COMPREHENSIVE INVITED REVIEW

Bioactive Fatty Acids in the Resolution of Chronic Inflammation in Skin Wounds

Carlos Poblete Jara,[1,2,†] Natália Ferreira Mendes,[1,2,†] Thais Paulino do Prado,[1,2] and Eliana Pereira de Araújo[1,2,*]

[1]Faculty of Nursing, University of Campinas, Campinas, Brazil.
[2]Laboratory of Cell Signaling, Obesity and Comorbidities Research Center, University of Campinas, Campinas, Brazil.
[†]These authors contributed equally to this work.

Eliana Pereira de Araújo, PhD

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*Correspondence: Faculty of Nursing, University of Campinas, Rua Tessalia Vieira de Camargo 126, Campinas 13083-887, Brazil (e-mail: earaujo@unicamp.br; pa.eliana@gmail.com).

Significance: Optimal skin wound healing is crucial for maintaining tissue homeostasis, particularly in response to an injury. The skin immune system is under regulation of mediators such as bioactive lipids and cytokines that can initiate an immune response with controlled inflammation, followed by efficient resolution. However, nutritional deficiency impacts wound healing by hindering fibroblast proliferation, collagen synthesis, and epithelialization, among other crucial functions. In this way, the correct nutritional support of bioactive lipids and of other essential nutrients plays an important role in the outcome of the wound healing process.

Recent Advances and Critical Issues: Several studies have revealed the potential role of lipids as a treatment for the healing of skin wounds. Unsaturated fatty acids such as linoleic acid, α-linolenic acid, oleic acid, and most of their bioactive products have shown an effective role as a topical treatment of chronic skin wounds. Their effect, when the treatment starts at day 0, has been observed mainly in the inflammatory phase of the wound healing process. Moreover, some of them were associated with different dressings and were tested for clinical purposes, including pluronic gel, nanocapsules, collagen films and matrices, and polymeric bandages. Therefore, future research is still needed to evaluate these dressing technologies in association with different bioactive fatty acids in a wound healing context.

Future Directions: This review summarizes the main results of the available clinical trials and basic research studies and provides evidence-based conclusions. Together, current data encourage the use of bioactive fatty acids for an optimal wound healing resolution.

Keywords: fatty acids, skin, wound healing, inflammation, bioactive compounds

SCOPE AND SIGNIFICANCE

Lipids are involved in several aspects of the inflammatory process such as vascular contraction, chemotaxis, adhesion, diapedesis, cell death, and tissue restoration. Many studies have analyzed the effects of several lipids, particularly fatty acids, and their bioproducts, in skin inflammation. In this study, the inflammatory response and the involvement of fatty acids in skin wound healing were assessed. In addition, we discussed the main effects of fatty acid treatment, including various cellular features for healing, the activation of specific fatty acid receptors, their inflamma-

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tory and immune functions in the skin, as well as their possible applications in clinical practice.

TRANSLATIONAL RELEVANCE

In the past decade, many experimental studies investigated the role of fatty acids in skin regeneration. Basic research and clinical trials have shown the effectiveness of fatty acids as therapeutic or preventive approaches. However, these findings have not been fully incorporated in clinical practice. The translational relevance of this review is that topical treatment with bioactive fatty acids may provide novel therapeutic strategies for the treatment of acute or chronic wounds, as well as to prevent pressure ulcers.

CLINICAL RELEVANCE

Chronic wounds are defined as having full-thickness and a slow healing propensity. They represent a silent epidemic affecting about 1–2% of the world's population, impacting negatively on the quality of life and resulting in a high cost for public and private health systems. Chronic inflammation, decreased angiogenesis, an imbalance between mature and immature collagen synthesis, extracellular matrix (ECM) deposition and degradation, and dysfunction in cellular migration and proliferation are some of the mechanisms responsible for abnormal healing. Understanding the effects of low-cost bioactive fatty acids on healing may provide insights into therapeutic approaches and improve their applicability to accelerate wound closure.

AN OVERVIEW OF WOUND HEALING PROCESS

The skin is the largest organ of humans and its main function is to serve as a protective barrier against the environment. As a barrier, the skin is highly exposed to distinct external stressors (physical, chemical, or biological), which results in frequent damage.[1] To withstand these injuries, evolution has provided the skin several complex mechanisms aimed at restoring tissue integrity. The wound healing process involves the activation of platelets, neutrophils, macrophages, endothelial cells, keratinocytes, and fibroblasts, as well as the secretion of growth factors, cytokines, chemokines, and other substances needed to coordinate tissue repair.[2] The healing process is divided into three overlapping phases: inflammation, proliferation, and remodeling.[3]

The inflammatory phase (Fig. 1) is characterized by vasodilation and subsequent increase in vessel permeability nearby the wound. This facilitates the migration of monocytes and neutrophils attracted by chemokines, growth factors, and cytokines primarily secreted by platelets aggregated at the lesion's site during the development of the hemostatic clot.[2–4] An important aspect of this phase is mono-

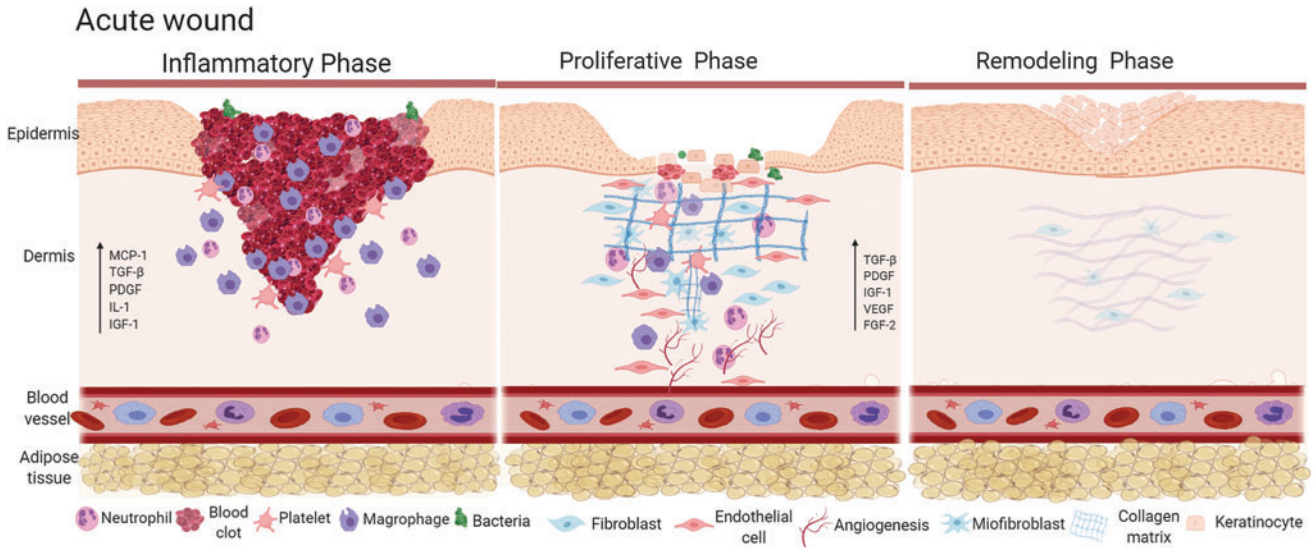

Figure 1. Acute wound healing. *Left-hand panel*, in acute wound healing, inflammatory phase is characterized by clot formation, chemotaxis of neutrophils and monocytes followed by the production of chemokines, cytokines and growth factors. *Middle panel*, as wound healing progresses, proliferative phase is characterized by intense angiogenesis, proliferation of fibroblasts, differentiation of myofibroblasts and collagen deposition; during this phase there is production of growth factors. *Right-hand panel*, during remodeling phase there is intense deposition of, initially type III collagen and then, type I collagen; this is accompanied by reepithelization. Color images are available online.

cyte infiltration that occurs in response to specific chemoattractants such as protein fragments of the ECM and monocyte chemoattractant protein 1 (MCP-1). Thereafter, monocytes differentiate into active macrophages that release growth factors involved in tissue granulation development.[5,6] Transforming growth factor β (TGF-β) and platelet-derived growth factor (PDGF) are some of the most remarkable substances secreted during this phase[6,7] as they are responsible for the formation of new ECM, blood vessels, and activate fibroblasts, which develop at the edges of the lesion. In addition, activated fibroblasts secrete interleukin-1 (IL-1) and insulin-like growth factor (IGF-I), which play important roles in the initiation of the proliferative phase.[6–8]

During proliferative phase (Fig. 1), the continuous macrophage secretion of TGF-β, MCP-1, PDGF, IGF-1, and fibroblast growth factor-2 results in ECM replacement by a stronger and elastic connective tissue.[6–8] The main events taking place during this phase are the establishment of a permeability barrier in the new tissue, the formation of adequate blood supply and the strengthening of the wounded tissue.[6–8] At the end of the healing process ECM becomes mature and remodeled. At the remodeling phase (Fig. 1), the scar develops its highest tensile force as strong collagen deposition begins. Initially there is type III collagen that forms disorganized fibers, which is followed by type I collagen deposition in an organized manner providing the final aspect of the scar.[6–9]

