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Review

Nitric oxide: a gas transmitter in healthy and diseased skin

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Abstract

Numerous physiological processes in the human skin are mediated by nitric oxide, a gaseous signalling molecule. Almost every type of skin cell may produce nitric oxide, it is possible to generate nitric oxide without the need of enzymes. Nitric oxide plays a crucial role in regulating apoptosis, keratinocyte differentiation and proliferation, the protective properties of the epidermal barrier, and the structure and functions of the microcirculatory bed. Nitric oxide is involved in immunological and inflammatory responses, hair growth regulation, and wound healing processes. It mediates ultraviolet-induced processes such as erythema and edema development and participates in melanogenesis. Furthermore, the ability of nitric oxide to bind reactive oxygen species and prevent lipid peroxidation gives it antioxidant qualities. This coordinated action of nitric oxide on gene expression and membrane integrity effectively protects cells from ultraviolet A-induced apoptosis and necrosis . Furthermore, nitric oxide can be considered as a molecule that inhibits the development of cancer and photoaging. It directly harms microorganisms and indirectly activates the immune system, exhibiting antibacterial, antiviral, and antifungal qualities. Notably, nitric oxide is effective against antibiotics-resistant bacteria. All of the aforementioned findings suggest that nitric oxide is a gaseous mediator that can protect skin function.

Key Words: gas transmitters; keratinocytes; microcirculation; nitric oxide; nitric oxide-gas mediators; skin protection

Introduction

Nitric oxide (NO) is a colorless gas that is just as vital to life as oxygen and is involved in many biological processes.[1] It is a transient free radical with multifaceted effects.[2] NO-acting medications (nitroglycerin sublingually, sodium nitroprusside intravenously) are prescribed for life-threatening illnesses such angina attacks and hypertension.[3] The ability of this gas molecule to act as a signaling molecule, which facilitates "communication" between cells, is its primary relevance in cellular activities.[4] The enzyme NO synthase (NOS) converts the amino acid L-arginine into NO, which permeates cell membranes.[5] The quick diffusion of NO greatly influences its range of activity. At 37°C, it was discovered that NO had a diffusion coefficient that was 1.4 times greater than that of carbon monoxide or oxygen. The study of the function of NO in dermatology is relevant because of its lipophilicity, which allows it to readily pass through the stratum corneum of the epidermis.[6]

The discovery that nitrites and nitrates are produced from endogenous sources, and that this process increases dramatically during inflammation, was crucial to the study of the regulation of the "L-arginine-NO system." It was determined that the oxidation of reduced forms of nitrogen produces nitrites and nitrates, with NO emerging as an intermediary product.[7,8]

Cyclic guanosine monophosphate, a second messenger that controls a number of cellular functions, including smooth muscle relaxation, platelet aggregation inhibition, and neurotransmission, is produced when NO-gas mediators bind to the heme component of soluble guanylylate cyclase.[3,9,10] By attaching to the thiol group of cysteine residues in proteins and enzymes through a process known as S-nitrosylation, NO helps control the activities of these molecules.[11] As a result, the NO gas mediator can alter gene expression and have an impact on apoptosis, mitochondrial respiration, and protein aggregation.[12] As a neurotransmitter, NO functions in the nervous system and is crucial for neuronal growth, synaptic plasticity induction, and neurovascular connection modulation.[13] Additionally, this gas contains antibacterial properties that either kill or stop the growth of viruses, bacteria, and other pathogens.[14,15] It also affects inflammatory processes, immunocompetent cell activities, and immune response regulation.[16] As a ubiquitous molecule that preserves the body's homeostasis, NO thus carries out significant and varied functions in several cellular processes. NO must be precisely regulated in the body because pathological disorders might result from an imbalance in its synthesis or activity.[17]

Dermatoses linked to an imbalance in the production of NO gas mediator have been the subject of intense research in recent years. NO operates as a signaling molecule in the skin at low concentrations, carrying out homeostatic and regulatory processes such as melanogenesis, vasodilation, and defense against environmental influences.[18] Excess NO can worsen the progression of immunological diseases, inflammatory processes, and conditions

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such as psoriasis, cutaneous lupus erythematosus, and allergic skin lesions.[19] The physiology of the skin, a potent store of nitrogen monoxide, its donors, and its derivatives, depends on NO.[20] NO gas mediators plays a role in immunological and inflammatory responses, keratinocyte proliferation and differentiation, wound healing, and hair growth regulation. NO mediates ultraviolet (UV) induced processes such as erythema and edema and plays a role in melanogenesis. Furthermore, NO can prevent lipid peroxidation brought on by UVA rays.[21] Cells are successfully shielded against UVA- and reactive oxygen species (ROS)-induced apoptosis and necrosis by the coordinated effects of NO on gene expression and membrane integrity.[22] Vascular endothelial growth factor, dermal and heme oxygenase-1 or Bcl-2 are among the stress-protective response genes whose expression is regulated by NO.[23,24]

There is convincing evidence that NO-gas transmitters, using various delivery options for this molecule, can serve as a potential therapy in dermatological practice.[19,20] Therefore, the purpose of this review is to examine the numerous functions that NO plays in the physiological and pathophysiological processes of the skin, as well as to consider the available data on its effectiveness in treating dermatological conditions.

