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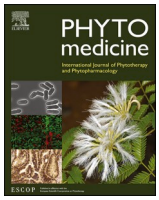

Review

A systematic review of natural products for skin applications: Targeting inflammation, wound healing, and photo-aging

A. Fernandes *, P.M. Rodrigues, M. Pintado, F.K. Tavaria

Universidade Católica Portuguesa, CBQF – Centro de Biotecnologia e Química Fina Laboratório Associado, Escola Superior de Biotecnologia, Rua Diogo Botelho 1327, 4169-005 Porto, Portugal

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Background: Every day the skin is constantly exposed to several harmful factors that induce oxidative stress. When the cells are incapable to maintain the balance between antioxidant defenses and reactive oxygen species, the skin no longer can keep its integrity and homeostasis. Chronic inflammation, premature skin aging, tissue damage, and immunosuppression are possible consequences induced by sustained exposure to environmental and endogenous reactive oxygen species. Skin immune and non-immune cells together with the microbiome are essential to efficiently trigger skin immune responses to stress. For this reason, an ever-increasing demand for novel molecules capable of modulating immune functions in the skin has risen the level of their development, particularly in the field of natural product-derived molecules.

Purpose: In this review, we explore different classes of molecules that showed evidence in modulate skin immune responses, as well as their target receptors and signaling pathways. Moreover, we describe the role of polyphenols, polysaccharides, fatty acids, peptides, and probiotics as possible treatments for skin conditions, including wound healing, infection, inflammation, allergies, and premature skin aging.

Methods: Literature was searched, analyzed, and collected using databases, including PubMed, Science Direct, and Google Scholar. The search terms used included "Skin", "wound healing", "natural products", "skin microbiome", "immunomodulation", "anti-inflammatory", "antioxidant", "infection", "UV radiation", "polyphenols", "polysaccharides", "fatty acids", "plant oils", "peptides", "antimicrobial peptides", "probiotics", "atopic dermatitis", "psoriasis", "auto-immunity", "dry skin", "aging", *etc*., and several combinations of these keywords.

Results: Natural products offer different solutions as possible treatments for several skin conditions. Significant antioxidant and anti-inflammatory activities were reported, followed by the ability to modulate immune functions in the skin. Several membrane-bound immune receptors in the skin recognize diverse types of natural-derived molecules, promoting different immune responses that can improve skin conditions.

Abbreviations: AD, atopic dermatitis; AKT, protein kinase B; AMPs, Antimicrobial peptides; AP-1, activator protein; APCs, antigen-presenting cells; ASCs, adipose-derived stem cells; BMDCs, bone marrow-derived dendritic cells; C5a, complement component 5a; C5aR1, complement component 5a receptor 1; CD, cluster of differentiation; CDP, Chlorella-derived peptide; COX 2, prostaglandin-endoperoxide synthase 2; CR3, complement receptor 3; CYR61, cysteine-rich 61; DAGs, diacylglycerols; DCs, dendritic cells; dDCs, dermal dendritic cells; ECM, extracellular matrix; EGCG, epigallocatechin gallate; ERK, extracellular-signal-regulated kinase; FBP1, fibronectin-binding protein 1; HA, hyaluronic acid; HDPs, host defense peptides; ICAM-1, Intercellular Adhesion Molecule 1; IFN, interferon.IL, interleukin; IRF, interferon regulatory factor; LCs, langerhans cells; LR, laminin receptor; LTA, lipoteichoic acid; MAPK, mitogen-activated protein kinase signaling pathways; MCP-1, monocyte chemoattractant protein-1; MKP-1, mitogen-activated protein kinase [MAPK] phosphatase-1; MMPs, matrix metalloproteases; MRSA, methicillin-resistant Staphylococcus aureus; MUFA, monounsaturated fatty acids; MyD88, myeloid differentiation primary response gene 88; NFκB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRs, Nod-like receptors; NO, nitric oxide; NPS, natural products; PDGF-BB, platelet-derived growth factor; PGE2, prostaglandin E2; PI3K, phosphatidylinositol-3 kinase; PRRs, pattern recognition receptors; PSMs, phenol-soluble modulins; PUFA, polyunsaturated fatty acids; RANKL, Receptor activator of nuclear factor kappa-B ligand; LacCer, lactosylceramide; RHAMM, Receptor for HA-mediated mobility; RNS, reactive nitrogen species; ROS, reactive oxygen species; SALT, skin-associated lymphoid tissue; SCF, Stem Cells Factor; SPF, sun protection factor; STAT, signal transducer and activator of transcription; Syk, spleen tyrosine kinase, TCR, T cell receptor; TGF, transforming growth factor; TLRs, toll-like receptors; TNF-α, tumor necrosis factor; Th, T helper cells.

* Corresponding author.
E-mail address: s-ansifernandes@ucp.pt (A. Fernandes).

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Conclusion: Despite the increasing progress in drug discovery, several limiting factors need future clarification. Understanding the safety, biological activities, and precise mechanisms of action is a priority as well as the characterization of the active compounds responsible for that. This review provides directions for future studies in the development of new molecules with important pharmaceutical and cosmeceutical value.

Introduction

Skin is one of the largest organs in the body, comprehending approximately a surface area of between 1.5–2.0 m^2s in an adult human, but when considering the appendices, the epithelial surface area significantly increases to approximately 25 m^2s. Three well-known functions are usually attributed to skin: It is the first line of defense against external factors (e.g., pathogens, chemicals, or physical interactions), water loss prevention, and temperature maintenance (Kabashima et al., 2019). The epidermis is the most external layer of the skin and consists essentially of specific cells: keratinocytes (90 – 95%), well-known for their capacity to synthesize keratin. It can be subdivided into the stratum corneum, stratum lucidum, stratum granulosum, and stratum basale. The stratum corneum comprises dead keratinocytes, and lipids establishing a highly hydrophobic barrier against the environment that prevents the entry or exit of water and/or water-soluble substances (Hsu et al., 2014; Ovaere et al., 2009). The dermis is fundamental to protect and support the other layers and contains fibroblasts, immune cells such as macrophages, lymphocytes, and mast cells, and an abundant extracellular matrix (ECM) rich in collagen and elastin that also acts as a platform for immune cell migration. The subcutaneous tissue is the most internal layer also known as the hypodermis layer and it consists largely of fibrocytes and adipocytes, rich in blood vessels and nerves. This layer also produces mediators such as growth factors, adipokines, and cytokines, and comprises multiple immune cells. It is essential in preventing heat loss since fat has poor thermal conductivity (Wolf et al., 2003).

Together with other tissues, the skin represents the interface of the host and the environment, being constantly exposed to many insults. For this reason, different types of immune cells reside in or are recruited into the skin to maintain homeostasis during inflammatory challenges (Kabashima et al., 2019). In the epidermis and dermis, immune cells and non-immune cells create a structure acting as a specific immunological unit, named skin-associated lymphoid tissue (SALT), which has an important role in cutaneous adaptive immunity. This concept was proposed in the early 1980s, highlighting that skin cells can capture, process, and present antigens. At this point, this hypothesis suggests that the skin is not only a physical barrier but also a component of the lymphatic system (Hsu et al., 2014; Ovaere et al., 2009). Antigen-presenting cells (APCs) and resident T cells are important players to understand the antigen presentation in SALT, as well as Langerhans cells and dermal dendritic cells (dDCs) that are the first immune cells to contact with the antigens. On the other side, when keratinocytes contact with foreign antigens, quickly produce several proinflammatory mediators, such as interleukin 1 (IL-1) and tumor necrosis factor (TNF-α), in an antigen-nonspecific manner (Streilein, 1983). Keratinocytes and other skin cells become important mediators not only of the innate immune system, but also of the adaptive immune responses, playing multiple functions during the initiation, maintenance, and amplification of the immune and inflammatory skin responses (Natsuaki et al., 2014). Despite immune and non-immune cells, the skin is home to millions of bacteria, fungi, and viruses that together form the skin microbiota, also essential in the skin's immune response. A deeper knowledge of the interaction between immune cells, non-immune cells, and even skin microbiome is important for a clear understanding of the basic mechanisms of cutaneous immune reactions, allowing the development of novel treatments for skin disorders.

For decades, molecules derived from natural products (NPs) have been studied for the most diverse applications in health and disease, due to their versatility, safety, and cost-effectiveness. Several molecules derived from NPs have demonstrated their effectiveness as modulators of the immune system, such as fatty acids, polyphenols, polysaccharides, probiotics, etc. (Albanesi et al., 2018; Chen and Yu, 2016; Wang et al., 2021). At present, many of these molecules are in clinical trials, particularly molecules with antioxidant, anti-microbial, or anti-cancer potential but the way how NPs interact with immune cells is not totally clear (Butler, 2005; Chen et al., 2010; Noh et al., 2019). The antiviral activity of these molecules also have been extensively explored to overcome the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic (Brogi et al., 2022; Quimque et al., 2023). In the same way, targeting skin inflammatory disorders or other skin conditions (such as premature aging, chronic wounds, skin infections) with NPs may provide the key to controlling them or ultimately, defeating them.

In fact, several studies have proved the effectiveness of NPs against multiple skin conditions. The increasing need for new molecules with antibiotic, anti-inflammatory potential has increased the search for different ways to overcome antibiotic resistance (Mahdi et al., 2022; Yousefi et al., 2021). Chronic wounds frequently develop bacterial infections, leading to several complications mainly in patients with other chronic diseases (i.e., diabetes). Despite their immunomodulatory ability, polysaccharides for instance can offer excellent materials to construct drug delivery systems (DDSs) and to develop wound dressings (Zhao et al., 2020). On the other hand, polyphenols act directly to decrease oxidative stress in cells, well-known for their role in inflammatory conditions. The protective effects of polyphenols represent different ways to decrease the negative effects of solar radiation and treat and/or prevent de skin diseases associated with photo-aging (OyetakinWhite et al., 2012). A less explored class of molecules are lipids and fatty acids. In skin, these molecules can prevent water loss, and are essential to maintain the integrity of the epidermal barrier. However, more studies are needed to understand their biological activities and mechanisms of action on skin cells. The biological effects of bioactive peptides also have been reported. These molecules show high activity, specificity, and stability and aroused significant interest in the related field of research. Bioactive peptides have diverse pharmacological bioactivities, including antimicrobial, antioxidant, and immunomodulatory activities. At least, probiotics have been shown to prevent infection, regulate inflammation, and potentially increase healing. Moreover, probiotics have shown achievements in both topical and systemic skin inflammatory conditions such as atopic dermatitis and skin infections (Knackstedt et al., 2020b).

In this review, we summarize the recent considerations on the skin immune system and immune skin responses in inflammation, infection, wound healing, and photoaging, followed by the advancements made in utilizing NPs for immunomodulation and their molecular targets in the skin. The goal of this review is to analyze the present achievements in the field, aiming at the development of new candidates for future therapeutical molecules. This manuscript also includes the skin microbiome as a crucial player, especially in inflammation and wound healing processes, being the commensal microorganisms able to modulate immune functions as well as natural compounds (as prebiotics) can be able to modulate the activity of these microorganisms.

The Skin's immune system

In the human body, more than 1600 genes regulate the innate and adaptive immune responses sustaining life in a hostile environment. The

immune system is immature when a child is born but over the years, it matures and acquires memory with several exposures to foreign challenges. With old age, the immune system will progressively suffer profound remodeling and decline, negatively affecting the health of the individuals. The human immune system has been molded by evolution, it responds efficiently to viruses, bacteria, fungi, and parasites and plays important roles in tissue repair, wound healing, microbiome, and recognition of cancer cells (Simon et al., 2015).

Skin is an active organ of the human immune system, playing a dual role in the body's defense. It provides a physical barrier between the internal systems and the environment and continuously fights against microorganisms and foreign agents through innate and acquired immune mechanisms. Understanding these mechanisms of immune responses is essential to a more detailed knowledge of several conditions such as inflammation, allergies, and auto-immune diseases. In the skin, a complex network of immune cells plays an important role in host defense and homeostasis, preventing infections and being essential in tissue healing and regeneration. Deregulations in immune responses contribute to the pathogenesis of inflammatory skin diseases and retard the natural processes of wound healing (Kabashima et al., 2019; Varade et al., 2021).

Immune and non-immune cells

The skin is home to several immune populations that create an immune network including antigen-presenting cells, mast cells, tissue-resident phagocytes, and T lymphocytes, as well as innate lymphoid cells well distributed in the epidermis and dermis layers. Moreover, it is important to mention that the immune system of the skin consists not only of specialized immune cells but also of other skin cells that together establish what is designated SALT (Kabashima et al., 2019).

Both myeloid and lymphoid cell subclasses are found in the skin: the myeloid cells consist of Langerhans cells, dermal dendritic cells, macrophages, mast cells, and eosinophils. More rarely it is possible to find neutrophils but often linked to inflammatory conditions; he lymphoid population includes T lymphocytes and natural killer T cells, important in both normal state and inflammatory responses. APCs are another important population of skin immune cells, they consist of Langerhans cells (LC), dDCs, and resident macrophages. A well-known function of these cells is the production of inflammatory mediators in response to toll-like receptors (TLRs) (members of the pattern recognition receptors (PRRs family) (Nguyen and Soulika, 2019). The antigen presentation is represented more deeply in Fig. 1. Consequently, the Nuclear Factor Kappa-light-chain-enhancer of activated B cells (NFκB) and interferon regulatory factor (Dehghani et al.) will be activated, enhancing the antigen presentation (Iwasaki and Medzhitov, 2004).