However, pathological factors can disturb healing leading to the development of chronic wounds (Fig. 2). These factors vary widely and include abnormalities in blood supply, metabolic disorders, immune function, and others.[10–14] Diabetes and vascular disease are the main medical conditions leading to development of chronic wounds.[15–17] The main causes of diabetic foot ulcers are peripheral neuropathy and peripheral vascular disease. These abnormalities are caused by chronic hyperglycemia, which promotes formation of advanced glycation end-products and activation of the polyol and hexosamine pathways reducing the normal conduction of neurons.[18,19] In addition, hyperglycemia leads to an increase of reactive oxygen species and interruption of nitric oxide synthesis. Thus, there is an increase in oxidative stress in the nerve cells and an increase in vasoconstriction leading to ischemia, which will promote further nerve cells damage and eventually cell death.[20] Diabetes also impairs progenitor cells influx, proliferation, and release of growth factors at the wound site. In addition, it leads to a chronic inflammatory state and impaired

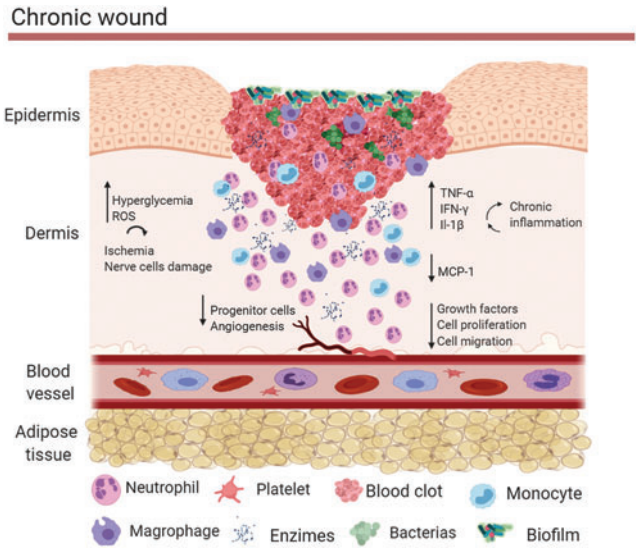

Figure 2. Chronic wound healing. In chronic wounds there is increased reactive oxygen species production and interruption of nitric oxide synthase, leading to ischemia and nerve cell damage. There is also reduction of progenitor cells influx, proliferation, and release of growth factors, accompanied by a chronic inflammatory state and impaired new vessel formation. There is also a delay in the production of chemokines, increased of cytokines and abnormal activation of macrophages. In addition, chronic wounds often suffer the damaging effects of microbes that can form thick biofilms, which increase wound adhesion, immune deficiency, and local resistance to antibiotics. Color images are available online.

new vessel formation.[10] There is a delay in the production of chemokines and cytokines such as MCP-1 in the wound bed, which delays the chemotaxis of monocytes and the activation of macrophages,[10,21] resulting in persistent accumulation of debris, apoptotic cells, and neutrophils. In addition, chronic wounds often suffer the damaging effects of microbes, such as *Streptococcus pyogenes*, *Enterococcus spp.*, and *Pseudomonas aeruginosa*, which colonize and reproduce in the wound bed.[22] These microbes can form thick biofilms, which increase wound adhesion, immune deficiency, and local resistance to antibiotics.[22,23] All these features contribute to chronicity and refractoriness of wounds.[23]

Taken together, these data suggest that the reversion of the abnormal wound microenvironment could mitigate cell damage and restore optimal healing. Thus, due to their bioactive properties, unsaturated fatty acids (monounsaturated fatty acids, MUFAs and polyunsaturated fatty acids, PUFAs), can play an important role in the chronic wound healing process.

Bioactive lipids as inflammatory mediators in skin

Nutritional deficiency is involved with impairments in wound repair and other inflammatory

skin conditions.[24–26] Thus, malnourished patients can develop pressure ulcers, infections, and delayed wound healing that result in chronic nonhealing wounds. In this context, attempts to recover the nutritional status are commonly used in clinical practice as an important therapeutic approach in wound healing; this includes the prescription of dietary supplements. Accordingly, the nutritional support should include bioactive compounds together with all the other essential nutrients.[27–29]

Eicosanoids, endocannabinoids, and sphingolipids are examples of bioactive lipids involved in skin biology as well as in the regulation of skin inflammation and immunity.[30] The structural and protective skin lipids are diverse and contribute to whole epidermal barrier integrity; nevertheless, if some insult results on its disruption, another source of lipids may be helpful for its complete recovery and remodeling. To explore why some lipid-derived inflammatory mediators have been studied for accelerating wound healing repair, it is important to briefly review their definition, classification, and main functions.

Lipids: definition, classification, and functions

Lipids correspond to a large heterogeneous group of hydrophobic organic molecules composed of hydrogen, carbon, and oxygen. In addition to supplying energy, they have other vital and structural functions. They are widely distributed in nature, being found as constituents of cell membranes (glycerophospholipids, sphingolipids, and cholesterol), steroids hormones (estradiol, testosterone, and aldosterone), and cortisol, fat-soluble vitamins (A, D, E, and K), among others. Due to their wide heterogeneity, lipids can be classified according to distinct features. The most common classification relies on the separation into four main subgroups: (1) glycerides (glycerol-containing lipids), (2) nonglycerides (sphingolipids, waxes, and steroids), (3) fatty acids (saturated and unsaturated), and (4) complex lipids (lipoproteins).[31] A schematic representation of the lipid classification is shown in Fig. 3.

The most abundant lipid found in the human diet is triglyceride, which consists of a glycerol molecule linked to fatty acids. The number of fatty acids bonded to one molecule of glycerol can vary between one and three, as well as its binding position (sn-1, sn-2, or sn-3). Fatty acids, in turn, are carboxylic acids with long aliphatic chains, which may be straight or branched. The generic structure of all fatty acids corresponds to a hydrocarbon chain with a reactive carboxyl group at one end and a methyl group at the other end. According to the length of the chain, they can be classified into short-chain (SCFA) (2–6 carbon atoms), medium-chain (MCFA) (6–12 carbon atoms), long-chain (LCFA) (13–21

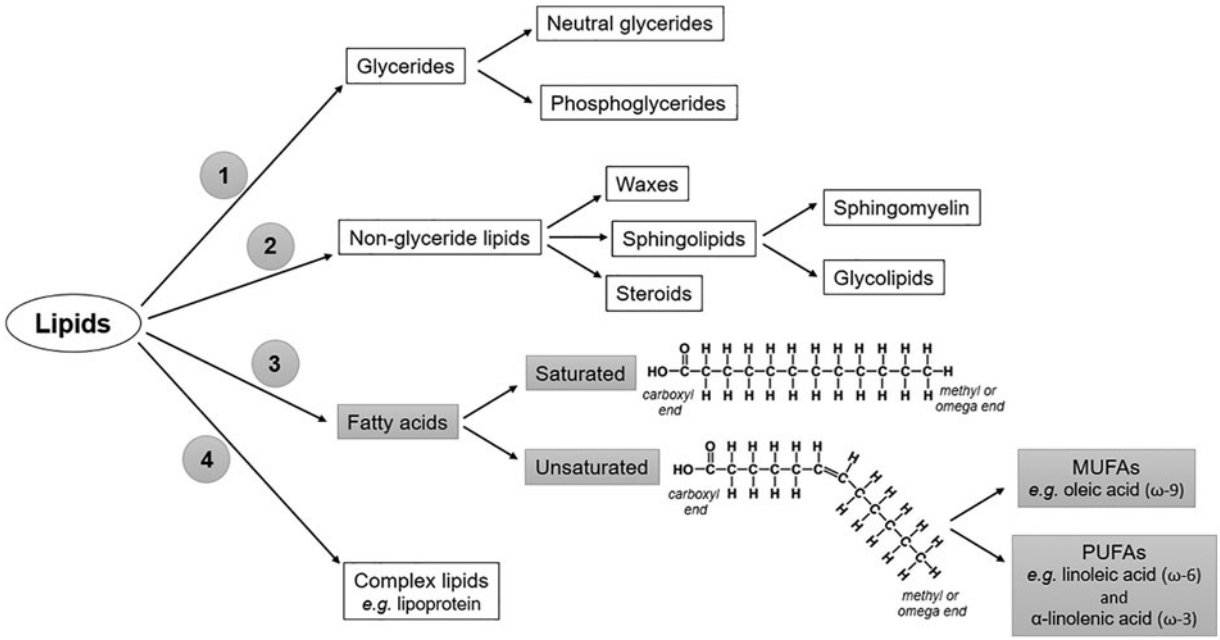

Figure 3. Schematic overview of the most common lipids classification. Highlighted in *gray*, fatty acids can be classified according to the presence of double covalent bonds in the chain. Besides, unsaturated fatty acids are classified in MUFAs, for example, oleic-acid from omega-9 family, or PUFAs, for example, linoleic acid and α-linolenic acid, from omega-6 and -3 families, respectively. MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid.

carbon atoms), and very-long-chain fatty acids (VLCFA) (more than 22 carbon atoms).[31,32]

Fatty acid chains can also be classified into saturated or unsaturated depending on the presence of double covalent bonds (-C=C-) between the carbon atoms. If saturated, there is only a simple bond between the carbon atoms (-C-C-). A fatty acid chain is monounsaturated if it contains one double bond and polyunsaturated if it contains more than one double bond.[31] The chain structure of the fatty acids, as well as their classification, is depicted in Fig. 3.