Data Selection

This review included a search and evaluation of articles related to the role of NO in the skin, in dermatological diseases, and the use of NO in the treatment of dermatoses. The electronic search was performed on PubMed and Scopus databases from October 1 to November 30, 2024. All articles referenced were written in the English language and the majority of them (~% of all references) were full-text articles published from 1995 to 2024. A search was conducted for published articles using a search strategy that included search queries for basic concepts, including “nitric oxide” and terms related to the structure or physiology of the skin such as “keratinocytes,” “melanocytes,” “fibroblasts,” “fibrocytes,” “Langerhans cells,” “keratinocyte differentiation,” “apoptosis,” “keratinization,” “microcirculation,” “angiogenesis,” “melanogenesis,” “skin inflammation,” “wound healing,” “hair growth” and ”epithelialization.” A separate search strategy was to search for publications on the role of NO in various dermatoses and the possibility of using NO donors in their treatment. We used the following keywords: [“nitric oxide” OR “nitrogen oxide”] AND [“psoriasis” OR “dermatitis” OR “skin disorder” OR “dermatosis” OR “skin disease” OR “wound” OR “skin infection” OR “pigmentation” OR “warts”]. We used a variety of search terms in order to find relevant literature on the topic. In addition, terms such as “L-arginine” and “NO synthase” have been included to describe studies investigating the synthesis pathways of NO. Further screening was performed by reading abstracts and titles.

Production of Nitric Oxide-Gas Transmitters in the Skin

The NOS enzyme family, which includes neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS), is responsible for the synthesis of NO-gas mediators.[25] The first two isoforms are constitutive and initially generate small amounts of NO, which are adequate for intracellular signaling and protein activity modulation. Inflammatory cytokines, bacterial polysaccharides, endotoxins, and neuropeptides all cause the isoform (iNOS) to be produced.[26,27] The identical reaction is catalyzed by all three NOS isoforms, which transform L-arginine into L-citrulline and NO. The terminal guanidine moiety of L-arginine, the special substrate for NO production, undergoes a five-electron oxidation to produce NO.[28] NADPH, flavin adenine dinucleotide, flavin mononucleotide, and (6R-)5,6,7,8-tetrahydrobiopterin are among the cofactors needed for this process.[29]

With distinct regulatory mechanisms governing each NOS isoform, the enzymatic process of NO production is strictly regulated. For instance, intracellular calcium levels largely control the activity of eNOS and nNOS, but iNOS is produced in response to inflammatory cues and generates NO without the need for calcium. Through interactions with calmodulin, physiological levels of intracellular calcium control the activity of eNOS and nNOS; elevated calcium levels enhance the binding of calmodulin to NOS, which in turn increases NO production.[30,31] Physical stimuli (including exposure to heat and light), irritants and allergens, sex hormones, cytokines, growth factors, and bacterial lipopolysaccharides all influence the expression levels of eNOS and nNOS. Nonetheless, NOS expression is regulated differently depending on the organ.[32]

Skin damage and certain growth stimuli might cause keratinocytes in the epidermis to express more nNOS. Both nNOS and eNOS in the epidermis produce more NO when the skin is mechanically stimulated, and keratinocytes express more iNOS when exposed to UVB and UVA radiation.[33,34] Increased *iNOS* mRNA expression was shown in a recent study after the epidermal permeability barrier was acutely disrupted.[35] The skin produces NO through both enzymatic and non-enzymatic processes. NO is produced by the non-enzymatic nitrate-nitrite-NO pathway in epithelial cells.[36] NO oxidizes quickly to nitrites and nitrates, having a half-life of a few seconds. Although this route is often less important in physiological settings, it can become active in the presence of exogenous nitrites or nitrates or under specific pathological circumstances.[21]

Various skin cell types express three distinct NOS isoforms. Keratinocytes and melanocytes have been shown to express NOS, while keratinocytes, fibroblasts, Langerhans cells, and endothelial cells can induce iNOS. eNOS expression has been found in basal epidermal layer keratinocytes, dermal fibroblasts, endothelial capillaries, and eccrine glands[3] (**Figure 1**). The fine-tuning of skin functions is made possible by the spatial and temporal control of NO synthesis, which is facilitated by differential expression and regulation of NOS.[37] Along with other roles, NOS and eNOS control epithelialization, hair growth, and skin pigmentation.[11]

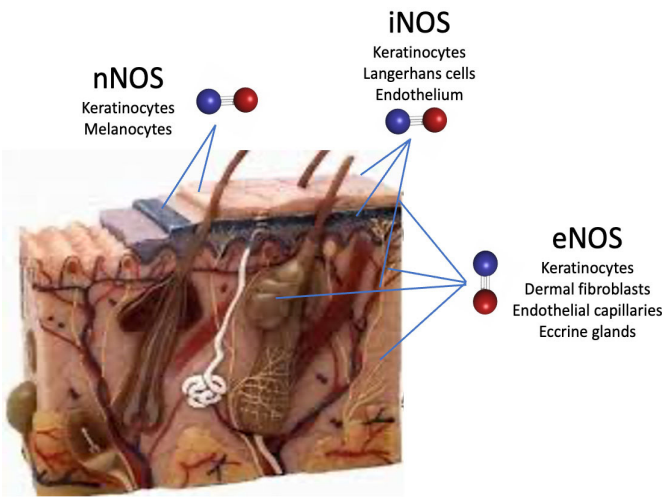

Figure 1 | **The production of NO-gas transmitters in the skin.**
Various types of skin cells express three distinct NOS isoforms (nNOS, iNOS, and eNOS). Created with Microsoft PowerPoint (Microsoft Office LTSC Professional Plus 2021). eNOS: Endothelial NOS; iNOS: inducible NOS; nNOS: neuronal NOS; NO: nitric oxide; NOS: NO synthase.