The macrophage population covers a wild range of scenarios: homeostasis, tissue repair, inflammation, and infection. They are highly plastic cells and they can only be distinguished based on their location within the epidermis, dermis, or hypodermis (Okabe and Medzhitov, 2014). In the epidermis, the resident macrophages are called Langerhans cells, present in all stratified epithelia. In this layer, they represent 3–6% of all cells but they are only considered mature after contact with antigens. The differentiation process depends on the circulating factors (including IL-15 and TGF-β) that have considerable differing levels over all inflammatory stages (Girolomoni et al., 2002). E-cadherin can retain the LCs in the epidermis by establishing homotypic connections with keratinocytes (Tang et al., 1993). After contact with antigens, LCs downregulate the E-cadherin expression, allowing them to migrate into the dermis. It is important to note that it is not possible to distinguish the migratory LCs from the APCs of the dermis (migratory DCs) (Merad et al., 2008). In the dermis, more precisely in the deeper layer named the

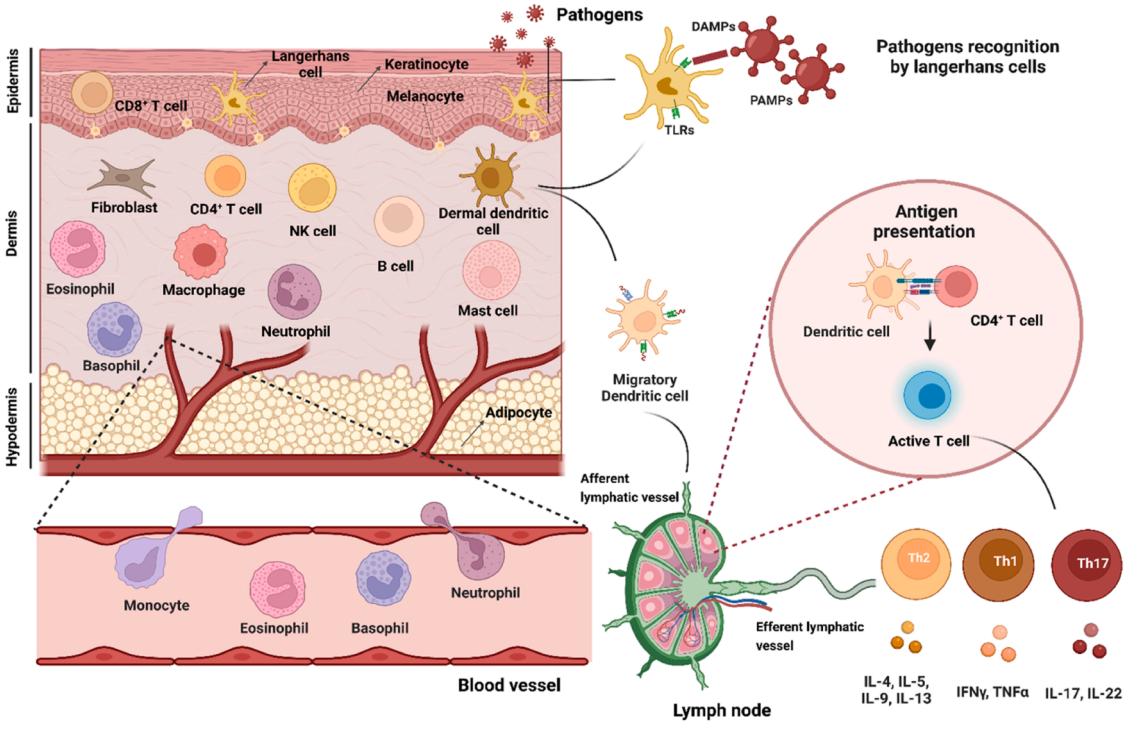

Fig. 1. Skin immune and non-immune cells during antigen presentation. The non-immune celpopulation are essentially keratinocytes, melanocytes, and adipocytes. Langerhans cells, dermal dendritic cells, and resident macrophages are antigen-presenting cells found both in the epidermis and dermis. The dermis is the place where most important skin immunological interventions take place. Fibroblasts, tissue-resident T-cells, mast cells, and others are also present in the dermis. PAMPs and DAMPs present in the pathogens bind to pattern recognition receptors, which include TLRs of Langerhans cells. The dendritic cells migrate to lymph nodes and become antigen-presenting cells and present the antigens to the lymph node resident T-cells. The antigen-experienced T-cells differentiated into T-helper cells that will migrate to the skin and release several types of pro-inflammatory cytokines and interleukins. Created with BioRender.com.
Abbreviations: NK, natural killer T-cells; Th, T helper cells; DAMPs, damage-associated molecular patterns; PAMPs, pathogen-associated molecular pattern.

reticular dermis, it is possible to find both macrophages and DCs. Some studies in mice suggest that macrophages have a poor antigen-presenting ability, and a poor capacity to activate T-cells compared to DCs (Tamoutounour et al., 2013). In clinical conditions such as obesity and diabetes, the number of macrophages found in the subcutaneous adipose tissue can be approximately 50% more than that found in healthy patients (Rodrigues and Gurtner, 2017; Weisberg et al., 2003). The role of macrophages in wound healing and inflammation stages will be more discussed in the next section.

The non-immune cells, despite the terminology, participate as regulators and effectors in immune responses beyond their structural role in the skin. These cells must sense each type of danger signal correctly, interpret it, and trigger the most suitable type of immune response (Dainichi et al., 2021). Non-immune cells are essentially keratinocytes, melanocytes, adipocytes, and endothelial cells, all of them expressing PRRs. When PRRs are triggered, non-immune cells release chemokines and cytokines, having an active role in the local immune response (Lebre et al., 2003).

Special attention has been given to keratinocytes once these cells express almost all intracellular and extracellular PRRs. Keratinocytes produce several numbers of cytokines, including interleukins (IL-1, IL-6, IL-10, IL-17, IL-18, IL-22), and tumor necrosis factor-alpha (TNF-α). Several pathways can mediate the release of the cytokines in keratinocytes such as NFκB, Signal Transducer and Activator of Transcription 3 (STAT3), and PRR signaling pathway in response to different stresses (UVB radiation, inflammatory processes, etc.) (Lebre et al., 2003; Tang et al., 2017; Xu et al., 2018). Some authors suggest that keratinocytes are involved in immune responses in two distinct phases: the initiation of primary immune responses and the dissemination of secondary responses. Moreover, keratinocytes interact with other immune cells such as macrophages, LCs, and neutrophiles, among others. In some cases, they act as atypical antigen-presenting cells to cooperate with T lymphocytes in an antigen-specific manner (Dainichi et al., 2019; Piipponen et al., 2020).

Melanocytes are strategically positioned along with keratinocytes and LCs to form a physical barrier in the epidermis. The fact that some skin infections affect in higher proportions individuals with fair skin than those with dark skin led the scientific community to explore the role of melanocytes and the melanization process in the skin's immune responses (Mackintosh, 2001). Human melanocytes express the same PRRs such as functional TLRs 2 – 5, 7, 9, and 10, and release a wide range of immunological molecules and several pro-inflammatory chemokines and cytokines that may affect lymphocytes, fibroblasts, keratinocytes, endothelial cells, and mast cells in the skin (Ahn et al., 2008b; Jin and Kang, 2010; Tam and Stepien, 2011). They also can trigger NFκB and/or mitogen-activated protein kinase signaling pathways (MAPK/ERK) (Ahn et al., 2008a). Therefore, these cells are not only melanin-producing cells but are also immunocompetent cells, expressing important surface markers such as intercellular adhesion molecule-1 and CD 40 (Lu et al., 2002). CD40 antigen has a crucial role in the T-cell-dependent activation, differentiation, and proliferation of B cells. Additionally, in the process of melanization, several intermediate molecules and melanin are released, which have strong antimicrobial activities (Burkhart and Burkhart, 2005). Like keratinocytes, melanocytes also display antigen presentation and phagocytosis (Le Poole et al., 1993).

In the same way, adipocytes also play important immunological functions capable of recruiting and activating immune cells and not only energy storage and endocrine functions. Like keratinocytes and melanocytes, they also release diverse cytokines such as leptin, resistin, TNF-α, and IL-6 to regulate the differentiation and function of B and T lymphocytes. Adipocytes also have the ability for antigen presentation in T-cell-mediated adaptive immunity (Song and Deng, 2020). The immunological function of non-immune cells has received increased attention, but the immunological potential of these cells is far from fully understood. In particular, the essential roles of non-immune cells in inflammatory processes and host protection should be a goal of more in-depth research.

Immune responses to skin discontinuities (wound healing)

At the beginning of the century, Engwerda and Kaye proposed the concept of organ-specific immunity dividing the pattern of tissue immune responses into three specific groups: complex organ immune responses, barrier epithelium immune responses, and immunologically privileged organ immune responses (Engwerda and Kaye, 2000). The skin has almost the same organization all over the body, but certain regions acquired specific adaptations. In harmony with other tissues such as mucosal surfaces, skin can respond to infectious and non-infectious hostile agents through innate and adaptive immunity mechanisms.

In normal conditions, wound healing is characterized by 4 distinct phases: hemostasis, inflammation, proliferation, and remodeling. The process starts when an injury occurs in the skin, and consequently, the skin tissue isolates the area from the environment by forming a clot, preventing further bleeding. In this initial phase, designated hemostasis, the coagulation cascade is started, where the platelets will adhere to components of ECM constituents and release granular contents. The wound clot acts as a scaffold for keratinocytes to begin re-epithelialization and for the infiltration of immune cells (Quaresma, 2019). The inflammatory phase has the goal of avoiding the entrance of pathogens and preventing infections and more severe complications. In this phase, the infiltration of immune cells (such as neutrophils, monocytes, and lymphocytes) occurs, and high levels of pro-inflammatory mediators essential to recruit other immune cells from the periphery, are easily found (Nguyen and Soulika, 2019). Next, in the proliferative phase, a large expansion of skin-resident cells (including fibroblasts, endothelial cells, and keratinocytes) occurs. The proliferative phase is marked by high levels of angiogenesis, where the new blood vessels formed will gradually replace the fibrin clot. Otherwise, the migration of keratinocytes will restore the barrier function of the epidermis (Akita, 2019; Trinh et al., 2022). Both fibroblasts and myofibroblasts are essential to produce collagen (immature type III fibers) for the formation of new ECM. The remodeling phase can be considered the longest, being able to extend for more than a year, post-injury. The goal of this phase is to restore the normal architecture of the skin. The remaining macrophages in the wound produce and secrete matrix metalloproteases (MMPs) that are involved in the remodeling of ECM by eliminating any collagen excess (Trinh et al., 2022). This step is very important to reduce scar tissue. Lastly, the collagen maturation into the terminal collagen type I conformation is complete (Turksen, 2017).

A problem in any of the phases described previously can cause impaired wound healing, including nonhealing wounds, fibrosis, and scarring. Nonhealing wounds are very common in diabetic or cardiovascular patients and represent a challenge in the clinic, leading frequently to hospitalization (MacLeod and Mansbridge, 2016; Nguyen and Soulika, 2019). It is now understood that the incapacity of the chronic wound to heal is caused by both cellular and molecular anomalies, however, these precise mechanisms are poorly understood. It is well-accepted that nonhealing wounds rarely enter the proliferative phase of wound healing, perpetuating the inflammatory phase (MacLeod and Mansbridge, 2016). Some modifications in macrophage phenotypes and cytokine patterns (such as IL-1, IL-6, IL-8, and TNFα) are reported in the pathogenesis of nonhealing wounds. Macrophages are a key in the switch from the inflammatory stage to a reparative stage, depending on their phenotype as shown in Fig. 2. While the M1 macrophages have an active role in inflammation upon skin injury releasing pro-inflammatory mediators, M2 and M2-like macrophages induce anti-inflammatory, regulatory, and reparative functions aiming at total wound healing (Murray and Wynn, 2011). They have been described as intracellular signaling pathways that regulate the transition of M1 to M2 macrophages, including p38/MKP-1 and microRNA-21 (miR21). Active

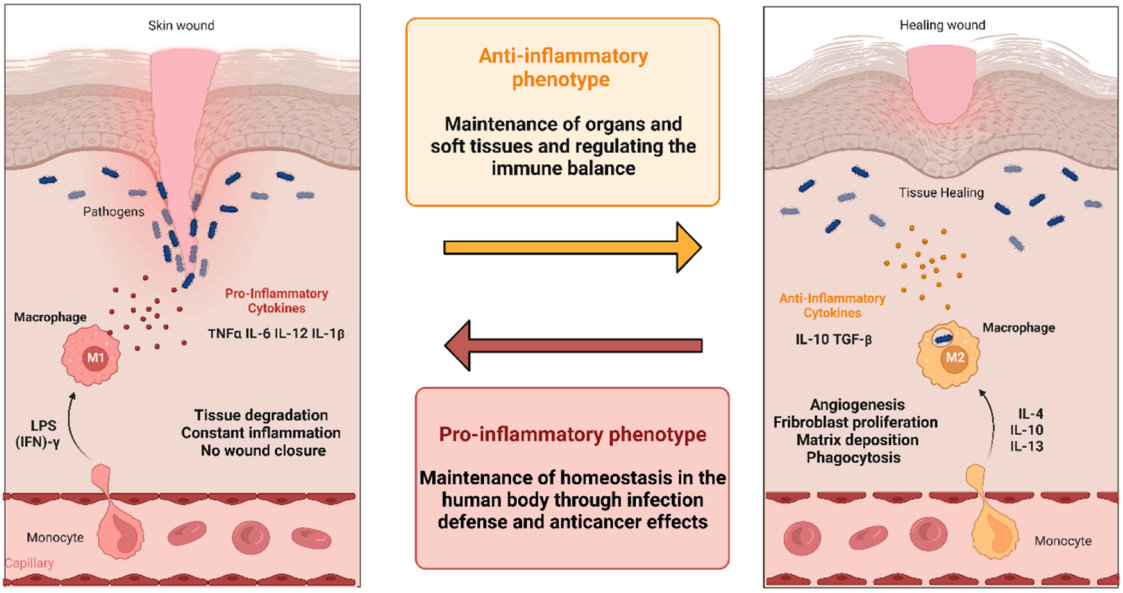

Fig. 2. M1 and M2 macrophages. Macrophages exert a variety of functions depending on their phenotype and are involved in the maintenance of human health and healing. M1 macrophages can be induced by IFN-γ and LPS, whereas M2 macrophages can be induced by IL-4, IL-10, and IL-13. M1 macrophages have pro-inflammatory, anti-infectious, and antitumor immunity properties; M2 macrophages display anti-inflammatory effects and tissue repair. M2 macrophages are also strong phagocytes, which act by scavenging debris and promoting both wound healing and angiogenesis. Created with BioRender.com.
Abbreviations IFN, interferon; TNF, tumor necrosis factor; LPS, lipopolysaccharide.

p38 regulates the production of inflammatory cytokines and at the same time induces miR-21 that activates protein kinase B (AKT), resulting in macrophage phenotype transition to M2 (Perdiguero et al., 2012, 2011). Failures in the healing process prevent this transition and the macrophage phenotype becomes unsuitable for the next healing stage, compromising the whole process of healing.

Impaired wound healing frequently leads to other complications, such as infections, severe pain in patients, and sometimes neuronal damage. Despite the efforts from the scientific community, a more in-depth understanding of the interactions between immune cells and skin-resident cells is crucial for new therapeutic approaches aiming at a faster healing process in chronic wounds.

