Recent advances on endogenous gasotransmitters in inflammatory dermatological disorders

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HIGHLIGHTS

• Endogenous gasotransmitters nitric oxide (NO), carbon monoxide (CO), hydrogen sulfide (H2S), and potential candidates sulfur dioxide (SO2), methane (CH4), hydrogen gas (H2), ammonia (NH3) and carbon dioxide (CO2), are generated within the human body.
• Endogenous and potential gasotransmitters regulate inflammation, vasodilation, and oxidation in inflammatory dermatological disorders.
• Endogenous and potential gasotransmitters play potential roles in psoriasis, atopic dermatitis, acne, and chronic skin ulcers.
• Further research should explore the function of these gases and gas donors and inhibitors in inflammatory dermatological disorders.

ABSTRACT

Background: Endogenous gasotransmitters are small gaseous mediators that can be generated endogenously by mammalian organisms. The dysregulation of the gasotransmitter system is associated with numerous disorders ranging from inflammatory diseases to cancers. However, the relevance of these endogenous gasotransmitters, prodrug donors and inhibitors in inflammatory dermatological disorders has not yet been thoroughly reviewed and discussed.
Introduction

Endogenous gasotransmitters are freely permeable, small and reactive gaseous messengers, produced endogenously by an organism, being involved in several physiological processes [1]. Nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H2S) are three classical gasotransmitters, implicated in signaling pathways [2]. Other molecules such as sulfur dioxide (SO2), methane (CH4), hydrogen gas (H2), ammonia (NH3) as well as carbon dioxide (CO2), although have not been thoroughly investigated yet, or do not fully meet the diagnostic criteria for endogenous gasotransmitters, are also considered as potential gasotransmitters candidates [1]. Due to adverse effects within the body, especially in the brain and heart, these gases have long been defined as harmful molecules. Indeed, some researchers have revealed that exogenous gases can damage most organ systems in the human body [3-7]. However, later discoveries have suggested that these oxygen/nitrogen radicals may play dual roles in which they might also be beneficial, although the specific mechanism needs to be further explored. In the past few years, an increasing number of researchers have studied these gases and explored their effects within the digestive, nephritic and cardiovascular systems as well as in tumor biology, and intracellular antiviral defenses [8-13].

The skin is the largest organ in humans and plays an essential role in homeostasis, protecting the internal organs. Emerging evidence indicates that endogenous gasotransmitters are relevant to cutaneous biology and might be involved in the pathogenesis of many dermatological disorders. Indeed, the roles of gasotransmitter H2S in some skin disorders have been highlighted [14]. However, to our knowledge, the role of these endogenous gasotransmitters and related prodrug donors or inhibitors in inflammatory dermatological disorders has not yet been thoroughly reviewed and discussed. In this review, we summarize research advances and provide perspectives on NO, CO and H2S to be used in inflammatory dermatological disorders. Furthermore, we also describe the possible roles for SO2, CH4, H2, NH3 and CO2 in the skin. Finally, potential therapies targeting these molecules are also reviewed.

The main biologic production process of endogenous gasotransmitters

The endogenous generation of gasotransmitters in mammals involves various processes and needs a plethora of materials and/or enzymes. These radicals are formed as natural metabolism products and act as signaling molecules, controlling physiological processes or participating in pathological conditions. In the following paragraphs, we shall review the production and biological function of these endogenous gasotransmitters.

NO

NO is a reactive oxygen and nitrogen species (RONS) that can be produced endogenously through enzymatic and enzyme-independent pathways [15]. When the skin is exposed to ultraviolet (UV) light, vasoactive NO is formed via the enzyme-independent pathway, with the photodecomposition of cutaneous NO derivatives like nitrite and S-nitrosothiols (RSNOs) [16]. UVA irradiation of human skin results in an obvious drop in blood pressure, attributed to UVA-induced NO release, eliciting a systemic response via the blood circulation. Furthermore, Pelegrino MT et al. reported that UVB with a peak at 280–285 nm also could trigger NO generation from its storage in the skin through a non-enzymatic pathway [17].

Enzymatic pathways are based on the action of nitric oxide synthase (NOS)-like enzymes including neuronal NOS (nNOS or NOS1), inducible NOS (iNOS or NOS2), and endothelial NOS (eNOS or NOS3), using L-arginine as the substrate, and molecular oxygen and nicotinamide-adenine-dinucleotide phosphate (NADPH) as the co-substrates [18]. Generally, NOS hydroxylates L-arginine to NO-hydroxy-L-arginine, which is further oxidized to L-citrulline and NO, the final product for the effects and actions of NOSs. Usually, nNOS is constitutively expressed in the nervous system and produces small amount of NO for neuronal signaling. Similarly, eNOS is constitutively expressed in the endothelium and the activation of eNOS results in the production of low level NO, mediating cutaneous vasodilatation [19]. Conversely, iNOS, which is primarily found in fibroblasts, keratinocytes, monocytes and macrophages, is mainly induced or stimulated by pro-inflammatory cytokines and/or bacterial lipopolysaccharide (LPS), leading to the production of NO at much greater levels, thus contributing to immune response and regulation [20,21]. The production process of NO is shown in Fig. 1A.