In addition to the number of carbons and double bonds, the location of the double-bond position and its geometric configuration (*cis* or *trans*) are determinants for the fatty acid metabolic rate. The double-bond position in the chain, defined by the number of carbon atoms from the terminal methyl group (omega or ω) (H_3C), determines the "metabolic family" to which the fatty acid belongs. This occurs because the human body has enzymes capable of inserting carbon atoms into the fatty acid chain, in a position next to the carboxyl group, changing the chain length and generating other fatty acids according to the demand. Because of the large variety in nature, some unsaturated fatty acids have been thoroughly studied due to their potential benefits for health.

Monounsaturated fatty acids

Oleic acid (OA) (18:1) and erucic acid (22:1) are the main MUFAs. Both belong to the omega-9 (ω-9 or n-9) family and have only one double bond in their carbon chain, making them more resistant to oxidation. Because of this, oils which are rich in MUFAs, such as extra-virgin olive oil (EVOO), present antioxidant properties which promote higher stability and longer shelf life compared to PUFA-enriched oils.[33] Although erucic acid is largely found in rapeseed, an important constituent of canola oil, OA is the main MUFA in the human diet with highly bioactive properties.

As the main component of EVOO, OA represents up to 80% of its total lipid composition.[34] Due to its antioxidant role, during the past decade, the effects of OA have been widely studied in the Mediterranean style diet, which is rich in EVOO, showing a potential reduction in cholesterol levels and on cardiovascular risk factors.[35,36] However, more recently, a new paradigm has emerged with the demonstration that EVOO consumption has effects on many other conditions, such as inflammation, oxidative stress, coagulation, platelet aggregation, fibrinolysis, endothelial function, and lipid metabolism.[37] Since the wound healing process depends on the orchestrated functioning of these mechanisms, it is important to briefly cite here some of the main benefits attributed to EVOO.

In the literature, most of the studies about the functions of OA, specifically, have been conducted from a classic study in the field known as PREDIMED (*Prevención con Dieta Mediterránea*): a large, parallel-group, multicenter, controlled, randomized 5-year clinical trial that aimed to characterize the effects of the Mediterranean diet on the primary prevention of cardiovascular disease.[38] Considering that EVOO shows high levels of OA beyond other phenolic compounds, which are also strong antioxidants and radical scavengers, it is hard to isolate their effects. In this way, we have described in the following paragraphs some of the OA-related anti-inflammatory roles, since most of the EVOO properties already mentioned can be related both to OA and phenolic compounds.

In the literature, the anti-inflammatory effects attributed to OA have been observed after the chronic consumption of EVOO, which reduces the serum levels of C-reactive protein, IL-6, IL-7, and IL-18; in addition to raising adiponectin levels in inflamed human adipocytes through the attenuation of JNK-mediated peroxisome proliferator-activated receptor (PPAR) suppression.[39–41]

Although some groups have already studied the benefits of EVOO on wound healing acceleration, the positive effects observed can be due to the phenolic compounds and not to OA. In this context, to provide a deeper understanding of the main effects of OA treatment in skin wounds, studies should be conducted isolating it from EVOO, thus, eliminating any bias from other antioxidant molecules also found in this oil.

Polyunsaturated fatty acids

From a nutritional point of view, the most important PUFAs are those from the omega-3 (ω-3 or n-3) and omega-6 (ω-6 or n-6) families, which have the first double bond in the third and the sixth carbon, respectively, counting from the terminal methyl group. α-linolenic acid (ALA) belongs to the ω-3 family and is an important precursor of other fatty acids with bioactive properties, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). On the contrary, linoleic acid (LA) belongs to the ω-6 family and is a precursor of arachidonic acid (AA), an important fatty acid with several metabolic effects, since it originates other eicosanoids from the ω-6 family, such as leukotriene, prostaglandins, and thromboxane. The detailed production of fatty acids derived from LAs and ALAs are depicted in Fig. 4.

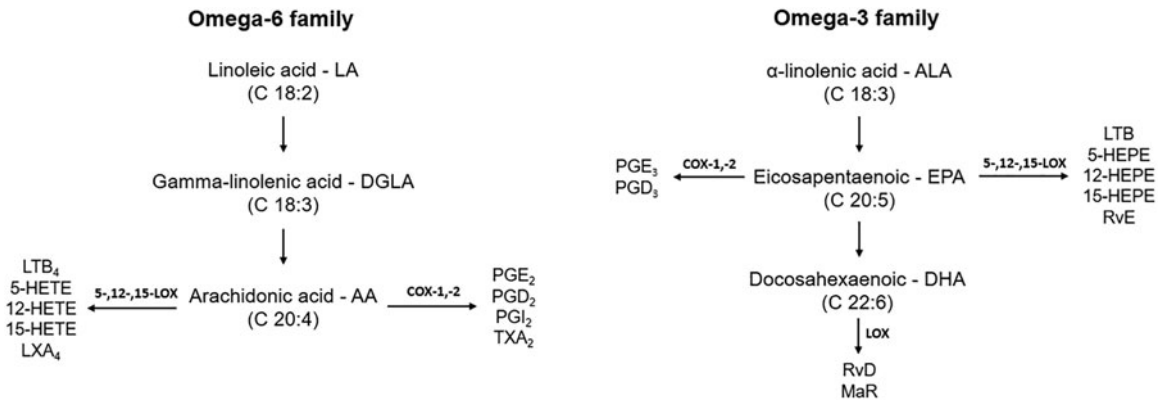

Figure 4. Schematic overview of the production of eicosanoids and other inflammatory mediators from PUFAs omega-3 and -6. LA is metabolized to DGLA, which is also converted to AA. Depending on which pathway is activated: COX or LOX, several eicosanoids are originated. Oxygenated eicosanoids derived from AA are predominantly pro-inflammatory, while those from EPA and DHA are predominantly anti-inflammatory. LA, linoleic acid; DGLA, gamma-linolenic acid; AA, arachidonic acid; COX, cyclooxygenase; LOX, lipoxygenase; LT, leukotriene; HETE, hydroxy-eicosatetraenoic acid; LX, lipoxin; PG, prostaglandin; TX, thromboxane; HEPE, hydroxy-eicosapentaenoic acid; Rv, resolving; MaR, maresin.

Even though the human body can produce saturated and unsaturated fatty acids from carbohydrates and proteins, it is not able to synthesize ALA and LA. In addition, some specific cells or tissues, like epidermal keratinocytes, do not express Δ5 and Δ6 desaturase[42]; therefore, they rely on the systemic provision of essential PUFAs originated from ALA and LA oxidation. Plants, on the contrary, synthesize both these PUFAs, and because of this, they are found in many seeds, nuts, seed oils, and seed oil-derived products. EPA and DHA, from the omega-3 family, are largely found in seafood, for example, tuna, salmon, and sardines, among others. AA, from the omega-6 family, is found in red meat, eggs, and visceral organs, such as the liver.

The information about which are the sources of fatty acids is important not only because many bioactive compounds are generated from these essential lipids, as already mentioned, but also because they are precursors of several structural constituents and eicosanoids with hormone-like functions, which will be discussed in the following topics.

Role of omega-3 and omega-6 polyunsaturated fatty acids in the inflammatory process

The interest in studying the health benefits from PUFAs emerged in the early 1970s when researchers observed the association between high levels of cold-water fish consumption and a low incidence of heart-related diseases in Eskimos from Greenlandic West-Coast.[43] The authors have also noted a lower incidence of autoimmune and inflammatory-related diseases in this population. These data have triggered a series of follow-up studies over the next few decades about the lipid content of these fish and how it could prevent the development of several diseases. Currently, it is known that the protective effect provided by the Eskimo diet is largely attributed to the high level of omega-3 and -6 PUFAs.

Generally speaking, these PUFAs are capable of modulating the systemic inflammatory response regulating several events in the inflammation and immune response, which includes leukocyte chemotaxis, adhesion molecule expression, leukocyte–endothelial adhesion interactions, platelet aggregation, and vasodilatation, among others.[44] Therefore, the main role of PUFAs in the inflammatory process is largely due to eicosanoid production.

Eicosanoids are 20-carbon bioactive products that are originated from omega-6 and -3 PUFA metabolism, such as prostaglandins, leukotrienes, thromboxanes, and lipoxins, which modulate the inflammatory response unevenly.[45] Eicosanoids from omega-6 PUFA metabolism, produced by AA oxidation, are potent inflammatory mediators, involved in infection, inflammation, tissue damage, immune system modulation, and platelet aggregation, and are directly linked to tumor development, growth, and metastases. On the contrary, ALA (omega-3 family) can be converted into EPA and DHA, which compete with AA for the enzymatic pathways of cyclooxygenase (COX) and lipoxygenase (LOX), also giving rise to eicosanoids, with a predominant anti-inflammatory role. DHA can also originate specialized proresolving mediators known as resolvins, protectins, and maresins.[32,46] A schematic overview of the production of eicosanoids and inflammatory mediators from PUFAs omega-3 and -6 is also shown in Fig. 4.