Abiotic factors affecting the skin's immune system

Skin is constantly exposed to many injuries such as heat, mechanical stress, microbes, xenobiotics, or radiation. Despite these exogenous factors, endogenous factors including cell respiration and enzymatic oxidation require a coordinated balance with the number of reactive oxygen species (Mnich et al.) produced by the antioxidant defense mechanisms. When the balance is disrupted, the high production of free radicals will eventually lead to oxidative stress, associated with lipid peroxidation, oxidation of proteins, and DNA mutations (Lohan et al., 2015). Oxidative stress can promote adverse effects in several signaling pathways or chemical processes in cells, leading to premature skin aging, tissue damage, carcinogenesis, and/or immunosuppression (Forman and Zhang, 2021). When the skin is exposed to exogenous inducers of oxidative stress, the fibroblasts in the dermal layer are the first targets, causing not only a reduction in the biosynthesis of collagen but also a degradation of the pre-existent collagen. When this process is compromised, also aberrant homeostasis of collagen will succeed, which eventually will result in the development of aging characteristics related to the loss of skin elasticity. In this context, ROS are believed to activate proliferative and cell survival signaling that can alter apoptotic pathways that may be involved in the pathogenesis of several skin disorders including photosensitivity diseases and some types of skin cancers (Buranasudja et al., 2021; Forman and Zhang, 2021; Li et al., 2017).

Ultraviolet radiation (Malaisse et al.) is considered the major promoter of skin aging, and more than that, it is associated with several changes in skin immune cells, directly affecting the immune responses in the skin. Inside the UVR, only type A and B reach the surface of the earth, however, with the climate changes the damaging effects of UVR may become increasingly higher (Bernard et al., 2019; Rass and Reichrath, 2008). The effects of UVR on skin have been described in detail over the years and are associated with immunosuppression and cancer development (Fisher and Kripke, 1977; Garssen et al., 2001; Wolf et al., 2009). Deep molecular changes are also extensively reported including DNA damage and generation of ROS, affecting not only the skin but all of the human body (Halliday, 2005). These molecular alterations can, in the same way, affect directly or indirectly, the immune cells promoting the production of different molecules related to the immune system, such as IL-10, IL-4, and prostaglandin E_2 (PGE_2) (Paz et al., 2008). The role of UVR on both regulatory T-cells and B-cells, mast cells, and tolerogenic dendritic cells has also been demonstrated in the process of immunosuppression in animal models (Byrne and Halliday, 2005; Byrne et al., 2008; Paz et al., 2008; Schwarz and Schwarz, 2010). Other non-immune cells can be affected by UVR; keratinocytes and melanocytes may suffer mutations that will eventually lead to malignant transformation. A process known as "immunosurveillance" which in normal conditions detects malignant transformation and consequently promotes the elimination of cancerous cells by immune cells, can be compromised in cases of dangerous UVR exposition. In these conditions, the capacity to fight cancerous cells is severely affected (Leiter et al., 2020). Regardless of these effects, UVR also promotes inflammation responses through activation of the pro-inflammatory factor NFκB, upregulates the activator protein (AP-1), and induces AP-1-regulated matrix-degrading metalloproteinase genes. Consequently, MMPs will degrade collagen and ECM components, promoting skin aging (Ding et al., 2010; Food and Drug Administration, 2012). The toxic effects of UVR, blue light, and infrared radiation are summarized in Fig. 3.

Preventing skin damage has gained more attention over the years and new molecules with antioxidant, anti-inflammatory, anti-mutagenic, anti-carcinogenic, and immunomodulatory activities are an asset in this field. Increasing the sun protection factor (SPF) value of synthetic sunscreens without increasing toxicity represents a major challenge in the near future.

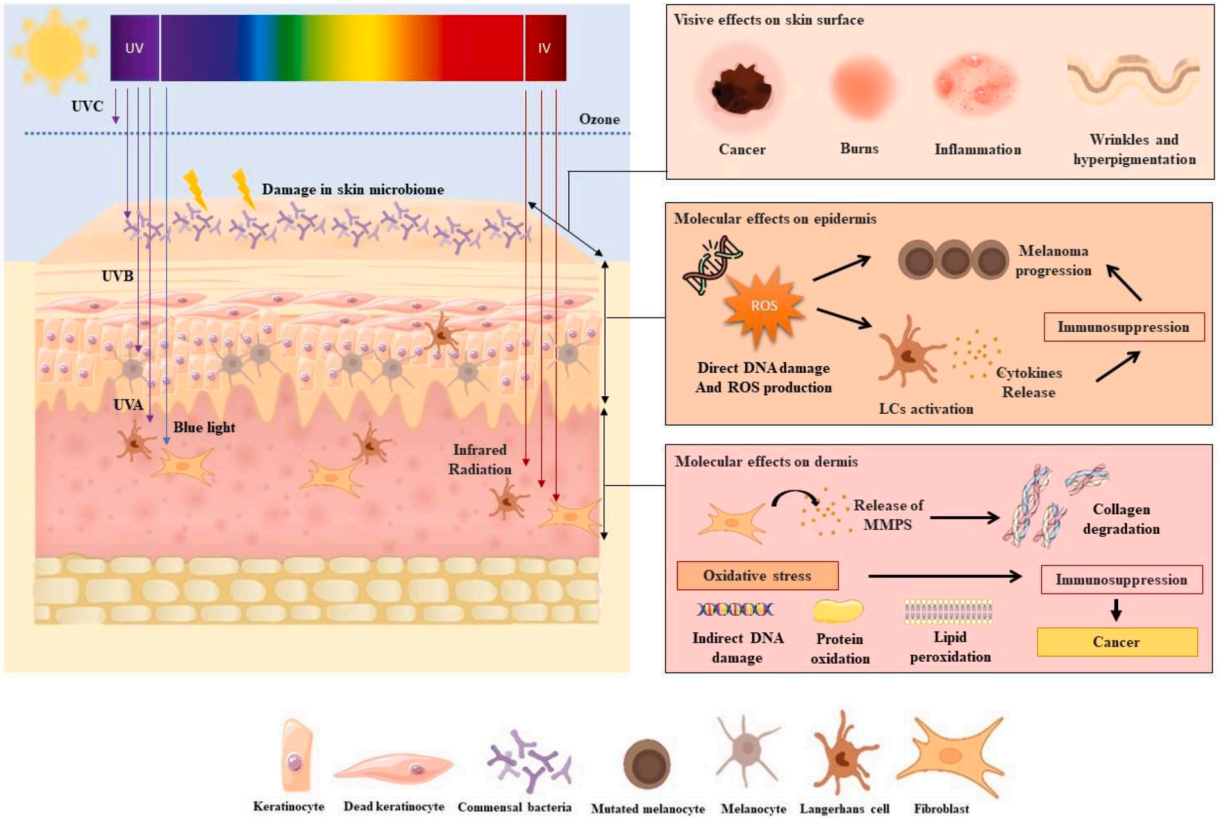

Fig. 3. Toxic effects of UVR exposure on the skin. The different types of radiation penetrate the skin and promote several modifications at molecular levels. The effects of UVB radiation are more superficial, but dangerous at the same time, causing burns and skin inflammation, destroying the skin barrier, altering the skin microbiome, and promoting hyperpigmentation by the high production of melanin by melanocytes. They can directly damage the DNA and generate ROS, which can lead to immunosuppression and skin cancer (melanoma). The increase of melanin released by melanocytes will consequently promote hyperpigmentation UVA, blue light, and infrared radiation can go deeper into the skin, they reach the dermis and promote significant modifications in the skin structure. The MMPs released by fibroblasts degrade the skin collagen, leading to the formation of wrinkles and contributing to premature aging. Oxidative stress is notable in proteins, lipids, and DNA, contributing to systemic immunosuppression and eventually, cancer. Created with BioRender.com.

The interplay between the skin microbiome and the immune system

Since birth, skin is colonized by highly variable microbial communities. Skin-resident microbes are crucial in the regulation of cutaneous homeostasis and the modulation of inflammatory responses. The balance between microbial communities and the host needs to be carefully balanced for healthy skin (Richardson et al., 2022). The skin microbiome has been deeply explored by researchers: *Actinobacteria, Bacteriodetes, Firmicutes*, and *Proteobacteria* have been identified as predominant phyla depending on the body site. In sebaceous (oily) sites it is possible to find *Staphylococci* and *Corynebacteria* species. On the other side, dry sites are mainly dominated by *Corynebacteria, Flavobacteriales*, or β-*Proteobacteria* (*Timm et al., 2020*). In opposite to bacterial communities, fungal community composition is similar across core body sites. It is possible to identify fungi of the genus *Malassezia* at the core body and arm sites, whereas in foot sites a more diverse combination can be found, including *Aspergillus* spp., *Rhodotorula* spp., *Epicoccum* spp., *Malassezia* spp., and others. Bacteria are the most abundant kingdom across sites, and fungi are the least abundant. Several factors can influence the microbiome composition such as temperature, pH, moisture content, and the available resources for the metabolic needs of the microorganisms. In contrast to fungi and bacteria, colonization by eukaryotic DNA viruses is specific to the individual rather than the anatomical site (Byrd et al., 2018; Timm et al., 2020). The interactions between the resident microbial community prevent colonization by pathogenic bacteria but in some cases bacteria that are typically beneficial to their hosts become pathogenic. Changes in the microbiota (dysbiosis) are described in many skin diseases, including acne, eczema, atopic dermatitis, and others (Al-Rashidi, 2022).

Over the past years, the scientific community has found evidence of extensive communication between bacteria, skin cells, and immune cells. Until now, most of our understanding of host-microbe immune mutualism was derived from studies of the gastrointestinal tract microbiota. These interactions have also singular importance in skin barrier repair, reinforce the defenses against pathogens and decrease the level of inflammation. Variations in this epidermal ecosystem are associated with diverse skin immune hypersensitivity disorders, and more than that affect the healing process, particularly in patients with chronic wounds (Grice and Segre, 2011; Kennedy et al., 2017; Kobayashi et al., 2015). The precise mechanisms underlying the microbial contributions related to pathological conditions are currently unknown, but it is well-accepted that maintaining the interactions with immune cells is crucial for microbiome survival. Skin-associated bacteria, for example, *Staphylococcus epidermidis* is responsible for the production of numerous antimicrobial components that can limit the establishment of biofilms by pathogenic species. Indeed, the colonization of *Staphylococcus epidermidis* in the skin interacts with the immune cells, inducing the migration of IL-17a+ CD8+ T cells to the epidermis enhancing skin immunity (Meisel et al., 2018). A recent study suggests that complement, an important mediator of inflammation and immune responses, can modulate the skin microbiota at the gene expression level, but in the same way, the skin microbiota can also modulate the activation of complement. Assessing the skin microbiota is relatively easy, for this reason, it can be targeted by aiming the treatment of several pathological conditions where complement dysfunctions are present. For

example, complement therapies involving small peptide inhibitors are good candidates to be used as immunomodulators (Kohl, 2006). These molecules with therapeutic potential can mainly act in complement component C5a/complement component 5a receptor 1 (C5a/C5aR1) signaling pathway, and downregulate the expression of several proinflammatory mediators with special relevance for the treatment of psoriasis where the activation of the complement system is associated (Zheng et al., 2019). This signaling pathway also appears to maintain microbial diversity not only in the skin but also in the gut, but its specific mechanism requires further investigation (Levy et al., 2017; Zheng et al., 2019). In the same way, other innate immune components including TLRs, Nod-like receptors (NLRs), and antimicrobial peptides can modulate the skin microbiome and remain poorly investigated for this purpose. The interplay between these receptors and the microbiome is more understood for the gut in the context of gastrointestinal diseases, once they are the interface among the intestinal epithelial barrier, microbiota, and immune system (Frosali et al., 2015). Commensal bacteria and bacterial products such as lipoteichoic acid (LTA) are in constant contact with epidermal and dermal immune cells and can stimulate the TLRs on the surface of mast cells and promote their migration, maturation, and localization in the skin. Wang et al. (2017) observed the importance of a normal microbiome for the full maturation of mast cells and their antimicrobial ability. Indeed, the authors showed the role of LTA in the differentiation of mast cells, triggering the production of Stem Cells Factor (SCF) in neighboring keratinocytes that eventually will transmit the signal to mast cells. Interestingly, without keratinocyte-SCF production, mast cells cannot be present in the skin (Wang et al., 2017). Other populations of skin immune cells such as skin resident dendritic cells can be modulated by the skin microbiome, enhance innate barrier immunity and limit pathogen invasion (Naik et al., 2015). Exploring the interactions of commensal bacteria with the immune system components, including skin immune cells represents one step forward in our understanding of tissue-specific immunity and associated pathologies, promising new preventative, and therapeutic targets.

Natural products: How can they modulate the skin's immune system?

Since ancient times, natural products have been used as anti-inflammatory, antioxidant, analgesic, and antitumoral drugs. Currently, natural products are still important to support the development of new drugs for the most diverse diseases. Indeed, in cancer research, for example, there are many molecules with antineoplastic activity derived from natural sources. Compounds derived from natural products have already proved their efficacy as therapeutic agents in other diverse areas, such as metabolic disorders, cardiovascular diseases, inflammation, and neurological disorders (Ding et al., 2018).

In some cases, the main challenge is understanding if the chemistry and composition of these metabolites is associated with sampling. To obtain detailed results, a considerable number of samples are required, and particularly in marine-derived products sampling could be a problem. Nowadays, modern technologies have made it possible to achieve unexplored sea depths, also making the marine biota available to researchers. Polyphenols, polysaccharides, alkaloids, and peptides are examples of the huge diversity of molecules that we can find. The complexity of the natural molecules involves a synchronized effort from the interaction of multidisciplinary research areas with new sophisticated analytical and technical expertise to extract, isolate, identify, and turn them into promising leads. It is expected that NPs will continue to play a significant role in drug discovery, highlighting the importance of databases that offer detailed information on the chemical, physical, and biological properties of compounds.

Different from other conventional synthetic molecules, natural-derived molecules are characterized by a vast scaffold diversity and structural complexity. Chemically, they usually have a higher molecular mass, higher numbers of H-bond acceptors and donors, a larger number of sp^3 carbon atoms and oxygen atoms but fewer nitrogen and halogen atoms and higher hydrophilicity compared with synthetic molecules. These features can bring the same advantages to drug discovery. For example, the higher rigidity of the molecules can be valuable in new drugs for attacking protein-protein interactions. This characteristic is mainly appreciated for increasing the stability of the drug, being able to efficiently fill biological space, and targeting specific proteins (Atanasov et al., 2021). In the next chapter, we will focus on the different immunomodulatory mechanisms triggered by the principal classes of natural products in the skin.