The production of NO gas mediators by eNOS in endothelial cells has a vasodilatory impact that increases blood flow to the skin. This is essential for removing metabolites, delivering nutrients, and controlling temperature. Furthermore, angiogenesis is stimulated by eNOS-derived NO, which is crucial for tissue repair.[38] An essential component of the immune response, the iNOS isoform produces NO in response to inflammatory cues or cellular stress. In macrophages and other immunocompetent cells, iNOS produces NO, which plays a role in pathogen killing and inflammation regulation.[39]

Psoriasis is one of the skin conditions linked to abnormal iNOS activity and NO generation. In contrast to healthy skin, it was demonstrated that iNOS was found in all layers of the epidermis in psoriatic lesions and was associated with the degree of inflammatory infiltration and keratinocyte proliferation. Only keratinocytes (in the granular layer) and eccrine sweat glands in healthy skin express iNOS. We were able to create a technique for instrumentally tracking the progression of dermatosis by measuring the amount of endogenous NO production in psoriatic lesions.[40,41] The activity of NOS enzymes is closely linked to the characteristics of NO gas mediators, which are both beneficial and possibly hazardous molecules in the skin. The functionality of the skin may be adversely affected by insufficient NO generation. Furthermore, too much NO causes tissue damage and dermatoses. Thus, research into the intricate function of NO gas mediators and their variants in the skin may lead to new avenues for dermatology practice.[42]

Effects of Nitric Oxide-Gas Transmitters on Microcirculation

The microcirculation in the skin is a complex network that facilitates the exchange of gases, nutrients, and waste products. It also plays a protective role for the skin in case of damage or inflammation. At the same time, changes in skin microcirculation are often observed in various dermatological diseases. These include, for example, common psoriasis, atopic dermatitis, localized scleroderma, lupus erythematosus, dermatomyositis, vasculitis, trophic ulcers and a large number of other skin pathologies.[20] The "L-arginine-NO system" has direct vascular effects, but it also regulates platelet aggregation, neutrophil adhesion, and platelet adhesion to the vascular wall. It also interacts with other factors that control these processes and thrombogenesis in general. When NO is synthesized in both endothelial cells and platelets, it inhibits the pro-aggregatory action of thromboxane A2, thereby implementing self-regulation of the platelets' own functional activity, in contrast to prostacyclin, a potent antiaggregatory factor produced by the vascular endothelium.[43]

When comparing the physiological and physicochemical characteristics of the endothelium-derived relaxing factor and the endothelium response to the introduction of bradykinin and acetylcholine with NO, an assumption regarding their identities was made.[44] The fact that endothelium-derived relaxing factor is a nitroso compound with NO as its active vasodilator component has now been established. Researchers' interest in the biological function of NO gas mediators has significantly expanded since the discovery of endothelium-derived relaxing factor.[45] As part of the metabolism of vasodilator nitrates, research on the nature of the endothelium vascular relaxation factor, non-adrenergic, non-cholinergic transmission in the nervous system, and immunogenic cytotoxicity of macrophages has shown promise.[46]

Research on the function of NO in dermal vasculature has demonstrated the range of its impacts. By enhancing the myogenic activity of arteriole and precapillary smooth muscle cells and decreasing vascular permeability, NO helps repair the microcirculatory bed's architecture and functions. This leads to a reduction in the cellular component of microcirculatory diseases, including leukocyte "plugs," platelet aggregation, microthrombosis, sludge phenomenon, and endothelial damage.[47] The physiological level of NO has been shown to increase venous outflow, decrease inflammation, and lessen microvessel reactivity using the laser Doppler flowmetry method. The degree of blood vessel lumen constriction and obliteration, as well as the restoration of pathologically altered amplitude-frequency characteristics of microcirculation, are long-term outcomes of using NO gas mediators. The skin's protective function improved as a result of the normalization of microvesselhemodynamics.[48] The information gathered significantly advances our understanding of the mechanisms underlying trophic skin lesions.