More specifically, mechanisms underlying the anti-inflammatory actions of EPA and DHA include changes in the phospholipid composition of the cell membrane, resulting in the synthesis of lipid mediators with a lower inflammatory potential than omega-6 fatty acid-derived mediators. Moreover, both EPA and DHA can act as agonists of PPAR-γ, whose activation exerts anti-inflammatory effects, and also can stabilize the NF-kB/IkB complex, suppressing the activation of the genes involved in the inflammatory process.[44]

The expression of eicosanoid receptors is cell and tissue-specific. Thus, eicosanoids have different physiological roles depending on the cell or tissue they bind to and according to the intracellular signaling pathway activated in each situation. Because of this, they can switch between proinflammatory and anti-inflammatory molecules, which makes the knowledge about their function a little confusing. For example, in neurons, when prostaglandin E2 (PGE_2) binds to its receptor (EP), it can lead to pain associated with inflammation. Conversely, autocrine EP signaling by PGE_2 in macrophages and leukocytes decreases tumor necrosis factor-alpha (TNF-α) synthesis and increases the expression of anti-inflammatory IL-10, thus attenuating the inflammatory response.[46] Hence, the inflammatory profile of eicosanoids depends on the prevalence of many terminal prostanoid synthases, which can generate series-2 and series-3 eicosanoids from the oxidation of AA and EPA, respectively. The role of the main eicosanoids specific in the inflammatory processes of the skin is depicted below.

Effects of main PUFAs-derived eicosanoids in skin inflammation

Independently of the uneven role of eicosanoids from different classes, they modulate many cellular functions related to improvements in tissue repair. Eicosanoids originated from omega-3 and -6 oxidation, such as PGE_2, PGE_1, PGE_3, PGD_2, $PGF_{2\alpha}$, PGI_2, and TXB_2, are produced by several cells in the skin.[30,47,48]

Among these, PGE_2 is considered the most important COX-2 product during skin wound healing. Also known as dinoprostone, PGE_2 is a product of AA (omega-6 family) oxidation through the COX pathway. All PGE_2 effects are mediated through four integral membrane G protein-coupled prostanoid receptors: EP_1, EP_2, EP_3, and EP_4.[46,49–51]

In the skin, PGE_2 is produced by epidermal keratinocytes and dermal fibroblasts and has proinflammatory actions, resulting in vasodilation, cell proliferation, and modulating the immune response.[52–54] As a potential inflammatory mediator, PGE_2 elicits vascular permeability and edema formation via EP_3 on mast cells (MCs) and facilitates Th1 differentiation and Th17 expansion via EP_4 on T cells and dendritic cells (DCs).[55] Beyond vasodilation and vascular leakage, PGE_2 also regulates fibroblast migration and collagen contraction, two crucial components of the fibrotic phase of dermal repair.[56] Furthermore, PGE_2 has an antifibrotic effect by increasing the expression of matrix metalloproteinase (MMP) 2 and 9, which are a type IV collagenase found at elevated levels in chronic wounds and inhibiting TGF-β1-induced collagen synthesis of dermal fibroblasts. The antifibrotic mechanism of PGE_2 is partly due to its termination of the TGF-β1/Smad pathway by the activation of EP_2 receptors.[57] PGE_2 is also involved in keratinocyte proliferation and differentiation, in the chemotaxis of keratinocytes, and in the modulation of dermal fibroblasts.[49,58–60]

In addition to PGE_2, other eicosanoids involved in the inflammatory response of the skin are generated through the action of COX enzymes, such as other prostaglandins (PGD_2 and PGI_2), prostacyclin (PGI_2), and thromboxane A2 (TXA_2).[61,62] For example, PGD_2, for example, is mainly produced by Langerhans cells and dermal MCs. Since PGD_2 is a potent antiproliferative and anti-inflammatory mediator, its biological effects are related to immune and allergic responses.[52,63] Its effects are mediated through CRTH2 and DPs receptors expressed in several skin cells, including keratinocytes.[64,65] Still, from the same family, prostacyclin (PGI_2) is produced by dermal fibroblasts. Its biological effects are the inhibition of platelet activation and vasodilatation. TXA_2 is produced by epidermal keratinocytes and has prothrombotic properties. Both PGI_2 and TXA_2 exert their biological effects through prostacyclin receptors (IP) and thromboxane receptors (TP), respectively, that are expressed by keratinocytes and other skin cells.[66,67]

Other inflammatory mediators generated from AA are the leukotrienes. Different from the previous ones, leukotrienes are synthesized through the 5-LOX pathway. The skin expresses not only 5- but also 12- and 15-LOX.[54] From leukotriene A4 (LTA_4), other inflammatory mediators can be generated, such as LTB_4, LTC_4, LTD_4, and LTE_4. As prostaglandins and thromboxanes, leukotrienes also exert their effects through G protein-coupled transmembrane receptors, including LTB_4 receptor type-1 (BLT_1) and type 2 (BLT_2).[68] There is not enough evidence about the cellular source of LTB_4 in the skin; however, recently, Zhu *et al.* showed

that epidermal keratinocytes can produce low levels of LTB_4.[69] Despite this, the major source of LTB_4 in the skin is infiltrating neutrophils.[70]

Another product of the 5-LOX pathway is peroxide 5-hydroperoxy-eicosatetraenoic acid (HPETE). Since it is unstable, it is quickly reduced to 5-eicosatetraenoic (HETE) acid and 5-oxo-eicosatetraenoic (ETE) acid.[71] Both leukotrienes and 5-oxo-ETE are potent chemoattractants that can contribute to cutaneous inflammation and allergy.[54]

12-HETE, a product of the 12-LOX pathway, is a potent proinflammatory chemotactic mediator that acts through the 12-HETE receptor (12-HETER).[72,73] It is synthesized by epidermal keratinocytes and dermal fibroblasts, and it is involved in cutaneous wound healing and inflammatory disease.[74] An *in vitro* study on keratinocytes indicated that 12-LOX pathway activity can be inhibited by 15-HETE; a product of the 15-LOX pathway.[75] 15-HETE, in turn, has an important anti-inflammatory role, reducing polymorphonuclear leukocytes infiltration in addition to acting as a biochemical precursor of lipoxin A4 (LXA_4).[76] Its effects rely on the activation of PPAR-γ. A summary of the biological effects of the main eicosanoids involved in the inflammatory process in the skin, which can be applied to wounds, is shown in Table 1.

In brief, the majority of oxygenated products obtained from AA (omega-6 family) through COX and LOX pathways are predominantly proinflammatory, while those from ALA and LA (omega-3 family) are mainly anti-inflammatory. Hence, they can improve or impair the mechanisms of wound healing depending on its phase: inflammatory, proliferative, or remodeling. Based on this, for the development of new topical treatments, additional work is still needed to identify the physiological roles of all eicosanoids and other bioactive lipids in each phase of wound healing. Moreover, it is important to provide advance to elucidate which intracellular mechanisms are involved in each signaling pathway activated by those lipids in the skin.

DISCUSSION OF FINDINGS AND RELEVANT LITERATURE

Receptor-mediated fatty acids intracellular signaling in the skin

Several studies have explored cellular mechanisms involving intracellular signaling activated by fatty acid receptors during skin wound healing. However, most of these experimental studies have not provided a precise description of how the activation of classical signaling pathways involving lipids and their bioactive products can modulate intracellular signaling. To clarify this subject, we searched for some intracellular signaling pathways involving fatty acid receptors in the skin, already experimentally described in the wound healing process (Table 2).

The data previously published have shown the participation of several G protein-coupled receptors (GPCRs) in this process.[77] GPCRs have a structure consisting of seven alpha helices capable of recognizing different ligands and thus altering their structural compliance of the receptors. G protein activation stimulates α-subunit and $\beta\gamma$-dimer dissociation by initiating intracellular signaling cascades involved in regulating the expression of genes related to survival, proliferation, differentiation, and other cellular processes. G proteins are classified according to its α subunit structure and sequence. The three main isoforms are Gs, Gq, and Gi; however, other isoforms, such as Gt (transducin protein), Go, and GK, also play important roles in calcium and potassium channel regulation.[78]

Generally speaking, when activated, Gq subtype receptors increase intracellular Ca^{2+} mobilization, Gs subtype receptors stimulate adenylyl cyclase and elicit the activation of phosphoinositide 3-kinase (PI3K) via the β-arrestin pathway and Gi

Table 1. *Summary of the metabolites from essential PUFAs involved in the inflammatory processes in the skin*

Metabolite	*Pathway*	*Receptors*	*Main Biological Effects*	*Cellular Origin in the Skin*
PGE_2	COX	EP_1, EP_2, EP_3, and EP_4	Vasodilatation, chemotaxis, cell proliferation, and modulation of immune response	Epidermal keratinocytes and dermal fibroblasts
PGD_2	COX	CRTH2, DP_2 or GPR44	Immunomodulation (platelet aggregation)	Epidermal keratinocytes, mast cells, and Langerhans cells
PGI_2	COX	IP	Vasodilatation and inhibition of platelet aggregation	Dermal fibroblasts
TXA_2	COX	TP	Vasoconstriction and platelet aggregation	Epidermal keratinocytes
LTB_4	5-LOX	BLT_1 and BLT_2	Chemotaxis	Infiltrating neutrophils and epidermal keratinocytes (lower levels)
12-HETE	12-LOX	12-HETER	Chemotaxis, leucocyte migration, cell proliferation	Epidermal keratinocytes and dermal fibroblasts
15-HETE	15-LOX	PPAR-γ	Counteract 12-HETE and LTB_4 effects, reduces polymorphonuclear leukocytes infiltration, and act as biochemical precursor of LXA_4	Epidermal keratinocytes, and dermal fibroblasts