Natural compounds have demonstrated their effectiveness in modulating the immune system in a pleiotropic manner, by regulating both the adaptative and innate immunological systems. For this reason, they are good candidates for molecules with immunomodulation capacity in the treatment of several immunologic and inflammatory conditions, including intestinal mucosal immune responses, allergic diseases, and antitumor immunity. Each different type of molecule targets and binds to specific receptors of immune cells, after that an intracellular signaling pathway is triggered that eventually will regulate or modulate the immune response (Carlet, 2001). The effects of NPs in the diet are currently well explored for the modulation of immune responses. They can affect epigenetic mechanisms, such as histone modification, regulatory DNA methylation, and microRNA-mediated posttranscriptional repression that modifies the expression of genes encoding crucial immune factors (Williams et al., 2017).

Polyphenols

A relevant number of studies have ascribed a range of biological activities such as anti-inflammatory, immunomodulatory, antioxidant, and anti-cancer to polyphenols. Most of these molecules are metabolites of plants and are also the most abundant group of chemicals in the plant kingdom. They can be classified according to their chemical structures into flavonoids such as flavones, flavonols, neoflavonoids, chalcones, isoflavones, anthocyanidins, and proanthocyanidins and nonflavonoids, such as phenolic acids, stilbenoids, and phenolic amides (Ding et al., 2018).

In general, a range of studies report the target receptors of polyphenols in immune cells such as mast cells, neutrophils, monocytes/macrophages, and T cells. For instance, the 67 kDa laminin receptor (67LR) is a target receptor of Epigallocatechin gallate (EGCG) and regulates the adhesion and inflammatory processes of these cells (del Corno et al., 2016; Fujimura et al., 2012). Other studies focus on baicalin (BA) target receptors: TLRs, T cell receptor (TCR) $\alpha\beta$, and IgM- (sIgM-) B-cell receptor, proving their efficacy in regulating adaptative and acquired immunity (Gong et al., 2011). The most frequently explored effects of the immunomodulatory capacity of polyphenols are related to cancer, virus, allergic diseases, and intestinal mucosal immune responses (Choi and Yan, 2009; de Leon et al., 2021; Xu et al., 2014; Yi et al., 2014). Polyphenols extracted from medicinal plants have revealed the ability of attenuate the NF-κB pathway and increase the NRF2 activity as showed by Notarte and collaborators for the plant *Uvaria alba*. The authors explored the inflammatory modulating properties of a Flavonol-Enriched *n*-Butanol fraction and found in vitro potential of attenuating proinflammatory mediators and cytokines in LPS-challenged RAW 264.7 macrophages. In the same way, the authors found the suppression of NO and PGE_2 by the downregulation of mRNA expression of iNOS and COX-2, respectively (Notarte et al., 2023).

In the skin, phenolic compounds have proved to be promising molecules in the prevention of skin disorders and in the reduction of the healing time (Karim et al., 2014). The antioxidant properties of polyphenols in the skin are well explored. Indeed, a range of molecules such as antioxidant vitamins (particularly vitamins C and E), curcumin, coenzyme Q, lipoic acid, melatonin, resveratrol, and other polyphenols have shown to be safe through the diet or external application in the skin

Table 1
Bioactivity and mechanism of action of different Polyphenols on skin cells and animal models.

Molecule/ compound	Cell /animal model	Bioactivity	Mechanism of action
Resveratrol	Human keratinocytes	Wound healing	IL-8 overexpression, ERK phosphorylation was inhibited, enhanced p65 and EGFR phosphorylation, c-Fos upregulation (Pastore et al., 2012).
	Human umbilical vein endothelial cells	Diabetic wound healing	Inhibition of hyperglycemia-triggered endothelial dysfunction. Restoration of the activity of the hyperglycemia impaired SIRT1 signaling pathway Pro-angiogenic effects involving the inhibition of FOXO1 and c-Myc expression (Huang et al., 2019a)
	Hypertrophic scar-derived fibroblasts	Apoptosis Anti-proliferative effects	Downregulation of mRNA expression of type I and III procollagen in fibroblasts, resulting in substantial decreases in hydroxyproline and collagen. Arrested cell cycle progression, triggered apoptosis in a dose- and time-dependent manner (ZENG, 2013).
Ascorbic acid	Mice	Anti-inflammatory Wound healing	Decreasing in the expression of pro-inflammatory mediators (IL-1 β, KC, TNF-α) and higher expression of wound healing mediators (TGF-β, VEGF) (Mohammed et al., 2016).
	Human neonatal dermal fibroblasts	Fibroblast proliferation and renewal	Increasing in IL-6 mRNA expression levels. Nanog and OCT4 gene expression. Decreasing in transcript levels of p27 (Mohammed et al., 2016).
Curcumin	Diabetic rats	Anti-inflammatory Wound healing	Reduction in the expression/levels of TNF-α, IL-1β and MMP-9 (Kant et al., 2014)
	Mice	Neoangiogenic effects Anti-inflammatory Wound healing	Downregulation of PI3K and pAKT and enhancing of the expression of IκB Macrophage polarization to M2-type (Dehghani et al., 2020)
Ferulic acid	Diabetic rats	Wound healing	Inhibition of the LPO and elevation on CAT, SOD, GSH and NO levels along with the increasing in serum Zn and Cu levels (Ghaisas et al., 2014)
Quercetin	Mouse	Angiogenic and anti-inflammatory Fibroblast proliferation	Decreasing in TNF-α, IL-1β, IL-6; upregulation on protein levels of Wnt and β-catenin; Increasing in VEGF and FGF expression (Mi et al., 2022)
	Mice and fibroblast cells	Antifibrotic Decrease scar formation	Increasing on surface αV integrin and decreased β1 integrin (Doersch and Newell-Rogers, 2017)
Cyanidin-3-*O*-glucoside	Mice	Anti-inflammatory UV protection	Decreasing on expression of COX-2 and IL-6 after UVB-induced chronic photodamage (Peng et al., 2020)
Epigallocatechin gallate	RAW 264.7	Anti-inflammatory	Decreasing of IL-1β and proteins of Notch signaling pathway (Notch-1, Notch-2, Cleave-Notch-1, and Hes-1 (Huang et al., 2019b)
	Diabetic mouse	Wound healing	Decreasing of IL-1β, TNFα, IL-6. Decreasing in Notch-1 and Notch-2 proteins (Huang et al., 2019b)

* CAT (catalase); FOXO1 (Forkhead Box O1); GSH (glutathione); LPO (lacto-peroxidase); NLRP3 (NLR family pyrin domain containing 3); SIRT1 (Sirtuin 1); SOD (superoxide dismutase).

(Cai et al., 2014; Sadowska-Bartosz and Bartosz, 2014). Detail descriptions of different polyphenols are shown in Table 1. The antioxidant activity of phenolics is associated with the inhibition of ROS generation and the reduction of chelated metal ions. Due to the clear link between ROS production and skin inflammation, polyphenols can mediate the inflammatory response through the neutralization of free radicals, ROS, and reactive nitrogen species (RNS), modulating the release of pro-inflammatory cytokines and interleukins (Pastore et al., 2009).

The application of polyphenols for the prevention of UVR-induced skin photodamage has been considered of great interest. Keratinocytes are essential players in the modulation of skin inflammation associated with UVR, being responsible for producing inflammatory mediators (cytokines, surface adhesion molecules, prostaglandins). Studies performed in these cells showed a significant improvement in blocking UVB-induced apoptosis and DNA damage. In the same study, the same compound (chafuroside B) showed the ability to suppress the production of UVB-induced immunosuppressive mediators, including TNF-α, PGE_2, IL-10, and mRNA expression of Receptor activator of nuclear factor kappa-B ligand (RANKL). In addition, the authors established that not only topical treatment but also routine consumption of chafuroside B in tea may offer some level of protection against the damaging effects of UVR in humans (Hasegawa et al., 2013). In the literature, there are other reports of different phenolic compounds that have shown protection of irradiated keratinocytes such as dihydrochalcone phloretin, veratric acid, afzelin, and luteolin, promoting in the same way, a decrease in the expression of inflammatory mediators (Shin et al., 2014, 2013a, 2013b; Wolfle et al., 2011). Potapovich and colleagues tested tree types of

plant-derived polyphenols (resveratrol, quercetin, verbascoside) in normal human epidermal keratinocytes (NHEK) and they detected molecular and cellular effects after the exposition to UVR. The authors induced the cells previously with UVR and pre- and post-treated them with polyphenols. The effects of polyphenols were less significant in pre-treated NHEK, and in opposite they enhanced UV-induced inflammatory and metabolic responses. However, the post-treatment with polyphenols eliminated pro-inflammatory cytokines and prevented UV-induced overexpression of IL-1 beta, IL-6 and COX2 mRNAs and Cyp1a1 and Cyp1b1 genes. The results obtained in the post-treatment with polyphenols suggest that they can be used as important components of post-sun skin care, but not as photoprotective agents (Potapovich et al., 2013). The potential of green tea as photoprotective agent also has been studied. The topical treatment with green tea extract decreased UV-induced p53 expression and the number of apoptotic keratinocytes (Mnich et al., 2009). Polyphenols can modulate the inflammatory response in keratinocytes through different signal transduction pathways, including NFκB, aryl hydrocarbon receptor (AhR), and EGFR–ERK pathway. NFκB is so far the most reported pathway due their major role in inflammation (Potapovich et al., 2011).

The diversity of these molecules has gained special interest also in anticancer therapies due to their pleiotropic properties on cancer and immune cells. Many studies also reveal the great potential of these molecules as micronutrients to protect against cancers. Polyphenols such as resveratrol, genistein, curcumin, and epigallocatechin showed ability to modulate the production of pro-inflammatory mediators in cancer cells (He and Sun, 2016; Sinha et al., 2016). Therefore, polyphenols could decrease several pro-inflammatory mediators and consequently, reduced the chronic inflammation that surrounds the tumor. The involvement of the immune system is described in all phases of the oncogenic process in a paradoxical cycle of both eradicating and supporting cancer cells (Jemal et al., 2010). Melanoma is an aggressive type of skin cancer, and its prevalence remains high, highlighting the importance of the search for effective treatments. IL-1β is an example of one of the critical cytokines that mediate cancer progression, immunosuppression, and chemoresistance. In metastatic melanoma cells, this cytokine is continuously activated and secreted mediating angiogenesis and macrophage chemotaxis, both crucial for sustaining the growth of melanoma cells (Focaccetti et al., 2019). Green tea polyphenol EGCG has shown potent anti-inflammatory bioactivity. The ability of this molecule to promote the decrease of metastatic melanoma cell growth, both in vitro and in vivo, has been described. These achievements are supported by the decrease of IL-1β secretion as well as the down-regulation of inflammasome molecules, and consequently the inhibition of caspase-1 activity. Therefore, decreasing the IL-1β contribution to the inactivation of the NFκB signaling pathway that eventually will lead to a decrease in cell proliferation (Ellis et al., 2011). Despite the promising activities as immunomodulatory compounds, few studies are performed on skin cancers with this proposal. For this reason, more studies should be developed to systematically analyze the potential of polyphenols in immunotherapeutic protocols for skin cancers.

Polyphenols also have shown good antimicrobial and regenerative activity, gaining a special interest in wound treatments (Graf et al., 2005). Due to their antioxidant properties, resveratrol, kaempferol, chlorogenic acid, and ferulic acid are some examples of phenolic compounds that promote wound healing in chronic wounds (Krausz et al., 2015). The upregulation of key anti-inflammatory gene pathways and enzymes by diverse types of polyphenols acts to decrease redox imbalance and promote the wound healing process, including extracellular matrix deposition, cell proliferation, and tissue remodeling. Exploring in more detail the different types of these molecules can bring us effective and economic options for the treatment of chronic wounds and prevent infections, especially in patients with impaired healing such as diabetic people (Johnson et al., 2022).

Polysaccharides

Polysaccharides are a class of macromolecules that have been isolated from different sources in nature such as plants, algae, fungi, animals, and bacteria. They are polymers of monosaccharides linked by glycosidic bonds and are by far, the most abundant class of natural polymers on earth. Due to their great availability, they are relatively inexpensive. These molecules are well-known for their multifaceted properties including, antioxidant, anticoagulant, antitumor, antiviral, and immunomodulatory, among others (Torres et al., 2019). These complex carbohydrates have also several chemical properties that support their applications, such as non-toxicity, biodegradability, biocompatibility, high chemical reactivity, poly-functionality, chirality, chelation, and adsorption capacity. They can also be used as membranes, gels, hydrogels, and even as drug delivery systems controlling the release of active drugs (Ribeiro et al., 2019).

These molecules have been extensively used in the cosmetic industry, mainly because of their ability to maintain the integrity and barrier function of the skin. The protective effects of hyaluronic acid, for instance, obtained by biotechnological processes could improve the efficiency of the formulations, maintaining the good health of the skin. In dermatology are frequent use as vehicles in formulations for the development of gels, ointments, or lotions (Maia Campos et al., 2021). Despite their applications in cosmetics, the interactions between polysaccharides and the skin's immune system are not entirely understood. In general, polysaccharides can promote several immune effects, mainly the activation and/or the improvement of macrophage response by increasing ROS production and the release of several cytokines (Shen et al., 2017). In fact, several polysaccharides have been used clinically to improve the body's immune function such as *Cheonggukjang* polysaccharides, *Ginseng* polysaccharides, and *Ganoderma atrum* polysaccharides. The number of in vitro and in vivo studies proved their non- or low toxicity, immunoregulatory capability, and few side effects compared to synthetic drugs (Chen et al., 2018; Park et al., 2019; Shukla et al., 2021; Zhou et al., 2018).

β-glucans

Within the diversity of polysaccharides, β-glucans from diverse origins have attracted research owing to their large spectrum of interesting biological activities including anticancer, antimicrobial, antioxidant, anti-inflammatory, and immune-modulating properties (Du et al., 2015; Rieder and Samuelsen, 2012). The bioactivity is dependent on the source of β-glucans (fungi, bacteria, algae, etc.), and more than that, it is dependent on their molecular weight, solubility, degree of branching, and the charge of polymers, and structure in aqueous media (Du and Xu, 2014; Rahar et al., 2011). β-glucans are natural cell wall polysaccharides of D-glucose monomers linked through β-glycosidic bonds and they can present multiple molecular structures with a high degree of complexity (Zekovic et al., 2005). In addition, the immune responses caused by β-glucans are also dependent on the type of cells and receptors involved. Therefore, not all β-glucans will show immunomodulatory activity, such as cellulose ((1,4)-β-linked glucan). It is important to note that high structural variability and sometimes the low purity of these molecules can also directly affect the binding to receptors and trigger different signaling pathways, leading to limitations in the research. For this reason, consistent well-designed experiments are necessary to correctly understand the receptor binding, the signaling pathway, and the activated immune responses induced by pure β-glucans (Chen and Seviour, 2007).