It is well known that the dermal blood vessels are surrounded by a large number of cells, including fibroblasts. In the dermis, fibroblasts are the most prevalent cell type. They are responsible for the production of the fibrous extracellular matrix that gives the skin its mechanical resilience. Human skin fibroblasts have been demonstrated to exhibit eNOS using immunocytochemistry and reverse transcription polymerase chain reaction. Following cytokine stimulation, fibroblasts have also been observed to express iNOS.[49] Fibroblasts actively produce NO during the healing of simple wounds, and this molecule functions as a regulator of the processes of collagen creation, accumulation, maturation, and fibrosis. High metabolic activity of cells is indicated by a rapid increase in the number of fibroblasts with a high cytoplasmic RNA content.[50] Human skin fibroblasts can spontaneously create NO, which is linked to the Ca^{2+}-dependent isoenzyme eNOS or, following cell activation with interferon gamma and lipopolysaccharide, to the isoform iNOS, as *in vitro* investigations have persuasively shown.[51] Numerous investigations have demonstrated a clear correlation between the amount of NO and the fibroblasts' synthetic activity and the amount of collagen generated.[52] NO-gas mediators influences various stages of the healing process, including the formation of blood vessels, the proliferation of fibroblasts, and the enhancement of cytokine release by activated macrophages.[53] In that way, NO could be considered a potential therapy for diseases associated with circulatory disorders, including autoimmune and trophic conditions, which are often difficult to treat.

Effects of Nitric Oxide-Gas Transmitters on Keratinocytes

The condition of keratinocytes plays a major role in determining the functions of the skin because they comprise 95% of all cells in the epidermis (**Figure 2**). Any disruption in the function of keratinocytes can have catastrophic consequences for the skin. As a signaling molecule that controls apoptosis, oxidative stress, cytokine production, and the protective properties of the epidermis, NO is essential.[21] Maintaining the protective role of the skin depends on the keratinization process, and NO gas mediators actively participates in regulating the growth and differentiation of keratinocytes.[54] All three NOS isoforms can be expressed by skin keratinocytes. Proliferating keratinocytes at the borders of wounds have been demonstrated to express iNOS in response to skin injury. About 10 years ago, the first line of data supporting the function of NO gas mediators function as a regulator of keratinocyte mitogenicity was acquired. As a result of the experiment, NOS inhibitors were used to limit NO generation in cells, hence inhibiting keratinocyte proliferation.[55]

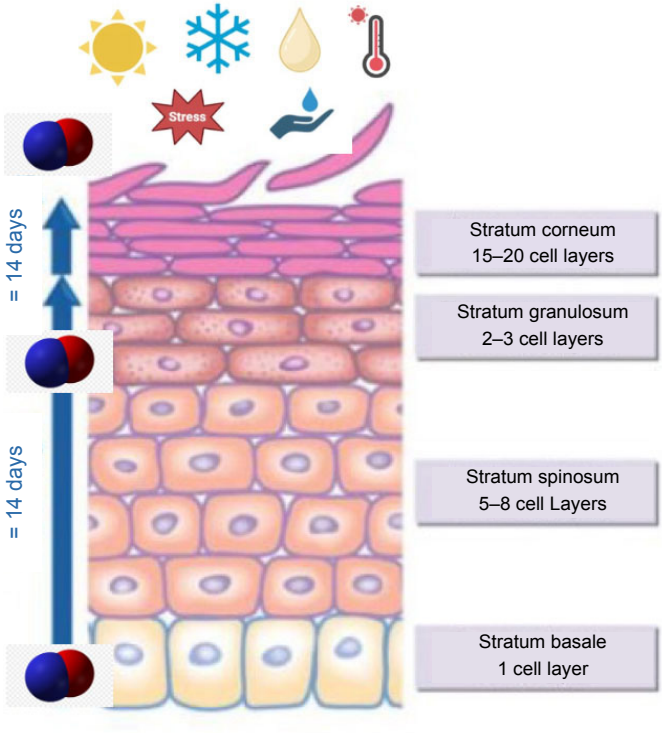

Figure 2 | The effect of NO-gas transmitters on keratinocytes.
Keratinocytes make up the majority of epidermal cells (95%). Their structural organization varies from the basal to the stratum corneum. Normally, basal keratinocytes divide every 200–400 hours. Created with Microsoft PowerPoint (Microsoft Office LTSC Professional Plus 2021). NO: Nitric oxide.

Furthermore, keratinocytes exhibit a biphasic response to NO, as demonstrated by *in vitro* experiments with NO donors. While NO slows down cell division and cytostasis at high concentrations, cell hyperproliferation is seen at low concentrations of this gas molecule.[56] Notably, the impact of NO gas mediators on intracellular superoxide levels seems to be the cause of their mitogenic potential on keratinocytes. Most significantly, several wound healing models may show that NO has mitogenic action for keratinocytes, which are the target cells. This is explained by a decrease in epithelial proliferation in burns, wounds, and damaged and photodamaged skin due to the suppression of NOS enzymatic activity. Exogenous NO can also cause keratinocytes to release key healing mediators, including polymorphonuclear leukocytes attracting CXC chemokine interleukin (IL)-8 and angiogenic vascular endothelial growth factor.[44] At the same time, there was a decrease in the expression of the CC chemokine macrophage chemoattractant protein-1.[55,57]

Notably, NO gas mediators control keratinocyte terminal differentiation in addition to proliferation, which is essential for the production of the structural proteins that make up the epidermal barrier. Mice lacking iNOS in an animal experiment displayed reduced mRNA expression of proteins linked to epidermal development. At the same time, filaggrin, loricrin, and involucrin mRNA expression levels were markedly elevated in iNOS mutant mice with local administration of chemical NO donors. Therefore, NO gas mediators are required for the epidermis to differentiate normally.[58]

We are aware of various pathological conditions that are accompanied by impairments in the integrity of the epidermal barrier and the differentiation and maturation of keratinocytes. Based on the above information, NO may be a potential target for addressing keratinocyte dysfunction and protecting the barrier.