Table 2. *Summary of the cellular mechanisms involving the intracellular signaling activated by fatty acid receptors during skin wound healing*

Title	*Author*	*Year*	*Agonist*	*Pathway*	*Resollution*
New Peroxisome Proliferator-Activated Receptor Agonist (GQ-11) Improves Wound Healing in Diabetic Mice	Silva	2019	GQ-11	PPARγ	Accelerates wound closure in diabetic mice by upregulated anti-inflammatory/pro-healing factors Il-10, Arg-1 and Tgf-b Il-10, Vegf, downregulated Il-1b, IL-6 and Tnf-a.
Macrophage PPARγ and impaired wound healing in type 2 diabetes.	Mirza	2015	Prostaglandin J2	PPARγ	Improved healing in diabetic mice, decreased expression of IL-1β, TNF-α, IL-6 and increased VEGF, IGF and TGF-β via NF-kβ signaling in wound diabetic mice
Topical Docosahexaenoic Acid (DHA) Accelerates Skin Wound Healing in Rats and Activates GPR120.	Arantes	2016	Docosahezaenoic (DHA)	FFAR4/GPR120	Wound healing was accelerated, reduction in the expression of interleukin (IL) 1β and an increase in the expression of IL-6, increase in expression of transforming growth factor β (TGF-β) and the keratinocyte marker involucrum
12-Hydroxyheptadecatrienoic acid promotes epidermal wound healing by accelerating keratinocyte migration via the BLT2 receptor.	Liu	2014	Arachidonic acid	BLT2	12-HHT/BLT2 axis promotes wound healing by accelerating keratinocyte migration through NF-kB–Dependent upregulation of TNF and MMP9
Prostaglandin E2 differentially modulates human fetal and adult dermal fibroblast migration and contraction: implication for wound healing.	Sandulache	2006	Prostaglandin E2	EP2/EP4	Inhibits fetal and adult fibroblast migration
Prostaglandin D2 inhibits wound-induced hair follicle neogenesis through the receptor, Gpr44.	Nelson	2013	Prostaglandin E2	gpr44	Decreased WIHN
Time heals all wounds—but 12-HHT is faster.	Gus-Brautbar	2014	12-hydroxyheptadecatrienoic acid 12-HHT	BLT2	Synthetic BLT2 agonist accelerated wound closure in a mouse diabetes model
Upregulation of prostaglandin EP4 receptor messenger RNA in fetal rabbit skin wound.	Li	2000	Prostaglandin EP4	EP4	In normal skin, the EP4 receptor messenger RNA levels were higher in adults than in fetuses. Twelve hours after wounding, the EP4 receptor transcript was remarkably induced in fetal skin wounds but repressed in adult skin wounds
Effects of TS-022, a newly developed prostanoid DP1 receptor agonist, on experimental pruritus, cutaneous barrier disruptions and atopic dermatitis in mice.	Arai	2007	Prostaglandin D2	Prostanoid DP(1) receptor	Suppressive effect on scratching and its effect of accelerating repair of the disrupted cutaneous barrier

subtype receptors; on the contrary, they inhibit adenylyl cyclase, decreasing intracellular cAMP levels.

Just after being synthesized, each prostanoid is released from the cells and acts on specific receptors on neighboring cells, which are coupled to specific G proteins. PGE_2, for example, acts on four receptor subtypes (EP1–EP4), each of which has distinct signal transduction properties, and exert diverse physiological functions. PGD_2 also acts on two different receptors, DP1 and DP2.[77] Based on this, we have listed below the main fatty acid receptors in the skin, including those ones from the GPCR family, and a brief description of their intracellular mechanisms during the healing process.

GPR120 or FFAR4

Many families of GPCRs are characterized in depth. GPR120, also known as free fatty acid receptor 4 (FFAR4), is a member of the rhodopsin family of GPCRs with seven alpha-helices that cross the cell membrane. They are regulated by accessory proteins that influence guanine nucleotide-binding, guanosine triphosphate hydrolysis, or subunit interactions.[79]

GPR120 ligands perform their action through a different mechanism from the GPCRs' classic mechanism. GPR120 signaling is dependent on β-arrestin-2 protein. Thus, the binding of an agonist activates GPR120, promoting the association of β-arrestin-2 to the receptor. Subsequently, there is an internalization of the GPR120/β-arrestin-2 complex. In the cytoplasm, β-arrestin-2 can bind to TAB1 protein, blocking the association of TAB1 with TAK1, and consequently activates TAK1. The lack of activation of this receptor prevents the signal transduction of the inflammatory pathway IκB/NFκB, thus blocking the inflammatory response.

Because of this, GPR120 has recently emerged as a potential therapeutic target for several inflammatory disorders.[80–83]

There is still a lack of knowledge in the field of wound care about the role of the lipid activation of GPR120 and the reduction of the inflammatory phase. However, a study has shown that DHA is able to speed up wound healing in mice, reducing the expression of IL-1β and increasing the expression of IL-6, TGF-β, and the keratinocyte marker involucrum, probably by GPR120 activation.[84]

DP1 and DP2

D prostanoid receptor 1 (DP1) is a member of the prostanoid family and was the first receptor identified for PGD_2. It belongs to a Gs subtype; thus, its activation leads to a rise in the intracellular levels of cAMP. DP1 is expressed by vascular smooth muscle and platelets causing vasodilatation.[85,86] In the skin, PGD_2-DP1 signaling plays an important role in MC maturation and MC-mediated inflammation.[77] DP1 is also expressed by DCs and invariant NKT (iNKT) cells and can reduce the production of IFN-γ through protein kinase A (PKA) activation.[87]

Prostaglandin D2 receptor 2 (DP2) or the chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2), is also known as GPR44 and was originally identified as an orphan receptor. DP2 is a Gi receptor with seven transmembrane alpha-helices that are preferentially expressed in $CD4^+$ effector T helper 2 (Th2) cells,[88] which act by reducing intracellular cAMP production,[89] mediating the chemotaxis of eosinophils, basophils, and Th2 lymphocytes generated during an inflammatory response. In the skin, PGD_2 can inhibit hair follicle regeneration through the GPR44 receptor, indicating that the inhibition of PGD_2 production or GPR44 signaling could participate in skin regeneration.[90]

EP1, EP2, EP3, and EP4

EP4 is a PGE_2 receptor that also belongs to the family of GPCRs. This receptor plays a variety of roles through cAMP effectors such as PKA, increasing cAMP levels. Recent emerging evidence has revealed that, in addition to cAMP and its downstream signaling, EP4 also modulates a variety of signaling pathways, such as PI3K, β-arrestin, and the transactivation of EGFR.[91] Similar to EP4, the EP2 receptor is also a Gs receptor, which increases cAMP levels after PGE_2 binding. On the contrary, EP3 is a G receptor, thus acts decreasing cAMP levels after its activation by PGE_2. EP1, from a different phylogenetic origin, acts through increasing intracellular Ca^{2+} levels.

PGE_2 is the major inflammatory mediator associated with dermal wound healing.[56,91] Recent studies have revealed that PGE_2 may facilitate Th1 differentiation and Th17 expansion via the EP4 receptor on T cells and DCs during chronic inflammation.[90,92,93] Moreover, PGE_2 increases vascular permeability and edema formation via EP3 on MCs and may raise the blood flow by eliciting vasodilatation via EP2/EP4 receptors on smooth muscle cells.[77]

BLT1 and BLT2

Leukotriene B4 (LTB4) is a potent inflammatory mediator derived from AA. Two GPCRs for LTB4 have been identified: BLT1 and BLT2, both Gi-like G proteins, which can induce cell migration.[94] They are also receptors for 12(S)-hydroxyheptadeca-5Z,8E,10E-trienoic acid (12-HHT). BLT1 is found in several helper T cells, DCs, osteoclasts, granulocytes, eosinophils, and macrophages, while BLT2 is mainly expressed in keratinocytes.[94,95]

12-HHT is found in the wound fluid of mice, and BLT2-deficient mice exhibited impaired re-epithelialization and delayed wound closure after skin punching.[95] The activation of BLT2 receptors facilitates wound healing by accelerating keratinocyte migration through NF-kB-dependent upregulation of TNF-α and MMP9 during the inflammatory phase of healing.[95,96]

Peroxisome proliferator-activated receptors γ

Different from the other receptors described in this section, PPARs are nuclear receptors that regulate a large number of genes involved in differentiation and lipid metabolism. They are localized in macrophages and are essential for switching these cells into an anti-inflammatory state. In the skin, PPARs control the expression of genes involved in cell proliferation, differentiation, and also the inflammatory response. Also, PPARs appear to be essential for maintaining skin barrier permeability, inhibiting keratinocyte cell growth, promoting keratinocyte terminal differentiation, and regulating the skin inflammatory response.[97]

PUFAs such as 15-hydroxy-eicosatetraenoic acids, 13-hydroxy-octadecadienoic acid, 15-Deoxy-Δ-12, and 14-Prostaglandin J2 (15d-PGJ2) can activate PPAR-γ receptors. The mechanisms of activation negatively regulate the gene expression of proinflammatory genes in a ligand-dependent manner by antagonizing the activities of transcription factors such as members of the nuclear factor κB (NF-κB) and activator protein-1 (AP-1) families.[98] Activation of these pathways by 15d-PGJ2 reduces the levels of proinflammatory cytokines such as IL-1β, TNF-α, and IL-6 in the wound,

and slightly increases the levels of prohealing growth factors, such as VEGF, IGF, and TGF-β1. Besides, PPAR-γ signaling activation downregulates the proinflammatory phenotype exhibited by macrophages isolated from wounds.[99,100]

A schematic overview of the major receptors for fatty acids and lipid-derived substances presents in the skin and downstream proteins implicated in their intracellular signaling is shown in Fig. 5.