Several membrane-bound immune receptors that recognize β-glucans are described namely, the PRRs family, such as scavenger receptors, lactosylceramide (LacCer), complement receptor 3 (CR3); CD11b/CD18), dectin-1, and TLRs (Camilli et al., 2018). Some of these receptors are also expressed in immune cells (macrophages, neutrophils, DCs, and some T-cells, but not in NK cells). The signaling pathways are frequently mediated by the spleen tyrosine kinase (Syk), phosphatidylinositol-3

kinase (PI3K), and myeloid differentiation primary response gene 88 (MyD88) that eventually promote different immune responses (Ina et al., 2013). In the case of Lentinan (β-glucans derived from *Shiitake mushrooms*), their potential for cancer treatment is reported, promoting innate immune responses such as the induction of inflammatory cytokines, activation of phagocytosis, and ROS production (Ina et al., 2013; Jeff et al., 2013). β-glucans derived from the *mushroom Coriolus versicolor* have been known for their immune stimulator effects, inducing macrophage phagocytic activity (Kang et al., 2013). Otherwise, β-glucans from barley have shown significant antioxidant activity, exerting hydroxyl radical scavenging activity across a wide range of molecular sizes (Kofuji et al., 2012). β-glucans extracted from green eukaryotic microalgae also show stimulatory activity on macrophages and the proliferation of monocytes (de Jesus Raposo et al., 2014). The extraction of β-glucans from the *Laminaria* genus has shown more advantages than glucans obtained from other algae, because they have low molecular complexity, conferring benefits to biological activity including potent immunostimulatory effects, affecting both natural and adaptive immunity (Kofuji et al., 2012; Lipinski et al., 2013).

In the skin, β-glucans from diverse sources have revealed very promising results in diverse conditions. Topical application accelerates wound healing by stimulating tissue regeneration, collagen deposition, reepithelialization, and increasing wound tensile strength (Majtan and Jesenak, 2018). These molecules have shown properties of wound healing and repair, involving macrophage release of wound growth factors. Consequently, these wound growth factors will, directly and indirectly, modulate fibroblast activity and collagen biosynthesis. Collagen production is associated with the reduction of fine lines and wrinkles, improving the elasticity of facial skin. There is also evidence of the ability of β-glucans to penetrate the skin deeply and promote cellular changes (Pillai et al., 2005). The current data suggest that β-glucans can induce epithelialization, angiogenesis, fibroblast maturation, collagen, and ECM deposition as well as enhance surveillance for DNA-damaged skin. For these reasons, the interest in these molecules for skin rejuvenation is high. Other non-immune cells also express the receptors for β-glucans binding, such as keratinocytes. When β-glucans bind to Dictin-1, cell migration, and proliferation of keratinocytes occurs, enhancing wound re-epithelialization (Clark and Goldston, 2020; van den Berg et al., 2014). Another important function of β-glucans in the skin appears to be related to oxidative stress. Some studies demonstrated that these molecules increased the synthesis of the protective enzymes: superoxide dismutase and catalase as well as they upregulated the superoxide, hydroxyl, peroxide, and peroxynitrite scavenging activity. Since antioxidants can block UV-induced ROS generation; therefore, β-glucans should be considered good candidates for sunscreen formulations (Du et al., 2014).

More extensive research should be performed to understand the mechanisms underlying the immune responses presented by β-glucans for further practical applications. The variety of studies using crude extracts rather than purified β-glucans hinders the interpretation of data, highlighting the importance of good practices of extraction and purification.

Other polysaccharide-based formulations

Beyond the interesting biological activities shown by polysaccharides, they are also ideal candidate materials to construct drug delivery systems (DDSs) and develop wound dressings for the treatment of chronic and infected wounds. Tissue engineering has made excellent efforts to find good alternatives to traditional topical dresses, which usually offer acceptable absorption but also provide desiccation of the wound and can intensify skin damage when removed. Different types of solutions have been explored, such as hydrogels, hydrocolloids, films, and membranes, each one with specific applications in different types of wounds. It is expected that more advanced wound dressings can improve the safety and comfort of treatments, decreasing the dose and treatment occurrence. Infection and biofilm formation are two of the principal obstacles to wound healing, it is urgent the development of new strategies to treat infections being polysaccharides, including chitosan, fucoidan, alginate, carrageenan, among others, good materials for these proposes (Shen et al., 2021). The excellent biocompatibility of natural-derived polysaccharides made them also viable alternatives to synthetic materials.

Alginate is largely extracted from brown algae (such as *Ascophyllum nodosum, Laminaria hyperborea*, and *Macrocystis pyrifera*). It is comprised of α-l-guluronic acid and β-D-mannuronic acid, and it is an anionic and hydrophilic copolymer that forms gels by complexation with divalent cations, typically Ca^{2+}. The hydrophilic nature of this material allows multiple forms, including electrospun scaffolds, beads, blends, films, dressings, gels, hydrogels, microspheres, nanoparticles, etc. More than that, its biocompatibility, availability, and high absorption capacity make alginate a promising material for wound dressings (Kumar et al., 2019; Lee and Mooney, 2012). Diverse biological activities are linked to alginates, including the antimicrobial, anti-inflammatory, and immunomodulatory properties that have extreme relevance in the treatment of chronic wounds. Diverse clinical studies are published about alginate-based formulations for wound healing, such as the silver-releasing hydrogenate dressing (Silvercel) designed to treat patients with pressure ulcers (Meaume et al., 2005), and the antimicrobial dressing with silver alginate powder for the treatment of chronic wounds (Woo et al., 2012). Despite the high price, hydrogel is the most promising alginate form once it can absorb the excessive exudate, decrease the local pain by its cooling effect, and ultimately, it does not adhere to the wound (Barbu et al., 2021). Alginate hydrogel is frequently used to hold other active compounds, such as drugs with antimicrobial properties supporting the idea that it also can act as a carrier for bioactive compounds (Babavalian et al., 2015).

Chitosan is another material with interesting properties for chronic wound treatment due to its excellent biocompatibility, low toxicity, and immunostimulatory activities. This material is a linear hydrophilic amino polysaccharide found after partial alkaline deacetylation of chitin. After cellulose, chitin is the most abundant polymer found in the cells wall of fungi and in the exoskeleton of some living organisms like crustaceans. Chitosan is the most studied material for the designer of wound dresses, but it also can be used for incorporating antimicrobial compounds (Costa-Pinto et al., 2021). Different from alginate, chitosan has a cationic nature allowing its vast applications, such as bind and release growth factors (Saravanan et al., 2016). Several studies have demonstrated its ability to modulate and regulate cellular processes, in particular processes related to immunity. Between them is the ability to promote the migration of immune cells such as polymorphonuclear neutrophils and dermal fibroblasts, respectively (Younes and Rinaudo, 2015). Chitosan has been prepared in diverse forms, for example, chitosan acetate for the formulation of bandages with healing properties tested in an animal model (Burkatovskaya et al., 2006); hydrogel formulations loaded with bioactive compounds (such as colistin) to treat wound infections (Zhu et al., 2017); carboxymethyl chitosan nanoparticles used in photodynamic therapy against S. aureus and P. aeruginosa (Sun et al., 2019); thermosensitive chitosan/gelatin hydrogels loaded Adipose-derived stem cells (ASCs) to secrete several types of angiogenic growth factors (Cheng et al., 2017).

Hyaluronic acid (HA) is another polymer with significant importance and high popularity in the cosmetic industry. It is the main component of ECM with a simple structure and large molecular size that differentiate it from other glycosaminoglycans. Due to their availability, biocompatibility, and low toxicity, this polymer is also suitable for diverse biomedical applications In the skin, this molecule plays a crucial role in cellular migration and inflammatory pathways during tissue regeneration (Gupta et al., 2019). In the first stage of the inflammatory phase HA is the major component of the edema fluid, also responsible for the recruitment of immune cells such as neutrophils (Tavianatou et al., 2019a). Indeed, HA is central in all stages of wound healing having both pro and anti-inflammatory properties. It has been proven that high

molecular weight hyaluronic acid (HMWHA) displays anti-inflammatory activity and low molecular weight degradation products of HA (LMWHA) show pro-inflammatory activity. LMWHA bind to TLRs that are responsible for the activation of NFκB pathway, releasing pro-inflammatory cytokines. The release of inflammatory cytokines contributes to the fragmentation of HMWHA in LMWHA (Litwiniuk et al., 2016). In the last stage of the inflammatory phase, LMW-HA and fibronectin promote fibroblast invasion, essential for collagen deposition (Webber et al., 2009). At least, LMWHA has also an important role in the re-epithelization phase, interacting with keratinocytes for the regulation of this process (Aya and Stern, 2014). The topical applications of HA are currently explored to accelerate wound healing (Tavianatou et al., 2019a) and to treat skin infections, such as *S. aureus*-induced surgical-site infection (Park et al., 2017). Despite these results, the effects of HA in keratinocytes proliferation and differentiation are not clear and still controversial. Malaisse and co-authors found that inhibition of HA synthesis with 4-methylumbelliferone did not change the expression of the epidermal differentiation markers. They evaluated the involucrin, keratin 10, and filaggrin expression during tissue reconstruction, which are important markers of tissue regeneration (Malaisse et al., 2016). HA can also bind to cells through the membrane receptors CD44, Receptor for HA-mediated mobility (RHAMM), and Intercellular Adhesion Molecule 1 (ICAM-1). HMWHA can irreversibly bind to CD44 receptor and activate RhoA-like RhoGTPase signaling pathways that indeed can promote cell proliferation and migration. This phenomenon does not happen with LMWHA, which bond in a more reversible and weaker way, and activate Rac1-like pathways that support cell adhesion and differentiation (Bourguignon, 2014; Tavianatou et al., 2019b). The role of HA and skin cells proliferation, differentiation, and migration needs further investigations also considering its molecular sizes.

More than that, HA can be used as a carrier to locally deliver active compounds, such as antioxidants and growth factors that together will improve the wound healing capability. For example, a study performed with HA-based hydrogel with EDTA−Fe^{3+} complexes incorporated with platelet-derived growth factor (PDGF-BB) was successfully employed to treat wound infection triggered by *E. coli* (Makvandi et al., 2020; Tian et al., 2018). Different wound dressings are also currently available to be used in the clinic, such as Hyalomatrix®, Hyalosafe®, and HylaSponge® System. These wound dressings hold the necessary technologies to provide tissue regeneration, protection, and hydration to the wound site (Graca et al., 2020). Other interesting characteristic, namely related to Hyalosafe®, is the ability to promote the proliferation of epithelial cells in second-degree superficial burns. However, despite significant efforts in HA-based wound dressings, still present some limitations such as high production costs, low mechanical stability, and in some cases, limited cell adhesion/proliferation (Longinotti, 2014).

These and other polymers have made excellent progress in the development of wound dressings and drug delivery systems (Table 2 shows several examples about wound dressings). The synergetic effect of the polymers and the combined compounds can be responsible for the good results obtained so far, suggesting that they can be used as first-line treatment or as adjuvant therapy.

Table 2
Applications and properties of several polysaccharides for wound dressings.

Dressing composition	Active compound	Application/ properties	Ref.
Alginate	Asiaticoside (from the plant *Centella asiatica)*	Wound healing	(Sikareepaisan et al., 2011)
Alginate	Ibuprofen	Anti-inflammatory	(Thu et al., 2012)
Alginate	Gentamicin	Wound infection	(Ng and Leow, 2015)
Chitosan	Minocycline hydrochloride	Severe burn wounds (Antibiotic)	(Aoyagi et al., 2007)
Chitosan	Procoagulant (polyphosphate) and an antimicrobial (silver)	Hemorrhage (Hemostatic and antimicrobial)	(Ong et al., 2008)
Chitosan	Epidermal growth factor	Burn wound healing	(Alemdaroğlu et al., 2006)
Chitosan/ Alginate	*Aloe vera* gel and silver nanoparticles	Antibacterial	(Gómez Chabala et al., 2017)
Hyaluronic acid	Arginine Epidermal growth Factor	Wound healing	(Matsumoto and Kuroyanagi, 2010)
Hyaluronic acid	Arginine Vitamin C derivative Epidermal growth Factor	Wound healing	(Shimizu et al., 2014)
Hyaluronic acid and collagen	Epidermal growth factor	Diabetic wounds	(Kondo et al., 2012)
Xanthan	Silver nanoparticles	Wound infection	(Huang et al., 2017)

Lipids and fatty acids

Lipids, together with proteins and carbohydrates, are among the most vital nutrients for living organisms. They have distinct biological functions that can be applied for biomedical purposes. Chemically, lipids are hydrophobic and sometimes amphiphilic molecules (with both hydrophilic and hydrophobic properties), allowing themselves to arrange in the biophysical environment as bilayer structures. In the biological context they are mainly known as the building blocks of cellular membranes (phospholipids and cholesterol derivatives) and as molecules capable of storing energy (triglycerides), but they are likely involved in different cellular signaling pathways related to cell metabolism, proliferation, and apoptosis (Park et al., 2021). There are a considerable number of diseases associated with lipidic deregulations, including diabetes, cancer, obesity, neurodegenerative, autoimmune, and cardiovascular diseases suggesting they can be used both as bioactive molecules and molecular targets (Franky Dhaval et al., 2008; Matsuzaki et al., 2011; Missala et al., 2012; Park et al., 2021).

Specific lipids also contribute to maintaining the structure and function of skin from the surface to the hypodermis, where each layer contains different types of lipids with important roles to play. The stratum corneum comprises approximately 10 – 20% free fatty acids, 25% cholesterol, and 50% ceramides (sphingolipids) that together with corneocytes and other proteins contribute to the normal barrier properties of the skin (Feingold and Elias, 2014). Ceramides have received more attention from researchers because their lower levels are frequently associated with atopic dermatitis, psoriasis, and xeroderma pigmentosum (Moore and Rawlings, 2017; van Smeden et al., 2011). The topical application of ceramides is currently used in many formulations to improve the barrier function of the skin (Draelos and Raymond, 2018). Otherwise, phospholipids are not found in the stratum corneum, but they can be found in the viable epidermis and dermis layers, and particularly, they are the main subclasses present in viable keratinocytes (Sjovall et al., 2018). Abnormalities in the levels of phospholipids have also been observed in pathological skin conditions (Pietrzak et al., 2010). Most deep information related to skin diseases and lipidic deregulations is represented in Table 3. The skin has a unique lipidome, different from other organs the sebaceous gland produces exclusive species of lipids that there are not in other organs of the body. The accumulation of squalene, the synthesis of sapiens acid, and the presence of long-chain branched, or hydroxylated fatty acids are rare in other organs and very specific to the skin (Knox and O'Boyle, 2021).