Protective Effects of Nitric Oxide on Ultraviolet Rays-injured Skin

The methods by which NO in the skin protects against UV radiation were discussed (**Figure 3**). UV radiation-induced keratinocyte apoptosis has been thoroughly investigated. Both constitutive and induced isoforms of NO are released by the skin during UV exposure.[21,59] Numerous studies have now demonstrated the anti-apoptotic effects of NO. Depending on a number of variables, including cell type, NO gas mediator concentration, and the presence of additional active ingredients, NO can either promote or inhibit apoptosis.[60] eNOS-null mice demonstrated markedly elevated apoptosis in the epidermis and dermis in experimental animals exposed to UVB, indicating that NO has an anti-apoptotic impact.[61] Interestingly, the data show an increase in NO levels in psoriatic lesions, which may explain the hyperkeratosis and reduced apoptosis in this condition.[41] This may also be another indirect factor that determines the effectiveness of phototherapy for psoriasis. Therefore, inhibiting NOS could potentially be a solution for the treatment of psoriasis.

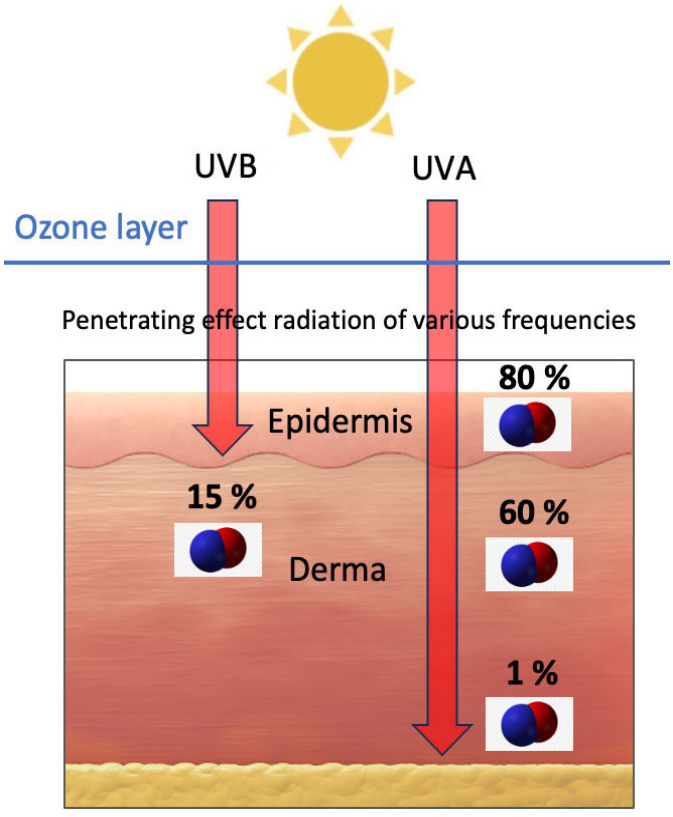

Figure 3 | NO in the skin protects against UV radiation.
Protective effects of NO, realized under the influence of UVA and UVB rays on the skin. Created with Microsoft PowerPoint (Microsoft Office LTSC Professional Plus 2021). NO: Nitric oxide; UV: ultraviolet.

Antioxidant activity of nitric oxide

The skin is the primary target of ROS when exposed to UV rays and pollutants. In addition, the high concentration of free radicals contributes to the deterioration of skin structures under adverse conditions. This may lead to processes such as slowed regeneration, disorganized collagen fibers, damaged skin microbiome, apoptosis induction, altered gene expression, metalloproteinase degradation, autoantigen protein modification, and autoimmune conditions, as well as the formation of tumor cells.[62] Antioxidant defense systems

may be linked to the anti-apoptotic impact of NO in the skin. Despite being weaker oxidants than Fenton ones, NO metabolites including peroxynitrite (NO_3^-), nitrogen dioxide (NO_2), and nitroxide (HNO) can cause oxidative stress. Lipid peroxidation also raises oxidative stress, which results in the production of several lipid oxidation products and peroxides.[63] Because of their uniform chemical makeup, NO gas mediators offer antioxidant defense against all three kinds of oxidants, mostly through interactions between ligands and metals or between radicals. Because NO may bind superoxide anion (O_2^-) to create NO_3^-, which is then swiftly transformed to nitrate, avoiding the production of ROS, NO has an antioxidant effect. Therefore, the catalytic production of ROS is inhibited by the conversion of O_2 to nitrate.[64] Numerous dermatoses are characterized by oxidative stress, which highlights the critical function of NO gas mediators in lowering the degree of oxidation in Fenton reactions.[62] It is important to remember that NO gas mediators prevent lipid peroxidation, which protects against ROS. Different lipid-oxygen and peroxyperoxide adducts are produced as a result of lipid peroxidation. Cell membrane damage may result from these chemicals' ongoing oxidation of lipids. NO provides inhibitory properties against lipid peroxidation processes by creating LOONO - a chemical comlex formed as a result of a reaction between nitric oxide and lipid peroxide radicals (LOO*). Additionally, NO inhibits lipoxygenase, which is involved in a number of lipid oxidation activities. Thus, another antioxidant characteristic of NO gas mediators may be the inhibition of lipid peroxidation.[65] Therefore, it is worthwhile to consider NO donors for use as antioxidants, especially in dermatoses, where free radicals play a role in the etiology and exacerbation of the condition.