BIOACTIVE FATTY ACIDS USED FOR WOUND HEALING: A SYSTEMATIC REVIEW

To identify the main fatty acids that have been tested for skin repair, in August 2019, we performed a systematic review with "Fatty Acids", "Skin", and "Wound Healing" as the keywords on PubMed database using: *"Fatty Acids"[Mesh] AND "Skin"[Mesh] AND "Wound Healing"[Mesh]* strategy. A second search was performed with the keywords "Bandages" and "Fatty Acids" also on the PubMed database using: *"Bandages"[Mesh] AND "Fatty Acids"[Mesh]* strategy. The inclusion criteria were original articles, full text available, English language, published at any time, any animal model, intervention using topical fatty acids applied on wound bed, comparison based in the control group, and articles describing outcomes in "wound contraction," "wound healing," or "wound area". The inclusion criteria were searched in every abstract, methodology, and results of each article.

Results

We analyzed the abstracts, methodologies, and results of 159 original articles. One hundred twenty eight articles were excluded for not meeting the inclusion criteria. In the end, 35 original articles were selected for the review (Fig. 6). The main result of the review was that topical treatment using fatty acids or their bioproducts accelerate the wound healing process, independently of the omega family origin (Table 3). Their effect, when the treatment starts on day 0, was observed mainly in the inflammatory phase of the wound healing process.

Data from included studies. Together, the data already published have shown that the topical use

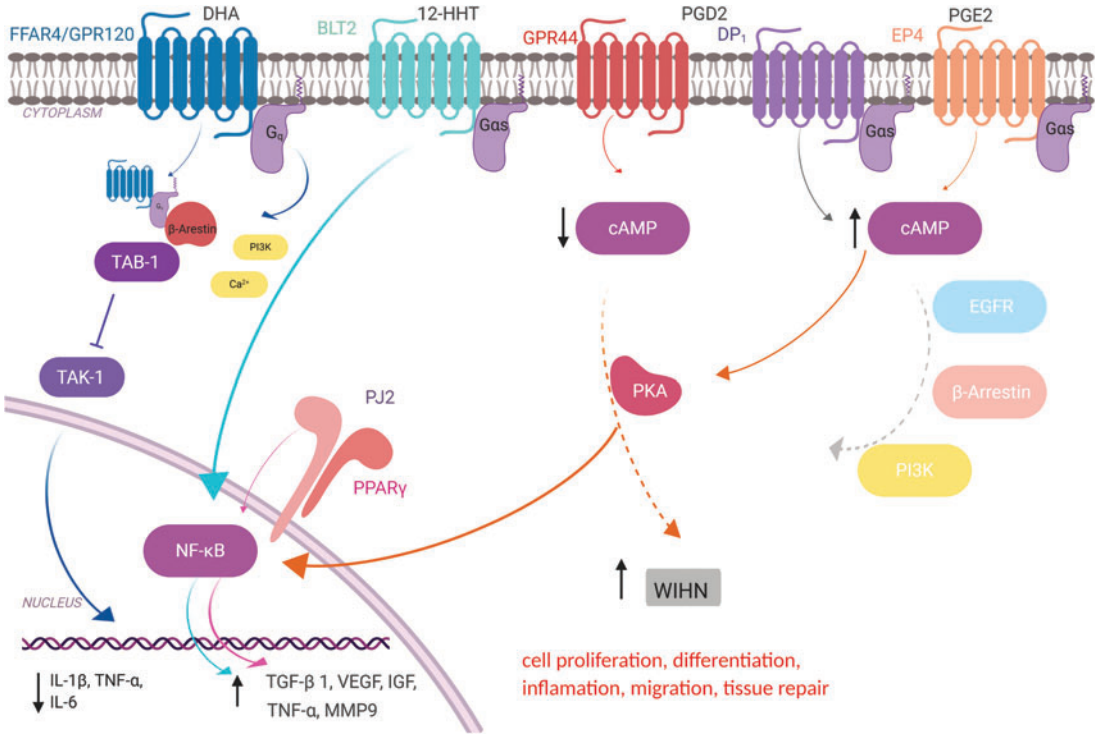

Figure 5. Schematic overview of the main receptors for fatty acids and lipid-derived substances presents in the skin and the downstream proteins involved in their intracellular signaling. FFAR4/GPR120, Free fatty acid receptor 4/G protein-coupled receptor 120 ; DHA, *Docosahexaenoic acid*; BLT2, leukotriene B4 receptor 2; 12-HHT, 12-hydroxyheptadecatrenoic acid; GPR44, G protein-coupled receptor 44; PGD_2, prostaglandin D2; DP1, prostaglandin D2 receptor 1 ; EP4, prostaglandin E2 receptor 4; PGE_2, prostaglandin E2; Gq and Gas, subtypes of the Ga protein; β-Arrestin, beta-arrestin; TAB-1, TGF-beta activated kinase 1 (MAP3K7) binding protein 1; TAK-1, mitogen-activated protein kinase 7; NF-kB, factor nuclear kappa B; Pj2, PPAR γ ligand PJ (2); PPAR-γ, peroxisome proliferator-activated receptor gamma; c-AMP, cyclic-AMP ; EGFR, epidermal growth factor receptor; PI3K, phosphatidylinositol-3-kinase; WIHN, wound-induced hair neogenesis. Color images are available online.

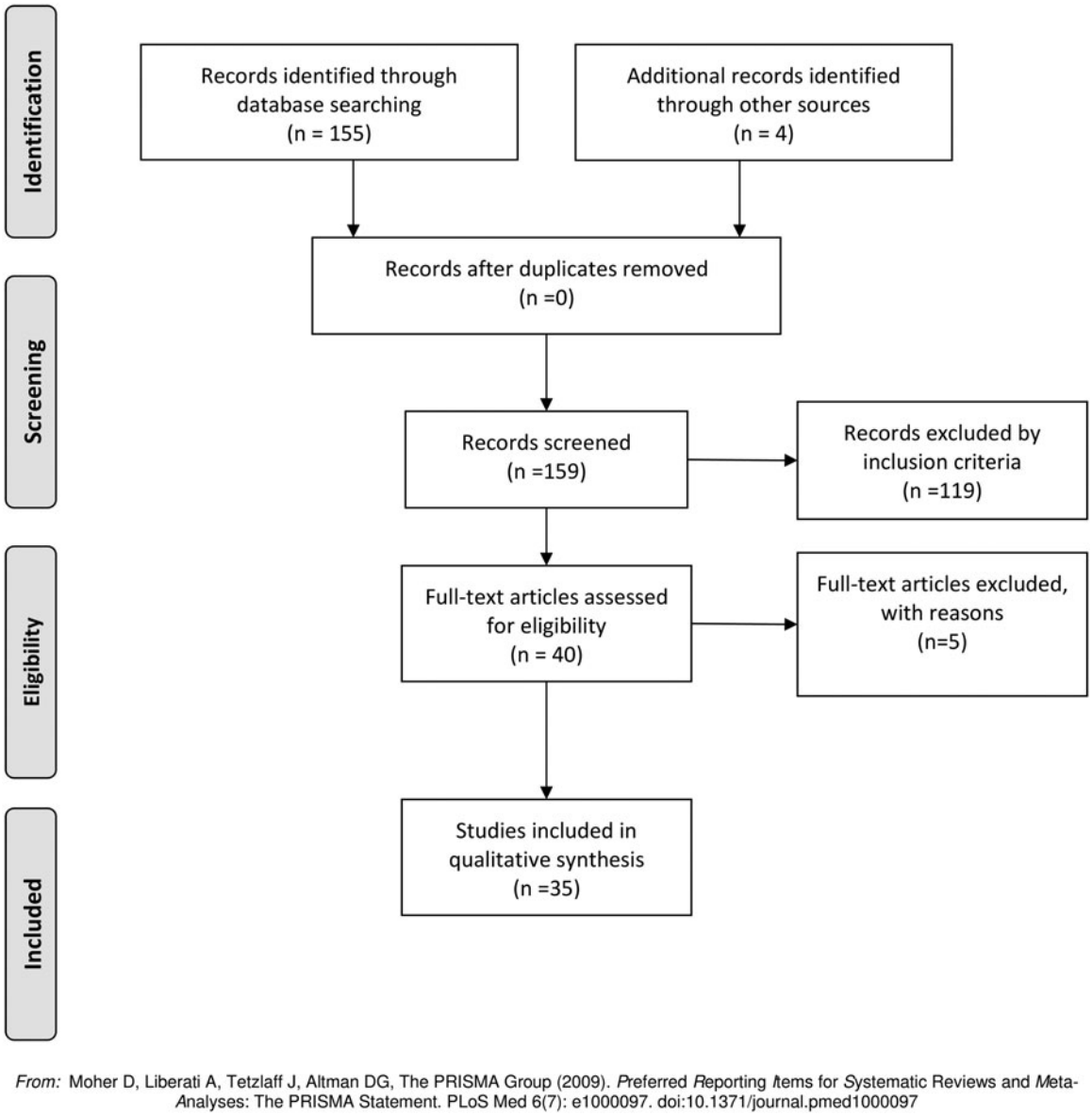

Figure 6. Systematic Review workflow. One hundred fifty-five articles were identified through database searching. Four additional articles were added from other sources. One hundred nineteen articles were excluded for not meeting the inclusion criteria. Finally, 35 articles were included for the review.