In general, the lipids present in skin cosmetic formulations are intended to improve the protective barrier of the skin and maintain it hydrated and soft. Nowadays, a considerable number of lipids in cosmetic formulations are derived from plant origin or obtained by biotechnological processes. Oils, waxes, or their derivates are easily found in cosmetic emulsions. The oils can be obtained from different

Table 3
Lipidic deregulations in common skin conditions/diseases and promising achievements for lipidic deregulations.

Skin conditions/ diseases	Lipidic deregulations	Targeting lipidic deregulations
Atopic dermatitis	Reduced levels of total ceramides and C20–26 fatty acids (Proksch et al., 2003)	Moisturizing agents containing ceramides enhance the barrier function (Jung et al., 2021; Lodén, 2003)
Psoriasis	Reduced ceramides level with long-chain fatty acids (Kim et al., 2022) Reduced levels of oxidized and native ceramides (Tyrrell et al., 2021) Increased concentrations of free arachidonic acid (Hammarstrom et al., 1975)	Emollients containing ceramides (von Martial et al., 2021) Lipid-based nanoparticles for topical delivery of Antipsoriatic agents (Almeida et al., 2022) ω−3 Fatty acid-based lipid infusion in patients with chronic plaque psoriasis (Mayser et al., 1998)
Acne vulgaris	Extremely high levels of DAGs (Camera et al., 2016) Increased levels of fatty acids, squalene, cholesterol, and wax esters (Camera et al., 2016) Increase in the relative number of Ceramides (mainly in infant and adolescent patients) (Drakou et al., 2021)	Topical applications of 8% omega-ceramides to complement the treatment with isotretinoin (Cannizzaro et al., 2018) Topical formulations containing Phytosphingosine (Ni Raghallaigh et al., 2012)
Rosacea	Increased amounts of fatty acids (C14:0), low levels of the long-chain saturated fatty acids (C20:0, C22:0, C23:0, C24:0), and monounsaturated fatty acid (C20:1) (Draelos, 2017)	Moisturizers mimic intercellular lipids composed of sphingolipids, free sterols, and free fatty acids (Wang et al., 2020)
Aged and dry skin	Decreased ceramide levels Reduction in squalene, wax esters, cholesterol, and triglycerides (Wang et al., 2020)	Vitamin C covalently conjugated to squalene is suitable for cream formulations (Gref et al., 2020) 82% Squalene formulations with antioxidant and photoprotection properties (Lacatusu et al., 2018) Oat-derived phytoceramides (Tessema et al., 2018) Formulations containing ω−3 and ω−6 fatty acids (Petruk et al., 2018)

sources in nature such as nuts, fruit seeds, and vegetables. Among these, vegetable oils are the most frequently used in cosmetics as emollients, preventing water loss and leading to the reduction of skin inflammation (Ahmad and Ahsan, 2020). Due to the chemical diversity found in plant oils, a high number of pharmacological activities are available, linked to the lipidic composition and fatty acids profiles. The chemical compositions of plant oils comprise mainly triglycerides with various fatty acid chains and small fractions of free fatty acids (FFAs). The plant oils by themselves do not penetrate further than the first few layers of the stratum corneum, they remain at the surface of the skin, and form an occlusive layer. Nevertheless, some conditions such as the manufacturing process can increase the FFAs content in the formulations. In other cases, FFAs are added to the formulations as emollients or emulsifying agents. Several studies had shown that some monounsaturated FFAs, particularly oleic acid can penetrate SC, disrupting the skin barrier, and when applied topically during a long period can induce dermatitis (Mack Correa et al., 2014) (Jiang and Zhou, 2003; Kezutyte et al., 2013). However, oleic acid can also act as a permeability enhancer for the different compounds present in plant oils such as vitamin E or transepidermal drug delivery, improving other abilities of the compounds (e.g., antioxidant potential) (Kato and Takahashi, 2012). Other studies explore the role of fatty acids in skin inflammatory responses. When topically applied to skin wounds, oleic acid can improve the closure of the wound faster than linoleic and linolenic acid, with a decrease in the production of nitric oxide (Malaisse et al.) in the wound site (Cardoso et al., 2004). Unsaturated fatty acids such as linoleic and linolenic acids are crucial arachidonic acid precursors, being important inflammatory mediators. The oleic and linoleic acids also promoted the in vitro release of pro-inflammatory cytokines by rat neutrophils during the wound healing process. The release of cytokines was followed by an increasing in the number of neutrophils that migrated to the wound healing site. It was observed that the wound mass increased, evidencing the effect of these fatty acids on cell migration (Pereira et al., 2008). In the mase way, Cardoso *et al.* also demonstrated the ability of oleic acid to induce the release of cytokines, mainly TNF-α and IL-17. Elevated levels of IL-10 in wounds treated with oleic acid also were observed, followed by reduced prostaglandin-endoperoxide synthase 2 (COX2) gene expression. In fact, IL-10 is an important mediator of the inflammatory process, inhibiting some pro-inflammatory pathways. The authors suggested that an increase in the IL-10 production balanced the pro-inflammatory effects of IL-17, modulating the inflammatory process of the treated wounds with oleic acid and, eventually resulting in faster wound healing (Cardoso et al., 2011). These results together suggest a relevant role and potential therapeutic applications for fatty acids on skin wound healing. Table 4 summarizes the most abundant fatty acids in different plant oils, as well as other important chemical compounds present with relevant bioactivities in skin conditions.

The polyunsaturated fatty acids (PUFA) found in Algae (macroalgae and microalgae) also have gained more attention for the development of cosmeceuticals and potential applications in a range of skin inflammatory diseases. The algae oils rich in essential omega-3 and omega-6 PUFA are already used in cosmetic formulations with hydrating, emulsifying, emollient, and whitening properties. The use of Algae lipids as antioxidant and anti-inflammatory products is less explored but they can be important in diverse skin diseases characterized by exacerbated inflammatory responses or chronic inflammation. More than that, Algae lipids are a sustainable alternative to replace ingredients of animal origin (Conde et al., 2022). Different bioactivities have been described, namely antioxidant, antimicrobial, anti-inflammatory, and anti-proliferative properties (Lopes et al., 2021). Lipid-enriched extracts have shown high antioxidant activity, inhibiting the expression of enzymes involved in the regulation of oxidative stress, such as metalloproteinases. Studies performed in dermal fibroblasts showed the photoprotective effects against UVB radiation of the ethanolic extracts of Arthrospira platensis, inhibiting the expression of metalloproteinases (Lee et al., 2017). Similar results were obtained with fucosterol from *Sargassum fusiforme* that decreased the UVB-induced production of MMP1 and IL-6 in fibroblasts (Hwang et al., 2014). In general, sterols derived from algae have been shown to downregulate the expression of MMPs by modulating mitogen-activated protein kinases (MAPKs) (Kim et al., 2013). Lipids derived from algae can also modulate inflammatory effector molecules including cytokines (*e.g.*, IL-6, TNF-α), and trigger inflammatory signaling pathways (*e.g.*,NFκB). A very promising study demonstrated the effects of macroalgae *Sargassum cristaefolium* ethanol extract on a skin mice model. Thus study confirmed the photoprotective activity against UVR; treatment with the extract, induced skin healing after UVR exposure. I was validated the inhibition of pro-inflammatory TNF-α and IL-6 expression and an increase in the anti-inflammatory IL-10 (Prasedya et al., 2020). Unfortunately, the study did not explore the identity of bioactive lipids, being impossible to establish a relationship between lipidic profile with bioactivities. Few studies are available exploring the bioactivities of lipids, in particular, algae lipids in skin cells, highlighting the need for new studies aiming at the application of these molecules in the treatment of skin inflammation and chronic inflammation.

Peptides

Peptides are versatile molecules with high cosmeceutical interest,

Table 4
Chemical composition of different plant oils for skin applications.

Plant Oils	FA composition	Other important chemical compounds	Effects on skin
Olive oil (Fruits of *Olea europaea* trees)	Oleic acid, with smaller quantities of other fatty acids such as linoleic acid and palmitic acid (Nasopoulou et al., 2014)	Sterols, carotenoids, triterpenic alcohols, and phenolic compounds (Nasopoulou et al., 2014)	Anti-inflammatory, antioxidative, and promoting dermal reconstruction (Donato-Trancoso et al., 2016) Detrimental effects on SC integrity and skin barrier function (Danby et al., 2013)
Coconut oil (*Cocos nucifera*)	FFAs including lauric acid, myristic acid, palmitic acid, caprylic acid, capric acid, oleic acid, linoleic acid, and stearic acid (Adenike et al., 2019) (Sahle et al., 2015)	Sterols, phenolic compounds (Ngampeerapong et al., 2018)	Improve skin barrier function (Evangelista et al., 2014) High antioxidants activity (Ahmad et al., 2017) Induce fibroblast cell growth and proliferation (Ahmad et al., 2017) Wound healing improvement (Ahmad et al., 2017) Photoprotection (Kaur and Saraf, 2010)
Argan oil (*Argania spinosa*l.)	Oleic acid, linoleic acid, palmitic acid, and stearic acid (Simoes et al., 2021)	Tocopherols (especially γ-tocopherol), sterols, squalene, and carotenoids (Cabrera-Vique et al., 2012; Kamal et al., 2019)	Improve skin elasticity (Boucetta et al., 2015) Wound healing improvement (Avsar et al., 2016) Skin hydration by restoring the barrier function and maintaining the water-holding capacity (Boucetta et al., 2014)
Safflower seed oil (From the seeds of *Carthamus tinctorius*)	Polyunsaturated linoleic acid and monounsaturated oleic acid, lesser amounts of stearic acid and palmitic (Chakradhari et al., 2020)	Flavonoids, tocopherols (mainly α-Tocopherol), carotenoids, and sterols (Chakradhari et al., 2020)	Skin hydration (Dakhil et al., 2018) Antimicrobial activity against several opportunistic skin pathogens and high antioxidant effects (Khemiri et al., 2020)
Avocado oil (From the pulp of the fruit of *Persea americana*)	Linoleic acid, linolenic acid, and oleic acid (de Oliveira et al., 2013)	β-sitosterol, β-carotene, lecithin, minerals, and vitamins A, C, D, and E (de Oliveira et al., 2013)	Faster re-epithelization, increase collagen synthesis and decrease the numbers of inflammatory cells (Nayak et al., 2008; Ramadan, 2019)
Almond oil (*Oleum amygdalae*)	Oleic acid, linoleic acid, palmitic acid, palmitoleic acid and stearic acid (Roncero et al., 2016; Takumi et al., 2021)	Tocopherols, phospholipids, phytosterols, sphingolipids, and squalene (Roncero et al., 2016)	Emollient and sclerosant properties, reduce the visibility of striae (Timur Tashan and Kafkasli, 2012) Photoprotection (Kaur and Saraf, 2010)
Jojoba oil (*Simmondsia chinensis*)	Eicosenoic acid, erucic acid and oleic acid (Matsumoto et al., 2019)	Quinones, terpenoids, tocopherols, and phytosterols (Shahin et al., 2011; Tietel et al., 2021)	Enhance the absorption of topical drugs (Shahin et al., 2011) Anti-inflammatory and antioxidant activities (Matsumoto et al., 2019) Restore the barrier function in diverse skin conditions (Meier et al., 2012)
Oat oil (Avena sativa)	Palmitic acid, stearic acid, oleic acid, linoleic acid, and linolenic acid (Anderson, 2001)	Avenanthramides (Sur et al., 2008) Ferulic acid, vanillic acid, and coumaric acid (Fernández-Acosta et al., 2019)	Antioxidant and anti-inflammatory activities (Fernández-Acosta et al., 2019; Sur et al., 2008) Increase ceramide levels (70%) through the activation of peroxisome proliferator-activated receptors (Chon et al., 2015)
Rose Hip Oil (From seeds of *Rosa canina*l.)	Linoleic acid, α-linolenic acid, and oleic acid (Ilyasoğlu, 2014)	Tocopherols and carotenoids Phenolic acids, especially p-coumaric acid methyl ester, vanillin, and vanillic acid (Aladedunye et al., 2014)	Antioxidant and anti-inflammatory activities Anti-inflammatory potential in diverse skin conditions(Chrubasik et al., 2008)

they have been developed in response to different skin conditions in the field of cosmeceuticals. A wide range of these peptides target skin aging, regulating mainly collagen turnover, and blocking or promoting specific neurotransmitters, aiming decreasing age-induced wrinkles. Many of these peptides are synthetic peptide-based categorized as neurotransmitter inhibitor peptides, carrier peptides, and signal peptides. All these classes were well-reviewed by Errante et al. (Errante et al., 2020). Nevertheless, peptide-based molecules can be also obtained from vertebrate and invertebrate animals, plants, bacteria, fungi, and protozoans with distinct biological bioactivities. Recently, more attention has been given to agro-industrial by-products and residues comprising significant amounts of protein (10 – 50%) such as rice bran, coconut pulp, and soybean meal which are excellent and promising sources of bioactive peptides (Gorguc et al., 2020). The biological activities of peptides will also diverge according to molecular weight, sequence, and type of amino acids. In the literature, a range of bioactivities is described, including antioxidant, antihypertensive, antimicrobial, and antidiabetic, among others (Freitas et al., 2019; Karami and Akbari-Adergani, 2019; Piovesana et al., 2018). In the skin, they also have been used to treat pigmentation, improve extracellular matrix synthesis, and modulate innate immunity and inflammation. The use of peptides has some advantages such as their selectivity, the absence of premarket regulatory requirements for their use, and their lack of immunogenicity. In contrast, the low lipophilicity and high molecular weight of peptides can negatively affect their absorption in the skin. Therefore, more clinical evidence must prove the efficacy of peptides for dermatological uses (Pai et al., 2017).