Nitric oxide-mediated synthesis of melanin

It is well known that there are two ways that UV-induced NO generation in the skin can happen: enzyme-dependent (caused by NOS activity) and enzyme-independent. Nitrites, nitrates, and S-nitroso compounds break down into NO during enzyme-independent production when exposed to UVA.[60,66] Through NO, which has been referred to as an "evolutionary advantage," healthy skin shields cells from harm caused by outside aggressions. It is thought that UV-induced NO contributes to the mediation of pigmentation processes. Following UVA and UVB exposure, keratinocytes and melanocytes in culture release NO, which increases Cyclic guanosine monophosphate regulation, tyrosinase stimulation, and melanin synthesis.[22,40] NO-gas mediators can affect the eumelanin-pheomelanin ratio, melatonin-induced melanosome aggregation, and dendritic branching of melanocytes. This implies that a single gas molecule is intimately linked to every connection in melanogenesis. The development of post-inflammatory, endocrine, hereditary hypo- and hyper-melanosis can be influenced by dysfunction of the regulating effect of NO-gas mediators.[67]

Nitric oxide reduces pigmentation and photoaging

Photoaging and pigmentation are not limited to cosmetic dermatology. The dual nature of NO gas mediators allows them to be employed as safe tanning agents while minimizing photodamage.[68] NO gas mediators lower the risk of skin neoplasms via promoting melanogenesis. At the same time, NO slows down the aging process of the skin and the development of cancer by acting as an antioxidant and reducing the harmful effects of ROS.[69] Furthermore, fibroblasts produce more collagen type I when this signaling molecule is present during the process. Since collagen type I photodegradation is a major factor in skin photoaging, this is clinically expressed as a reduction in the depth of wrinkles.[70] Consequently, by minimizing the negative effects of sunlight while preserving the aesthetic appeal of a tan, the employment of NO gas mediators in the future can lower the dangers to the health of the skin and the human body overall.

Antibacterial and Antiviral Effects of Nitric Oxide-Gas Transmitters

NO-gas mediators, which function as cytotoxic effectors and signaling molecules, are essential for the skin's innate and adaptive immunological responses. In response to pathogen invasion, neutrophils and macrophages generate NO as part of the application of innate immunity. Inducible NOS, which is intimately linked to immunological and inflammatory processes, enables NO to fulfill its protective role. When pattern recognition receptors, including Toll-like receptors, identify pathogen-associated molecular patterns, iNOS is triggered.[71,72]

NO mediators have a bimodal, concentration-dependent antibacterial effect. By promoting immune cell proliferation, differentiation, and death, cytokine production, adhesion and costimulatory factor expression, and the creation and deposition of extracellular matrix components, they boost the immune system at low concentrations. Moreover, when bacterial LPS, endotoxins, and proinflammatory cytokines activate iNOS, a component of innate immunity, it generates a lot of NO.[73]

Macrophages are activated, their lysosome content increases, and hydrolytic enzymes, peroxidases, and catalases are triggered when different bacteria, viruses, foreign materials, etc. enter the body. The "L-arginine-NO system" was found to be a major mediator of these and other activities that make up the chemical basis of phagocytosis.[74] The O_2^-, which is also released by activated macrophages, neutrophils, and other cells, usually works in tandem with the NO released in high amounts over an extended period. The cytotoxic effects of NO_3^-, NO_2, and other reactive forms of NO (RNOS) that arise from the reaction of two radicals (NO and O_2^-) are particularly potent. The induction of nitrosative and oxidative stress, either direct or indirect (due to the production of hydrogen peroxide, alkylating agents, and inhibition of DNA repair), damage to microbial DNA, and lipid peroxidation-induced destruction of viral and microbial cell membranes are what guarantee the antimicrobial effect of RNOS.[75,76]

NO gas mediators impair mitochondrial function by suppressing ribonucleotide reductase (one of the essential enzymes in DNA replication), preventing electron transport, destroying DNA, and breaking down proteins that contain iron and copper with the release of Fe^{2+} and Cu^{2+}, among other effects. Bacterial and other foreign cells, including cancer cells, die as a result of all of this. Therefore, non-specific protection of the organism and its integuments is provided by the release of NO gas mediators under the effect of iNOS.[77]

As a potent chemotactic agent, NO gas mediators influence the activity of local cells, neutrophils, and inflammatory mediators. NO affects the recruitment and activation of immune cells at the site of infection by controlling the expression and function of several cytokines, chemokines, and adhesion molecules, which in turn controls the inflammatory response.[78] NO gas mediators have an impact on T and B cell activity during the adaptive immune response. According to studies, NO functions as a negative regulator of the immune response by preventing T cell growth, cytokine production, and death. NO gas mediatorssupport T cell activation and regular operation in specific circumstances.[79,80] As a result, NO plays an important role in the immune response's execution, guaranteeing a prompt reaction to a range of adverse consequences. It is still unclear how NO contributes to immune control in some specific ways. Additional research on the precise mechanisms underlying the effects of NO on immunity could lead to the development of novel treatment approaches for a number of illnesses linked to immunological problems.