of fatty acids modulates inflammatory and immune responses during wound healing. We found that topical OA (omega-9 family) treatment significantly increases the number of neutrophils present in the wound bed.[101] A similar effect has been shown in the commercial formulation of the OA-LA mixture with acceleration of the wound healing rate and augmentation of neutrophils infiltrate.[102]

We also identified that topical treatment with olive oil (up to 80% of OA) and primrose oil (77% of LA) showed a higher wound closure rate than the control group.[103] In the same way, topical treatment with OA (omega-9) accelerated the wound closure when compared to the α-linolenic (omega 3) treated group, and modulated the inflammatory phase of wound healing, beyond enhancing the reparative response.[104] When studied separately, the topical application of OA induced faster wound closure than LA (omega-6).[104] However, treatment with ALA (omega-3) showed slower wound healing.[105] OA-based polymeric bandages speed up the wound healing time.[106] On the contrary, solid emulsion gel, as a vehicle for the delivery of the EPA-DHA mixture, achieved better speed closure than OA.[107] These data indicate that linoleic and ALA, *per se*, may not be effective to accelerate the

Table 3. *Summary of systematic review*

Year	*Fatty acids*	*Start*	*Outcome*	*Treatment*	*Model*	*Author*
2019	16% Linseed oil, 13% evening primrose oil, 16% olive oil	D0	Speed up WH	Topical	Healthy rat	Ishak[103]
2018	100 ng of RvD1, RvD2, or RvD4	D0	Speed up WH	Topical	Healthy mice	Hellmann[120]
2018	100 μM palmitoleic acid	D0	Speed up WH	Topical	Healthy rat	Weimann[121]
2017	50 μM 16,16-dimethyl PG E2	D0	Restored WIHN	injected	Healthy mice	Zhu[69]
2017	2% jasmonic acid derivative	D0	Speed up WH	Topical	Human suction blister	Henriet[130]
2017	60–70% linoleic acid from hyperoxygenated fatty acids	D0	Prevented facial PU	Topical	RCT high risk of PU	Otero[123]
2016	30 μM of Docosahexaenoic Acid	D0	Speed up WH	Topical	Healthy rat	Arantes[84]
2016	100 μM alprostadil	D0	Speed up WH	Topical	Healthy mice	Naska[110]
2015	10 μM Arachidonic acid	D0	Speed up WH	Topical	Healthy mice	Oh[113]
2015	2 mM T26A PG transporter inhibitor	D0	Speed up WH	Topical	non- and Diabetic Rat	Liu[117]
2015	50 μM PG J2 in F-127 pluronic gel	D0	Speed up WH	Topical	Diabetic mice	Mirza[99]
2015	Olive oil vs. hyperoxygenated fatty acid	ND	ND preventing PU	Topical	RCT, high risk of PU	Lupianez-Perez[126]
2014	10 μM Leukotriene B4	ND	Speed up WH	Topical	non- and Diabetic Rat	Liu[95]
2014	Extra-virgin olive oil vs. hyperoxygenated fatty acids	ND	ND preventing PU	Topical	RCT, risk of PU	Díaz-Valenzuela[125]
2013	2.5 mg/mL Lipoic Acid–loaded nanocapsules or LA	D0	Speed up WH	Topical	Healthy rat	Külkamp-Guerreiro[127]
2013	10% oleic-linoleic mixture in collagen-based films	ND	Speed up WH	Topical	Healthy rat	Santos[102]
2013	10 μg PG D2	D7	Decreased WIHN	Topical	Healthy mice	Nelson[90]
2013	hyperoxygenated fatty acids vs. triisostearin	ND	Prevented PU	Topical	RCT, high risk of PU	Torra i Bou[124]
2012	30 mg/g α-lipoic acid	D0	Speed up WH	Topical	Healthy mice	Leu[128]
2012	0.003% PGE_1	D0	Speed up WH	Topical	Rabbit ear	Arai[118]
2012	100 μg PGE_1	D0	Speed up WH	injected	Healthy rat	Takikawa[109]
2012	2 mM PG transporter inhibitor	D0	Speed up WH	Topical	Diabetic mice	Syeda[118]
2012	oleic acid based polymeric bandage	D0	Speed up WH	Topical	Healthy rat	Mohanty[106]
2011	50 ng/wound 14S,21R-dihydroxy-DHA	D2	Speed up WH	Topical	LOX-deficient Mice	Tian[115]
2011	50 ng/wound 14S,21R-dihydroxy-DHA	ND	Speed up WH	Topical	Diabetic mice	Tian[116]
2011	30 μM linolenic or 30 μM oleic acids	D0	OA Speed up WH	Topical	Healthy mice	Cardoso[104]
2010	50 ng 14S,21-diHDHA or 14R,21-diHDHA	D0	Speed up WH	Topical	Healthy mice	Lu[114]
2010	0.1 g fatty acid extracts of dried Lucilia sericata larvae	D0	Speed up WH	Topical	Healthy rat	Zhang[129]
2008	99% 300 μL linoleic acid or 99% 300 μL oleic acid	D0	Increased WBC	Topical	Healthy rat	Pereira[101]
2008	99 mg/g oleic acid or 48 mg/g icosapentaenoic acid	D0	EPA Speed up OA	Topical	Healthy Pig	Shingel[107]
2008	23% PA and 21% EPA or 19% AA and 16% PA	ND	Speed up WH	Topical	Burned Rat	Badiu[122]
2004	30 μM linolenic, 30 μM linoleic, or 30 μM oleic acids	D0	OA Speed up LA Speed down WH	Topical	Healthy mice	Cardoso[105]
2003	8 μg PGE_2	D0	Restored WIHN	Topical	COX inhibited Mice	Kämpfer[119]
2001	10 μg PGE_1 in collagen matrix	D0	Speed up WH	Topical	Healthy Rabbits	Ono[111]
1999	100 μg/g prostacyclin analogue SM-10902	D0	Speed up WH	Topical	Diabetic mice	Yamamoto[112]

Fatty acids and by-products used in wound healing.
All outcomes $p < 0.05$.
WH, wound healing; PU, pressure ulcers; LOX, lipoxygenase; WBC, white blood cell; AA, arachidonic acid; PA, palmitic acid; OA, oleic acid; LA, linoleic acid; EPA, eicosapentaenoic acid; WIHN, wound-induced hair neogenesis, start ND, not described; outcome ND, no difference; RCT, randomized controlled trial.

wound closure, but their bioactive products, generated by COX and LOX actions, such as prostaglandins, thromboxanes, and leukotrienes, could be more effective.

In fact, some prostaglandins have also been shown to enhance wound closure. PGE_1 by itself,[108–110] or in a collagen matrix,[111] speeds up wound healing time. Moreover, accelerated wound closure and epithelization were increased using an agonist of PPAR-γ, which is activated by 15-deoxy-Δ-12,14-prostaglandin J2 (15d-PGJ2), in diabetic animals.[99] This article observed that this agonist raised the chemotaxis of $CD31^+$ cells in the wound, and raised VEGF concentration, which probably acted together to facilitate the acceleration of wound closure in these diabetic animals. Another study with prostanoids showed that topical treatment with an analog (SM-10902) of prostacyclin, also known as PGI2, increased skin blood flow, the formation of new vessels, and decreased the wound lesion area in diabetic mice.[112] Even treatment with AA has been shown to be effective for accelerating wound closure.[113] In addition, Leukotriene B4, produced by the oxidation of AA via the LOX pathway in neutrophils and macrophages, also accelerated wound closure in diabetic animals.[95] Treatment with 14,21-dihydroxy-DHA, a novel bioproduct from the omega-3 family, has been shown to accelerate wound epithelialization, increase the number of new vessels, and increase chemotaxis of $CD31^+$ cells both in healthy and diabetic rodents.[114–116]

The data published also indicate that not only treatment with fatty acids is effective, but inhibition of prostaglandin transporter (PGT), for example, also improves wound healing in diabetes

and healthy animals, decreasing the wound area during the proliferative phase.[117,118] This occurs because PGT inhibition modulates arterial blood flow, mobilizes endothelial progenitor cells and human epidermal keratinocytes, and leads to vascularization and epithelialization in wound healing by regulating vasodilatory and proangiogenic prostaglandins.