Antimicrobial peptides

Antimicrobial peptides (AMPs) are a specific type of peptides, they are normally small (12–50 amino acids), positively charged amphiphilic molecules with α-helix or β-sheet linear motifs, and linear or cyclic configurations. The most frequent applications of AMPs include kill or inhibit the microbial growth and protect the skin from infections against bacteria, yeast, fungi, protozoa, and viruses (Liu et al., 2013; Pai et al., 2017). It is important to note that AMPs can be found in all living animals (from microorganisms to mammals) as part of their primary mechanisms used in the early stages of immune defense. The human skin can equally secrete them onto the skin surface, while others are expressed in the healthy skin but only upregulated in specific conditions such as the presence of microorganisms, proinflammatory cytokines, chemokines, radiation, wound healing, etc. (Herman and Herman, 2019; Miazga-Karska et al., 2020). Deregulations on AMPs secretion by the skin contribute to the pathogenesis of several skin diseases such as atopic dermatitis, acne vulgaris, and psoriasis (Mangoni et al., 2016). Nowadays, with the emergence of bacterial resistance, nature-derived

AMPs can be a viable alternative to classic antibiotics when the immune system is unable to deal with the infection. These positively charged AMPs interact with the negatively charged bacterial cell membranes without causing any damage to Eukaryotic membranes. The most frequently described mechanism of action of AMPs is the disruption of membrane potential that ultimately caused cell death (Hammami et al., 2009). Other AMPs can translocate across the bacterial membranes without any detrimental effects on themselves but destabilize other cell functions (including inhibition of nucleic acids, proteins, or cell wall synthesis).

A great number of AMPs have been isolated from plant species, including roots, seeds, flowers, and leaves. The high content of thionins and defensins (cysteine residues) in plants produces two to six disulfide bonds that eventually will affect resistance to proteolytic degradation (Mangoni et al., 2016; Miazga-Karska et al., 2020). Compared with other kingdoms, plant-derived AMPs have larger diversity and abundance due to probably environmental evolutionary forces and redundant genomes. Every single plant can be an arsenal of AMPs for the most diversity of pathogens. A recent publication by Petre (2020) discusses the concept of host-defense peptides (HDPs), which are peptides with both antimicrobial and immunomodulatory activities. This concept arises from the ability of peptides to change the physiology of the plant and trigger a set of immunomodulatory mechanisms. However, no HDPs were reported in plants so far, as the concept of HDP has not been taken yet by the plant science community (Petre, 2020). Nevertheless, some progress has been achieved in AMPs for the treatment of skin infections. *Propionibacterium acnes* is a gram-positive human skin commensal, one of the most frequently found that makes difficult the treatment of acne. Miazga--Karska et al., 2020 isolated low molecular weight peptides from burdock roots (*Arctium lappa* l.) and assessed the level of antibacterial activity against Gram-positive and Gram-negative bacteria. Both tested peptides (Br-f and Br-p) only inhibited the growth of Gram-positive bacteria without cytotoxic effects in skin fibroblast cultures. More precisely, Br-p had bactericidal nature against all Gram-positive strains, while Br-f was only active against anaerobic Gram-positive strains. These properties of active peptides have allowed them to be used to produce therapeutic dressing material (Br-p/chitosan/sodium alginate) to be used in infections against Gram-positive bacteria in acne skin. These specificities allowed the development of a therapeutic dressing material (Br-p/chitosan/sodium alginate) to be used in infections against Gram-positive bacteria (Miazga-Karska et al., 2020). Indeed, the AMPs have revealed promising results against diverse acne pathogens, including also *Staphylococcus epidermidis, Staphylococcus aureus,* and *Candida albicans* strains (Ma et al., 2022; Theansungnoen et al., 2022). The following two ferns, *Adiantum Edgeworth* and *Adiantum capilllus-veneris* from the Himalayas have been explored for the presence of AMPs with antimicrobial activity for different pathogens, including *Staphylococcus aureus*. Proteins from both ferns showed antibacterial activity against this bacterium and the experiments confirmed the presence of AMPs. In this work, the isolation, characterization, and sequencing of purified AMPs were not performed, but the researchers highlighted the importance of addressing these experiments (Negi and Maurya, 2020). Other AMPs have shown their efficacy against Staphylococcus *aureus*, mainly in cases where there is resistance to conventional treatments. Pardaxin (GE33) is a peptide isolated from Red Sea flatfish (*Pardachirus marmoratus*) with antimicrobial activity against both Gram-positive and Gram-negative bacteria. Like other antimicrobial peptides, Pardaxin disrupts bacterial membranes, but it also stimulates the arachidonic acid cascade to affect the extracellular-signal-regulated kinase (ERK) and other signaling pathways in treated cells (Bloch-Shilderman et al., 2001). Huang et al. (2014) evaluated the suitability of this AMP as a wound-healing agent in a mouse model of methicillin-resistant *Staphylococcus aureus* (MRSA) infection and obtained the same consistent results. Pardaxin demonstrated to have antibacterial activity against MRSA in vitro and decreased MRSA-induced TNF-α at the wound site. The data also showed the increased recruitment of macrophages and monocytes to the site of infection, and the stimulation of signaling pathways responsible for the induction of specific chemokines. In mice treated with Pardaxin, the reepithelialization and dermal maturation were also faster than in mice treated with vancomycin. The untreated mice and mice treated with methicillin died, but in contrast, mice treated with pardaxin survived. The authors support the idea that Pardaxin may be suitable for conditions in which there is a high risk of infection once it showed prophylactic efficacy. Otherwise, this AMP is compatible with the use of several antibiotics and does not display any apparent immunotoxic effects (Huang et al., 2014). Similar results were obtained by Cunsolo et al. (2020) with novel AMPs from *Charybdis pankration*, a Mediterranean plant, well-known for its biological properties in traditional medicine. Polypeptide-enriched extracts from different parts of the plant were tested against two relevant pathogens, *Staphylococcus aureus,* and *Pseudomonas aeruginosa*. The critical antibiotic resistance of these two pathogens has increased the concerns about their ample diffusion in natural environments. They are the most recurrent causes of wound-associated infections (diabetic foot, venous leg, and pressure ulcers). In this study two peptides were identified to be good candidates as AMPs themselves, but also as chemical platforms to develop efficient antimicrobial drugs due to their physicochemical parameters, including their positive charge, the presence of hydrophobic residues, and their stability, which make them potentially able to approach and interact with bacterial membranes (Cunsolo et al., 2020).

In summary, several AMPs derived from plants have revealed antimicrobial activity against both Gram-positive and Gram-negative strains, but their action is not restricted to pathogens. They also can modulate several immune mechanisms related to inflammation and wound healing in the host. Therefore, more studies should be performed to understand their applications on the skin, as well as their safety for topical use (Moyer et al., 2021; Taniguchi et al., 2017).

Nature-derived peptides

Nowadays, innovation in cosmetics is based on new bioactive formulations such as oils, vitamins, protein hydrolysates, and peptides. Several amino acids are already included in skincare products mainly due to their ability to act as water-binding molecules. More than that, there is a growing interest in bioactive peptides for stimulating collagen and elastin synthesis in the skin. Although most peptides in cosmetics are of synthetic origin, natural peptide extracts represent a competitive alternative, not only because of the need to explore new natural products but also by their multifunctionality. The protein source, amino acid composition of peptides, enzyme selection for hydrolysis, peptide enrichment method, as well as stability of the peptides within the formulations, and bioavailability will be decisive for the biological activities observed in skin cells (Ahsan, 2019; Skibska and Perlikowska, 2021).

Marine sources are an excellent source of bioactive peptides for the most diverse applications, including cosmetic industries. The biological and functional properties of peptides derived from marine sources are already well-reviewed by Cunha and Pintado (2022) highlighting the versatility of these molecules (Cunha and Pintado, 2021). Many of these peptides have been isolated from algae that can be used in cosmetic formulations with different purposes, such as anti-aging creams, refreshing care products, depigmentation products, or emollients. Different from other species in marine biomass is relatively easier to abstain from higher amounts of protein from algae and consequently isolate and identify higher amounts of peptides. Peptides derived from algae are already used in cosmetic formulations such as the Dermochlorella® (isolated from *Chlorella Vulgaris*) that promises the stimulation of collagen synthesis (Martins et al., 2014). In fact, the genus *Chlorella* and *Arthrospira* represent the most recognized sources of molecules in the skincare market. The *Chlorella*-derived peptide (CDP) fraction has shown the ability to decrease the gene expression of several proteins in UVB irradiated fibroblasts, such as MMP-1 and cysteine-rich 61 (CYR61), and monocyte chemoattractant protein-1 (MCP-1). The

activation of the MMPs is associated with photoaging accelerating the degradation of skin collagen and inhibiting the collagen synthesis of ECM. The inhibition of MMP expression or activation of collagen synthesis may be a strategy to prevent wrinkle formation associated with photoaging (Chen et al., 2011). In the same way, peptide-enriched extracts from the microalga *Arthrospira platensis* were effective in promoting skin hydration, increasing the gene expression of several factors specifically involved in the water balance maintenance in keratinocytes (aquaporin3, hyaluronic acid synthase 3, and filaggrin). In addition, it was observed the inhibition of ROS production was caused by oxidative stress agents (Chien et al., 2013).

Several plant-derived peptides have shown their efficacy as anti-aging promoters in skin formulations, mainly in skin creams of personal care. Peptides that contain similar amino acid sequences to the ECM proteins present in the human skin have a great potential to stimulate dermal ECM synthesis, stimulating re-epithelialization, promoting cell adhesion, and supporting tissue regeneration. *Glycine* max (soy) lysate has shown these properties, being considered with excellent wound healing properties (Apone et al., 2019; Chien et al., 2013). *Lotus japonicus* have also in their composition key amino acids that will promote the renovation of some ECM components, including collagens and periostin (Tito et al., 2019).

Some limitations of nature-derived peptides must be considered such as the interactions with other unspecific biological components and the risk of potential allergens. On the other way, the isolation and characterization of a single peptide faction may be very challenging with elevated costs. For these reasons working with synthetic peptides became sometimes more attractive. To avoid these problems, the peptides can be derived from plant tissue cultures, that are grown in the laboratory, under controlled and axenic conditions. Different from peptides derived from plant extracts, these ones decrease the risk of the presence of potential allergens, and the environmental pollutants are almost completely abolished (Guzmán et al., 2007; Jack et al., 2013).

Probiotics

In the last decades, studies proving the importance of microbiota in health and disease substantially increased. The focus on cutaneous microbiota is more recent but sufficient to prove that it plays a key role in skin homeostasis, already considered as “a second barrier” to the environment. The beneficial effects of the application of probiotics are described for some pathological skin conditions such as atopic dermatitis and acne but less explored for others, including psoriasis and rosacea (Knackstedt et al., 2020a). A range of studies establishing the link between microbiota and immune system functions have raised interest in microbiota modulation and bacterial therapeutics through pharmaceutical solutions, cosmetic formulations, and dietary. Dietary is the most frequent form of probiotic consumption (e.g., yogurt), being the gastrointestinal tract their primary site of action. The topical applications of probiotics on the skin are less explored and there are not many clinical trials looking at topical probiotics for skin pathological conditions (Lehtoranta et al., 2020).

The effects of probiotics can be local and often extended to the organism. In animal models has been observed that oral probiotics improve insulin sensitivity, as well as modulate the release of inflammatory cytokines in the skin through their interface with gut-associated lymphoid tissue (Hacini-Rachinel et al., 2009; Hsieh et al., 2013). The most recent findings have also revealed that not only do diverse skin diseases play an important role in altering the gut microbiome in humans but also the presence of several skin diseases are linked with a pre-existing altered gut microbiome (Kober and Bowe, 2015). Several studies have demonstrated that skin and gut microbiomes are intrinsically related. This relationship has been denominated as the gut-skin axis and it seems to be mediated by the host immune system. Therefore, the gut and skin can interact with one another through the diet, microbial metabolites, neuroendocrine pathways, and the central nervous system (De Pessemier et al., 2021). This association has been explored in some skin disorders, including atopic dermatitis (Varade et al.), acne, and psoriasis. In patients with AD, the presence of high concentrations of *Staphylococcus aureus* in the skin is frequently observed, and correlated with the physiopathology of this disease, including disrupting the skin barrier and a dysfunctional immune response (Totte et al., 2018). *S. aureus* colonizes the skin in 20–30% of the population but in some of these patients, it does not represent any danger (Peterson and Schora, 2016). Their role in AD is complex but already well explored by researchers. The *S. aureus* secondary infection is also a frequent complication in AD patients, being urgent clarifying factors that may trigger it. A possible explanation is the constant oscillations observed in AD due to inflammation, allowing the presence of other pathogens or foreign antigens that eventually will compete with *S. aureus* for survival (Chung et al., 2022). In response, *S. aureus* secretes several virulence factors, including the fibronectin-binding protein 1 (FBP1). The role of this protein in AD patients is explored by Farag and colleagues (Farag et al., 2022). They found that it contains immunodominant peptides capable of inducing a specific pro-inflammatory T helper (Kant et al.) cell response. They also detected high levels of the type 2 cytokines IL-13 and IL-4 mediated by Th2 cells. The high Th2 cells can mediate immune responses that easily drive allergic inflammations in sensitized AD patients, mainly in moderate and severe cases (Farag et al., 2022). Other virulence factors released by *S. aureus* are likely explored in AD pathogenesis, among them α- and δ- hemolysin and a family of proteins called phenol-soluble modulins (PSMs). All these toxins leaded to higher inflammatory reactions and worse reported symptoms (Damour et al., 2021; Hong et al., 2014; Nakamura et al., 2013). Nowadays, cutaneous bacterial dysbiosis in AD physiopathology is well-known as a characteristic hallmark. For this reason, the use of probiotics to try to overcome this disease has risen the interest of researchers. Randomized trials were already performed and oral supplementation with probiotics is beneficial in improving the severity of AD in adults and young children (Kalliomäki and Salminen; Weston et al., 2005). The symbiotic preparations also seem to significantly improve the results when compared with the single administration of probiotics (Wu et al., 2012). Table 5 summarizes different probiotics and symbiotics that showed benefits in clinical trials for AD treatment. The *Lactobacillus* strains, including l. *salivarius*, l. *casei, and* l. *acidophilus* are the most used in clinical trials to treat AD in childhood. However, even with these efforts, the evidence supporting the use of probiotics for the treatment and prevention of AD is still very limited. Studies in vitro also have contributed to understanding the mechanisms of probiotics in immune cells. In the gut, Lactobacilli and bifidobacteria are recognized by PRRs, TLRs on the surface of DCs. Different maturation patterns induced in DCs, NK, and T cells are described. Weiss and colleagues reported that *Lactobacillus acidophilus* strains promoted large amounts of IFN-β and induced a viral defense phenotype in murine DCs. Despite their non-pathological phenotype, l. *acidophilus* stimulated a pro-inflammatory and antiviral response by a TLR-2-dependent mechanism, explaining the ability to prevent virus infection reported for the probiotic bacterium l. *acidophilus* NCFM (Weiss et al., 2010). Moreover, they proved that the ability of a great number of lactobacilli strains could promote a strong Th1 polarized DCs phenotype, characterized by a high IL-12 dependent on IFN-β. When the authors added bifidobacteria and l. *reuteri* strains to previous DCs stimulated with l. *acidophilus* NCFM, the induction of IFN-β appeared to be almost completely blocked (Weiss et al., 2011). This study highlights that different bacteria can display significant immunomodulatory differences when selecting the suitable strain(s) for probiotic purposes. In another study, a supplement named Duolac ATP, containing four probiotic strains: l. *casei*, l. *plantarum*, l. *rhamnosus*, and *B. lactis* were tested in bone marrow-derived dendritic cells (BMDCs) and in AD mice model to understand the immunomodulatory mechanisms. The results confirmed that Duolac ATP effectively induced a regulatory immune response in BMDCs and induced a significant amount of IL-10 and TGF-β. Furthermore, they found that

Table 5
Clinical trials with potential probiotics and symbiotics for the treatment and prevention of AD.