Every year, the problem of developing new antibiotics—including those for infected dermatoses—becomes more pressing and challenging. New antimicrobial medications of non-microbial origin are desperately needed in light of antibiotic resistance. One advantage of previously shown microbicidal action of NO gas mediators is that bacteria do not develop resistance to them.This is thought to be caused by the various ways that NO works, which will force microorganisms to develop new defense systems, mutations, and other forms of variety. Numerous investigations have observed feeble compensatory mechanisms of bacterial resistance to NO, which vanished at elevated NO concentrations.[80,81] It should be mentioned that the biological characteristics of bacteria were altered by the use of NO gas mediators; specifically, previously resistant strains of bacteria showed signs of developing sensitivity.[82] Both early and later phases of the infectious process development are affected by NO-gas mediators.[83] As a result, NO is a promising chemical that could aid in the future battle against antibiotic resistance (**Figure 4**).

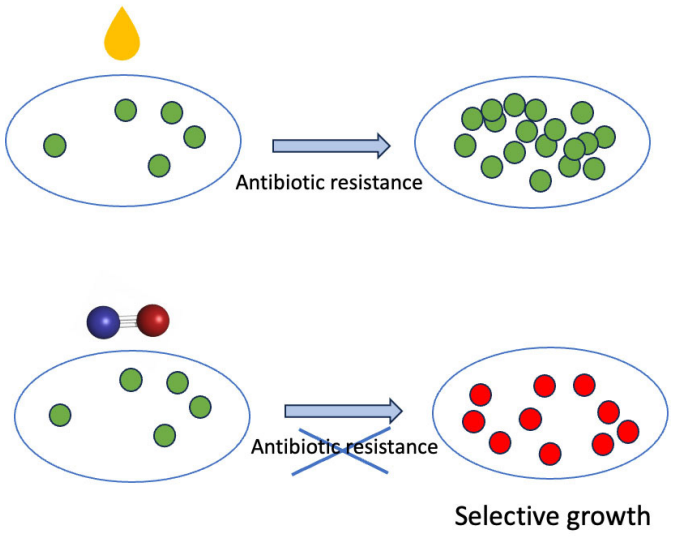

Figure 4 | **Antibacterial and antiviral effects of NO-gas transmitters.** Created with Microsoft PowerPoint (Microsoft Office LTSC Professional Plus 2021). NO: Nitric oxide.

Nitric Oxide-Gas Transmitters and Immune Disorders

Human skin, as the largest organ of the body, has a large number of cellular interactions that regulate basic physiological processes such as inflammation, immune responses, and wound healing. These processes are regulated by the immune system, which plays a protective role against both internal and external threats to the body. However, in a variety of inflammatory and autoimmune skin conditions, this complex network of interactions is disrupted, leading to the development of various skin diseases. Unfortunately, there is currently no etiological therapy available for these conditions.[20]

According to numerous studies, NO and NO gas mediators can contribute to the mechanisms underlying the development of the inflammatory process in any location, including the skin's surface. Numerous skin cell types, such as keratinocytes, fibroblasts, and immunocompetent cells, all contribute to the inflammatory response by synthesizing NO. In reaction to inflammatory stimuli, macrophages generate copious amounts of NO, which strengthens the skin's defenses.[84,85] It's interesting to note that NO itself can mimic how activated macrophages interact with target cells. It was initially shown in research on macrophages that the oxidation of amino groups in the guanidine residue of L-arginine results in the formation of NO. NO produced in Langerhans cells has cytotoxic effects, influences antigen synthesis, has antimicrobial properties, and can influence nearby melanocytes and keratinocytes.[85]

But NO, which is created when inflammation occurs in the skin, serves purposes beyond defense. Additionally, NO may play a role in the onset and advancement of inflammatory dermatoses. For instance, the development of psoriasis and atopic dermatitis is linked to excessive NO generation. Excess NO levels in some dermatoses might cause irritation and rashes to grow more often.[19,86,87]

As a result, NO plays a crucial role in controlling skin inflammation. It diffuses into the underlying tissues after being released as a result of chemical interactions, where it activates immune cells, causes blood vessels to dilate, and causes pro-inflammatory chemicals to be released from them. Therefore, NO gas mediators play a crucial role in preserving skin homeostasis by aiding in the start, progression, and cessation of inflammatory processes. The adaptability of this molecule is confirmed by the fact that NO gas mediators can have an anti-inflammatory impact via analogy with different systems and organs.[20,88] The above data are encouraging for the development of treatments for autoimmune and inflammatory skin conditions, including vitiligo, psoriasis, atopic dermatitis, scleroderma, lichen sclerosus, hyper-IgE syndrome, annular granulomas, keloid scars, pyogenic hydradenitis, and other skin conditions.