Wound-induced hair neogenesis (WIHN), that is, the *de novo* generation of hair follicles, is a rare phenomenon in adult animals. Interestingly, we found that topical or wound-bed injected PGE_2 increased new hair follicles in the scar tissue.[69,119] Also, several histological differences were described in wounds treated with DHA. The topical application of DHA in wounded skin facilitates the formation of a new hair follicles-like structure in the scar tissue.[84] On the contrary, the topical use of PGD_2 decreased wound-induced hair follicle neogenesis.[90] WIHN using PGE_2 and DHA started when the treatment was performed during the inflammatory phase of wound healing, unlike PGD_2, where the treatment started 7 days after the wound creation. Altogether, this evidence suggests that prostaglandins could modulate WIHN and wound closure in a time-dependent manner.

Resolvins also could modulate the wound healing velocity. Topical application of resolvin D1, D2, or D4 has improved epithelialization during skin wound healing in healthy animals.[120] It is important for clinical practice since resolvin receptors are highly expressed in epidermal keratinocytes.

From another omega family, topical treatment using palmitoleic acid, an omega-7 MUFA, also decreased the wound area in healthy and burned rats.[121,122] These authors have attributed the anti-inflammatory activity of palmitoleic acid for healing, especially in the stages of granulation tissue formation and remodeling, although this fatty acid has inhibited LPS-stimulated neutrophil migration, accelerating wound healing via an anti-inflammatory effect.

It is well known that fatty acid treatment is used to prevent the development of pressure ulcers in bed-bound patients. Consistently with the prohealing benefits shown in basic research, one study has described that olive oil is more efficient than hyperoxygenated fatty acids (HOFA) for preventing pressure ulcers in bedridden patients.[123,124] On the contrary, another study performed a comparison of topical treatment using olive oil versus HOFA, it showed that there is no difference between olive oil and HOFA for preventing pressure ulcers.[125,126]

Other lipids, not fatty acids, have also demonstrated some benefits in the wound healing process of healthy animals. Alpha-lipoic acid, a natural compound with antioxidant properties and other potential health benefits, when topically applied, accelerated wound healing in healthy animals.[127,128] Also, unsaturated fatty acid extracts from dried *Lucilia sericata larvae* increased wound contraction and VEGF quantification in healthy animals.[129] More recently, the topical application of jasmonic acid, which has a similar chemical structure to prostaglandins, has improved skin healing by accelerating epithelial repair in healthy volunteers who received a suction blister induction.[130]

SUMMARY

Concluding remarks and future directions

Many efforts have been made in the field of wound care to attenuate the suffering of patients. Although wound healing is a physiological process, various disorders can delay it, which makes the injury chronic and more susceptible to infections and other related complications, especially in the skin. Different treatments have been tested in experimental and clinical studies, as well as new products have been designed, but the problem remains unsolved.

In the past few decades, lipids have emerged as a potential therapeutic target for the treatment of wounds. Due to their bioactive properties, unsaturated fatty acids (MUFAs and PUFAs) are the most studied and have been showing great results. However, most of the studies are still from basic research and, although they have shown effective results, the molecular mechanisms involved are not completely clear. It happens, in part, because fatty acids can bind to different receptors, and each receptor can activate different intracellular pathways, resulting in several possible physiologic and metabolic changes.

In this way, many experimental attempts have been performed using analog substances of lipids, or even testing receptor agonists, which can show different results from the ones observed when fatty acid is used for the treatment of wounds directly. In these cases, despite the fact that the chemical structure of the synthetic molecule is similar to the fatty acid chain, the bioactive properties cannot be mimicked completely. Besides, when fatty acids bind to their receptor, they can meddle other intracellular pathways.

Furthermore, the clinical use of these lipids depends on their stability, since they can quickly oxidize, and of their metabolization, since many enzymatic pathways such as LOX and COX can be

activated, changing the course of the fatty acid. This is an explanation for the increased use of eicosanoids and other metabolized products instead of AA or EPA/DHA in experimental studies; this should be considered especially in studies with oil blend or olive oil. These oils present different percentages of fatty acids, but their action also depends on other bioactive compounds. Olive oil, particularly, has shown many benefits in several metabolic processes, but its effect is due not only to OA but also to phenolic compounds.

Finally, the use of bioactive lipids in clinical practice can improve wound care, but there is still a lack of knowledge of the action of each fatty acid in wound repair. In this way, future studies must be conducted to clarify this subject and thus, enable the development of new effective therapeutic approaches.

TAKE-HOME MESSAGES

- Skin wound healing is an orchestrated physiological process, which occurs after the onset of a cutaneous lesion to restore the damaged tissue.
- Wound closure involves a series of events that can be divided into three phases: inflammatory, proliferative, and remodeling.
- Lipids are involved in the whole process involving wound resolution such as vascular contraction, chemotaxis, cell adhesion, and tissue restoration.
- Due to their bioactive properties, unsaturated fatty acids have emerged as a potential therapeutic target in the field of wound care.
- Oleic (ω-9), linoleic (ω-6), and α-linolenic (ω-3) acids, as well as their bioactive products, are the most common fatty acids tested in skin wounds, showing an effective role in accelerating the wound closure.
- Topical treatment with fatty acids' analogs as well as their receptors' agonist has also been demonstrating similar positive effects.
- Bioactive lipids' effects, when the treatment starts on day 0, occur mainly in the inflammatory phase of the wound healing process.
- Different bandages associated with lipid formulations have been developed and tested in clinical practice, but the incidence of complications associated with late wound closure persists.
- Future studies should be conducted for elucidating the main intracellular mechanisms of each bioactive lipid in each wound healing phase.
- Other alternatives and more efficient treatments will be better designed from this novel knowledge.

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ABOUT THE AUTHORS

Carlos P. Jara is a clinical and research nurse, Master in Health Institution Management, Master in Health Science, and PhD Student in Health Sciences at Faculty of Nursing in State University of Campinas. His expertise are skin repair and healing process, both *in vitro* and in animal models.

Natalia F Mendes is a Nutritionist, Master in Nutrition, Sports, and Metabolism, and PhD Student in Health Sciences at Faculty of Nursing, University of Campinas. Her research interests are the molecular mechanisms involved in the central and peripheral inflammation mediated by fatty acids, particularly neuroinflammation and gliosis in the hypothalamus.

Thais P. Prado has graduation and degree in nurse, Master in Health Science, and PhD Student in Health Sciences at Faculty of Nursing in State University of Campinas. Her research interests are wound healing, *in vitro* and *in vivo* animal models and humans.

Eliana P. de Araújo, MSC, PhD, is a Professor of the Nursing School, and research of the Obesity and Comorbidities Research Center, University of Campinas, Brazil. Her research focuses on molecular and cellular mechanisms of tissue repair and regeneration and mechanisms involved in the central and peripheral inflammation mediated by fatty acids.

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Abbreviations and Acronyms

12-HETE = 12-Hydroxyeicosatetraenoic acid
12-HETER = 12-HETE receptor
12-HHT = 12(S)-hydroxyheptadeca-5Z,8E, 10E-trienoic acid
15d-PGJ2 = 15-Deoxy-Δ-12,14-Prostaglandin J2
15-HETE = 15-Hydroxyeicosatetraenoic acid
AA = arachidonic acid
ALA = α-linolenic acid
AP-1 = activator protein-1
BLT = leukotriene receptor
cAMP = cyclic adenosine monophosphate
COX = cyclooxygenase
CRTH2 = chemoattractant receptor-homologous molecule expressed on Th2 cells
DC = dendritic cell
DHA = docosahexaenoic acid
DP = D prostanoid receptor
ECM = extracellular matrix
EGF = epidermal growth factor
EP = prostaglandin receptor
EP = prostanoid receptor
EPA = eicosapentaenoic acid
ETE = 5-oxo-eicosatetraenoic
EVOO = extra-virgin olive oil
FFAR4 = free fatty acid receptor 4
FGF-2 = fibroblast growth factor 2
GPCR = G protein-coupled receptor
GPCR = G protein-coupled receptor
HETE = 5-eicosatetraenoic

HIF-1 = hypoxia-inducible factor-1
HOFA = hyperoxygenated fatty acids
HPETE = 5-hydroperoxy-eicosatetraenoic acid
IFN-γ = interferon-gamma
IGF-1 = insulin-like growth factor 1
IkB = inhibitor of kB
IL = interleukin
JNK = c-Jun N-terminal kinase
LA = linoleic acid
LOX = lipoxygenase
LT = leukotriene
LXA_4 = lipoxin A4

MC = mast cell
MCP-1 = monocyte chemoattractant protein 1
MMP = metalloproteinases
MUFA = monounsaturated fatty acid
NFkB = factor nuclear kappa B
OA = oleic acid
PDGF = platelet-derived growth factor
PG = prostaglandin
PGT = prostaglandin transporter
PI3K = phosphoinositide 3-kinase
PKA = protein kinase A

PPAR = peroxisome proliferator-activated receptor
PUFA = polyunsaturated fatty acids
Rv = resolvin
TGF-β1 = transforming growth factor β1
TIMPs = tissue inhibitors of metalloproteinases
TNF-α = tumor necrosis factor-alpha
TP = thromboxane receptor
TX = tromboxane
VEGF = vascular endothelial growth factor
WIHN = wound-induced hair neogenesis