Probiotic/Symbiotic association	Administration	Patients age	Time of the trial	Main conclusion	Ref.
Lactobacillus fermentum VRI-033 PCC	Oral 1×10^9 CFU* Twice a day	6 – 18 Months old	8 weeks	Significant reduction in SCORAD*	(Weston et al., 2005)
Lactobacillus sakei KCTC 10755BP	Oral 5×10^9 CFU twice a day	2 – 10 years	12 weeks	Clinical improvement and a significant decrease in chemokine levels	(Woo et al., 2012)
Lactobacillus plantarum CJLP133	Oral 0.5×10^{10} CFU twice a day	1 – 13 years old	12 weeks	Significant reduction in SCORAD Significant decrease of v IFN-γ and IL-4	(Han et al., 2012)
Lactobacillus salivarius PM-A0006 and FOS	Oral 2×10^9 CFU Plus 45 mg of FOS twice a day	2 – 14 years old	8 weeks	The effect was superior to the prebiotic alone for alleviating the severity of AD symptoms	(Wu et al., 2012)
Lactobacillus rhamnosus HN001 *Bifidobacterium animalis* HN019 (Different groups)	Oral 6×10^9 CFU and 6×10^9 CFU once a day (respectively)	Pregnant women from 35 weeks pregnant and their children (0–2 years old)	2 years	Supplementation with *l rhamnosus*, but not *B. animalis,* reduced the prevalence of eczema, but not atopy, by 2 years.	(Wickens et al., 2008)
Lactobacillus salivarius LS01	Oral 1×10^9 CFU* Twice a day	Adults	16 weeks	Significant improvement in clinical manifestation	(Drago et al., 2011)
L. acidophilus LAVRI-A1	3×10^9 CFU once a day	Pregnant women from 35 weeks pregnancy and their children (0–1 years old)	1 year	Probiotic did not reduce the risk of AD in high-risk infants and was associated with increased allergen sensitization in infants	(Taylor et al., 2007)
ProBiotik®	2×10^9 CFU of four types of probiotic bacteria	1 – 13 years old	10 weeks	Probiotics were effective in reducing AD patients' SCORAD index Reduced IL-5, IL-6, IFN-γ, and total serum IgE levels	(Yesilova et al., 2012)

*CFU (colony-forming units).
*SCORAD (Scoring of Atopic Dermatitis).
*FOS (fructo-oligosaccharide).
*ProBiotik® (mixture of *Lactobacillus salivarius,* l. *casei,* l. *acidophilus*, and *Bifidobacterium bifidum)*.

Duolac ATP regulated transcription factors and cytokines to drive naïve T cell differentiation toward Th1 lineages in an AD mice model (Weiss et al., 2011). These results show that Duolac ATP has great preventive potential in the management of AD symptoms and their immunomodulatory agent for AD patients should be more explored.

Different from oral probiotics, there is very little information and clinical studies that have explored the efficacy of topical applications of probiotics. In the last decade happened a dramatic rise in commercially available topical probiotics mainly due to their increasing popularity. More than treating skin disorders, topically applied probiotics are promising molecules for deaccelerate skin aging and preventing photoaging. Patients with acne show significant improvement through oral probiotics that target the immune system beyond the gut, and after expanding them toward the skin (Kim et al., 2018; Porubsky et al., 2018). The most important achievement was understanding the role of topical probiotics and their effects on ceramide production in the skin. Di Marzio and colleagues added the bacterium *Streptococcus thermophilus* to human keratinocyte cell cultures and reported an increasing in the production of ceramides. This ability is possibly linked with the sphingomyelinase present in *S.* thermophilus (Di Marzio et al., 1999). This enzyme is responsible for the hydrolyzation of sphingomyelin into ceramides. Sphingomyelinase is reported to be present in other bacteria, including the genera *Bacillus, Listeria, Staphylococcus, and Mycobacterium*, among others. Despite sphingomyelinases together with phospholipases have been reported as virulence factors, they represent an opportunity to treat patients with acne that shows a decrease in the levels of ceramides (Flores-Diaz et al., 2016). The current topical medications used to treat acne have been shown to disrupt skin barrier function contributing to dryness, flaking, and erythema. At least, adjunctive treatments are important to help in irritation to improve patient compliance and outcomes (Breiden and Sandhoff, 2014). However, probiotics that increase the levels of ceramides in the skin can improve other skin pathologies such as AD, xerosis, and psoriasis as reported in the lipids chapter of this review. Acne treatment normally requires the prescription of antibiotics by dermatologists (e.g., doxycycline, minocycline, and clindamycin) which in part may contribute to increasing the concerns about bacterial resistance to antibiotics. For this reason, alternative therapies need to be developed. The use of topically applied probiotics can offer a viable option to modulate cutaneous microbial interactions and host inflammatory responses in patients with acne. *Lactobacillus* strains have been currently explored also to treat acne. Selected l. *rhamnosus* GG, l. *plantarum* WCFS1, and l. *pentosus* KCA1 inhibited the growth of *C. acnes* and *S. aureus* in vitro. In the same study, the topical application of a cream containing the live lactobacilli previously reported was able to substantially decrease the acne lesions and the associated inflammation in 10 patients (Lebeer et al., 2018). In the same way, the application of probiotics through the diet seems to be equally effective in the treatment of acne. A clinical trial tested *Bifidobacterium breve* BR03 DSM 16,604, *Lacticaseibacillus casei* LC03 DSM 27, 537, and *Ligilactobacillus salivarius* LS03 DSM 22,776) and the botanical extract (lupeol from *Solanum melongena*l. and *Echinacea* extract) in patients with mild to moderate acne. In this study, the symbiotic supplement showed to reduce acne symptoms, associated with a decrease in *C. acnes* and *S. aureus* (Rinaldi et al., 2022). Understanding the role of these bacterial strains in inhibiting skin pathogens associated with acne is important to explore new skin therapeutics based on microbiome modulation.

The probiotic bacteria *Bacillus coagulans* can release bioactive molecules, including exopolysaccharides that protect themselves under starvation conditions, at extreme pH, and temperature conditions (Kodali and Sen, 2008). These effective molecules display strong antioxidant and free radical scavenging activities that make them possible candidates for pharmaceutical formulations. The oral administration of l. *paracasei, Bifidobacterium lactis*, l. *rhamnosus*, and l. *acidophilus* increases the levels of type I collagen in the healing of skin wounds in rats, followed by reduction of the wound area. Similar results were abstained by Poutahidis et al. with the oral supplementation of l. *reuteri* in mice. The authors reported an accelerated maturation of the granulation tissue and collagen deposition in the probiotic group compared to the control group (Tagliari et al., 2019). TLRs have an essential role in the action of probiotics, they are expressed both in the gut and skin and trigger the release of several chemokines that eventually will modulate the activity of immune cells such as dendritic cells and T-lymphocytes, essential for the healing response. It is important to note that this ability can be

related to AMPs released by probiotic bacteria (reviewed in the previous chapter) that in the same way stimulate and increase TLR pathways (Lai et al., 2009; Ruiz-Ramirez et al., 2022; Sato et al., 2010). Other studies also establish the ability of probiotics to promote dermal thickness, equilibrate sebum production, and improve skin brightness (Levkovich et al., 2013; Szanto et al., 2019). Fig. 4 represents the diverse mechanisms by which topical and oral application modulate the immune responses in the skin. Despite the increase of studies exploring the role of probiotics in the skin, potential side effects also need to be considered. Allergic reactions, bacteremia, and antibiotic resistance transfer among pathogens are possible described side effects (Tagliari et al., 2019). On other hand, studies to clarify which is the best way of administration (topical or oral supplementation) also should be performed to increase the selection of the most helpful method.

Conclusions and future directions

This review attempts to shed light on the role of natural products in modulating several immune functions, and skin immune-related conditions. At present, different opportunities from natural products are currently available for researchers to achieve better treatment options. However, despite the several efforts made in the last years, a lot of information is lacking. In some cases, the low availability of these compounds can directly interfere with the necessary quantities for clinical use. Therefore, the development of novel isolation techniques to improve the number of pharmaceutical applications needs more attention from researchers. Nanotechnology and other delivery strategies should also be explored to improve their efficacy when administered to humans.

Concerns about environmental impacts and the search for more sustainable formulations are also urgently needed. Regarding this last aspect, UV filters have gained more concerns because of their negative impact on marine organisms, their putative human toxicity, and their low photostability. Nowadays, it is possible to design UV filters with no toxicity for human cells, applying some strategies to avoid the systemic effect, but they are still poorly eco-friendly. Natural products can eventually offer more effective, and safer future photoprotective agents with a lesser environmental impact on the ecosystems.

The urgent demand for novel molecules to treat life-threatening infections, mainly caused by the global spread of drug-resistant bacterial pathogens, diverges from the current level of investment in their development, mostly in the field of natural product-derived molecules. Unfortunately, there are approximately 4000 immuno-oncology agents in development, while there are only 30–40 new antibacterial compounds in clinical trials. More than that, there are no new classes of antibiotics since the 1980s, and the new molecules available are derived from already-known chemical structures. For this reason, it is necessary to promote and accelerate translational science aiming at novel molecules with antibiotic and immunomodulatory activities.

Compounds derived from natural sources are gaining attention for use in the cosmetic industry, and consciously they may be a possible solution to several skin conditions. In this review, we have outlined the different classes of natural products with great potential as immunomodulators. However, further research is greatly needed to fully understand the safety, biological activity, and precise mechanism of action of these molecules as well as to characterize the active compounds responsible for the activities.

Author contributions

Fernandes, A.: Conceptualization, methodology, writing and draft preparation. Rodrigues, P.M.: Editing and Reviewing. Pintado, M.: Supervision and validation. Tavaria, F.K.: Investigation, Supervision, Reviewing. All data were generated in-house, and no paper mill was used. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy. All data were generated in-house, and no paper mill was used. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

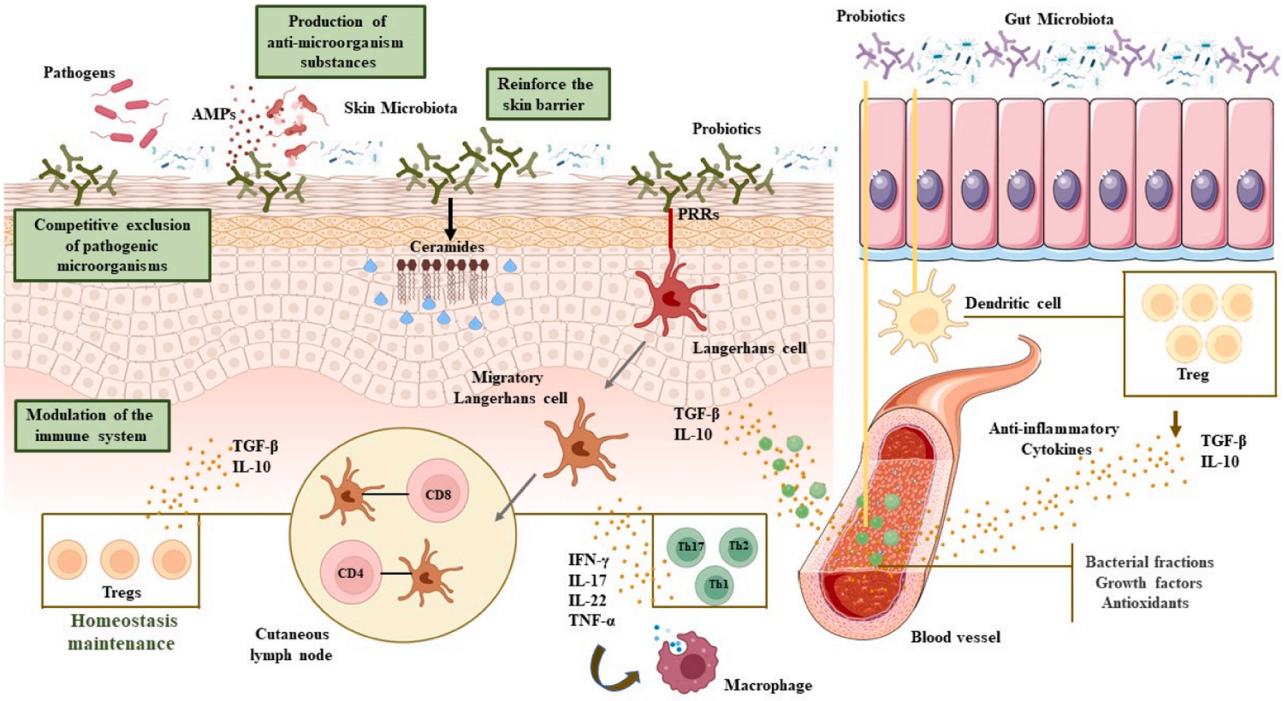

Fig. 4. Graphical representation of Topical application in the skin and oral supplementation of probiotics through the diet. There are diverse proposal mechanisms in which probiotics can modulate the immune system, including competition with pathogenic bacteria by nutrients and binding sites in the host cell; Production of antimicrobial substances that inhibit the growth of pathological microorganisms (such as antimicrobial peptides); Reinforce the skin barrier prevent the loss of water; Stimulation/modulation of the host immune response, involving epithelial cells, Langerhans cells, dendritic cells and regulatory T-lymphocytes (Tregs), both in the gastrointestinal tract or in the skin. Created with Biorender.com.

Founding

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Declaration of competing interest

The authors declare there is no conflict of interest.

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