Nitric Oxide-Gas Transmitters and Vascular Disease

NO has been linked to systemic vascular disease, according to certain reports. Specifically, the work by Ene and Nicolae,[89] revealed higher NO levels in systemic lupus erythematosus and suggested using laboratory analysis of NO levels to diagnose and track disease activity. In this instance, active endothelial cells and keratinocytes were the cause of the high NO levels. According to research by İşcan et al.[90] on the impact of NO on the progression of Behcet's illness, inflammatory processes are brought on by an elevated level of NO production. In Kawasaki disease, dysregulation of NO may result in aortic aneurysm and coronary arteritis, according to Tsuge et al.[91] The effects of exogenous NO in Raynaud's syndrome patients were examined by Tucker et al.[92] The skin of the forearm and fingers were treated with a solution of neutral gel and sodium nitrite, followed by ascorbic acid, which stimulated the skin's microcirculation.

Nitric Oxide-Gas Transmitters and Skin Diseases

Numerous clinical investigations have demonstrated the effectiveness of NO gas mediators in treating both infected and non-infectious skin conditions. A wide range of species, including gram-positive and gram-negative bacteria, fungi, and parasites, are susceptible to the similarly high activity of NO, which is produced by different technologies. Specifically, the application of a NO-releasing gel to treat molluscum contagiosum has demonstrated encouraging outcomes with few adverse effects.[93] When used in conjunction with hydrogel, SB206 showed excellent tolerance and efficacy in treating perianal and genital warts.[94] SB208 was successfully and well toleratedly applied topically to treat herpes zoster.[95] Numerous microbes, including *Burkholderia cepacia*, *Mycobacterium ulcerans*, *Cutibacterium acnes*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* (including Methicillin-resistant *Staphylococcus aureus*), *Tinea pedis*, and *Trichophyton spp.*, have been demonstrated to respond favorably to the application of nitrite creams.[40]

It has also been demonstrated that NO gas mediators are useful in treating ulcerative dermatoses. Thus, a study conducted by Edmonds and his colleagues[96] revealed that the medical device EX

110, which creates NO, can expedite the healing of ulcers in patients with diabetic foot syndrome. Exogenous NO therapy has also been shown to be beneficial in treating trophic ulcers in individuals with purulent-inflammatory soft tissue disorders and chronic venous and arterial insufficiency of the lower extremities. Furthermore, NO has demonstrated efficacy in treating cicatricial skin alterations and sports injuries.[97]

NO treatment for allergic contact dermatitis (ACD) has been shown to be effective. Nitrooleic and nitrophyric acids, which are produced when NO reacts with nitrite and unsaturated fatty acids, are known to dramatically lower inflammatory cytokine production and cell infiltration in the skin of mice with ACD. Nitro fatty acids decreased the levels of IL-1β and IL-6 in this study. These proinflammatory cytokines are crucial for Th17 cell differentiation that contributes to the development of ACD.[98] Moreover, NO can affect dendritic cell migration and maturation, which are essential for presenting allergens to T lymphocytes. As a result, modifications to the NO gas mediator signaling pathway may have an impact on the severity and presentation of ACD.[99,100]

Phototherapy has demonstrated clinical effectiveness in treating psoriasis, eczema, and acne vulgaris. It turns out that phototherapy improves the condition of the skin by increasing the synthesis of NO through NOS.[40] It is crucial to thoroughly consider potential treatment options because of the intricate nature of skin conditions and the several processes involved in their emergence. Furthermore, customized patient care plans and NO gas mediator-based medication delivery devices can greatly increase therapeutic efficacy and minimize adverse effects.

Limitations

In this review, we only used databases in English and Russian, and databases in other languages were not included. Therefore, there may be a lack of literature on the use of NO for other dermatoses that were not mentioned in this work. Since the use of NO gas mediators is not a primary treatment method for dermatological conditions, available research, including *in vitro* studies, animal experiments, and clinical trials, is limited. This makes it challenging to further analyze factors influencing the effectiveness of NO gas mediators.

Conclusion

NO, a molecule, is involved in many aspects of both healthy and diseased skin processes. Researching the function of NO gas mediators is urgent and crucial for both basic and applied medicine. NO treatment for skin conditions is a novel and exciting medical trend. First of all, because NO can restore damaged microcirculation, using NO-gas mediators is a pathogenetically valid therapeutic strategy. A reduction in telangiectasias and tissue edema is a clinical manifestation of the increased vasomotions and smooth myocyte contractile activity brought on by this gas.

NO readily permeates the stratum corneum and contributes to the development of a protective layer on the skin's surface because of its lipophilicity. However, the development of a delivery platform that can provide a consistent release of NO is required for the therapeutic use of NO gas mediators. The issue of antibiotic resistance in the future may be resolved with the use of NO gas mediators, which are novel and distinct antibacterial agents. Among the benefits of NO gas mediators are their beneficial effects on the skin's protective function and blood flow. A healthy protective function provides physiological as well as aesthetic benefits, which are critical for the overall health of the human body.

The use of contemporary technologies based on NO gas mediators in dermatology is justified by the limited efficacy of conventional methods for treating dermatoses and the range of the therapeutic effects of NO. At the same time, many issues related to the use of NO in clinical practice remain unresolved. These include the lack of data on the depth of penetration of nitrogen monoxide into the skin, depending on the state of the epidermal barrier, the dysfunction of which is noted in various dermatoses. In addition, issues related to the dependence of the metabolic rate on the patient's age, the NO dose, the instability of the gas molecule itself and the effects of its metabolites on the epidermis and underlying tissues remain to be fully elucidated. Therefore, further research is needed.

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