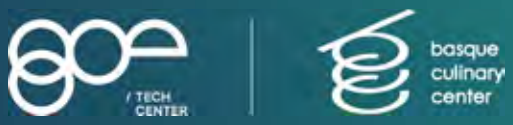
Dra. Cecilia Galbete Ciáurriz



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