CO

CO, another endogenously produced gas, is a biological signaling mediator. The formation of CO is generally dependent on the degradation of heme catalyzed by heme oxygenase (HO) enzymes, which are mainly divided into three subtypes (HO-1, HO-2, and HO-3), among which only the stress-inducible HO-1 and the constitutively expressed HO-2 are biologically active [22,23]. HO-1 is transcriptionally inducible by several stress events, such as oxidants, hypoxia, and cytokines. As the rate-limiting enzyme of heme catabolism, HO-1 breaks down the heme ring to biliverdin, free iron and CO, with the activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) kelch-like ECH-associated protein 1 (Keap1) signaling pathway [22]. HO-2 is mainly expressed in endothelial cells and neurons and can be induced by adrenal glucocorticoid, causing the production of CO and vasorelaxation [24]. In addition, NH3 can stimulate the expression of HO-1 in endothelial cells, which contributes to the generation of CO [25]. The production process of CO is shown in Fig. 1B.

H2S

H2S, the third endogenous gasotransmitter after NO and CO, is also a potential biologically active mediator and is generated by
either enzymatic or non-enzymatic processes [26–28]. In mammals, the enzymatic pathway is mainly attributed to L-cysteine, L-cystathionine, L-homocysteine, and \( b \)-mercaptopyruvate pyruvate, with the catalysis of cystathionine-\( \gamma \)-lyase (CSE), cystathionine-\( \beta \)-synthase (CBS), and \( 3 \)-mercaptopyruvate sulfur transferase (3-MST). In non-enzymatic production of H\( \text{2S} \) is derived from cysteine, with the presence of Vitamin B\( 6 \), pyridoxal (phosphate), and iron. (D) SO\( \text{2} \) is mainly produced via the metabolism of L-cysteine, with the catalysis of cysteine dioxygenase (CDO) and aspartate aminotransferase (AAT). H\( \text{2S} \) catalyzed by NADPH oxidases can produce sulfite, the hydrated form of SO\( \text{2} \). H\( \text{2} \) is primarily generated by hydrogenases-containing microorganisms. With the presence of H\( \text{2} \), methanogens reduce carbon dioxide, acetate, and some methyl compounds into CH\( \text{4} \). NH\( \text{3} \) is mainly produced from the breakdown of purines, pyrimidines, polyamines, amino acids, and urease-producing bacteria during cell metabolism.
amino acids L-cysteine, with the catalysis of cysteine dioxygenase (CDO) and aspartate aminotransferase (AAT) [34]. In addition, H$_2$S catalyzed by NADPH oxidases can produce sulfite [35], the hydrated form of SO$_2$.

In humans, endogenous H$_2$S is an energy source for electrons or a possible product of anaerobic metabolism and is primarily generated by hydrogenases-containing microorganisms present in the respiratory system, GI tract, oral cavity, and skin [36,37].

Meanwhile, the production of CH$_4$ or methanogenesis represents the energetic metabolism of methanogens such as Methanobrevibacter in the human intestine and skin. Methanogens are mostly involved in hydrogenotrophic metabolism requiring the presence of H$_2$ to reduce carbon dioxide, acetate, and some methyl compounds into CH$_4$ [38–40].

NH$_3$ is mainly produced from the breakdown of purines, pyrimidines, polyamines, and the deamination of several amino acids during cell metabolism [25]. In addition, urease-producing bacteria located in the GI tract can also generate NH$_3$ [41]. Finally, CO$_2$ is the gaseous product of oxidative phosphorylation in respiration. The production process of these molecules is shown in Fig. 1D.

**Design and preparation of endogenous gasotransmitters prodrug donors**

**NO**

L-arginine is a kind of amino acid serves as an endogenic NO donor, producing NO intracellularly catalyzed by NO synthase (NOS). To our knowledge, in addition to endogenic NO donor L-arginine, there are only a few small molecular NO donors that have been approved for several diseases, among which cardiovascular disease (CVD) is the most common indication. Indeed, congestive heart failure and life-threatening high blood pressure can be treated with sodium nitroprusside (SPN) [42] and organic nitrates such as glyceryl trinitrate (GTN), isosorbide mononitrate (ISMN), and pentaerythrityl tetranitrate (PETN) (Fig. 2A) [43]. Besides, inhaled NO can be used for the treatment of pulmonary diseases [44,45], and latanoprostene bunod ophthalmic solution (VYZULTA) can be used for high intraocular eye pressure in glaucoma patients [46,47].

With the discovery of nitrate tolerance and endothelial dysfunction, the development of novel NO donors has attracted significant attention from both the chemistry and medicinal fields. As a result, several recognized chemical scaffolds have been documented as parent compounds to develop novel and potent NO donors to be applied to treat diseases including not just cardiovascular disorders, but diverse cancer and neuroinflammation. Novel small molecular NO donors based on edaravone, ascorbic acid, butylated hydroxytoluene (BHT), carnosine, 3-n-butylphthalalde (NBP), ferulic acid, salicylic acid, flurbiprofen, curcumin and isostevel scaffolds are depicted in Fig. 2A [48].

Structural modifications based on edaravone, a clinical drug that can reduce ischemic injuries by scavenging free radicals, gave birth to phenylfuroxan and cyano-substituted furoxan derivatives 1 and 2, which showed remarkable antioxidant and vasodilation activities [49]. Alkyl chains containing nitrooxy or diverse furoxan moieties were added, to improve the lipophilicity of the hydrophilic antioxidant ascorbic acid, to the hydroxy groups, thus generating the derivatives 3–5 with potent antioxidant activity on lipid peroxidation [50]. Similar nitrooxy and furoxan NO donor substructures were added to other scaffolds, namely syringic acid derivative 6 and BHT derivatives 7, 8 generating LPO inhibitors and vasodilators [51]. Compound 9, derived from the histidine-containing dipeptide carnosine, was shown to have antioxidant and vasodilating activities in vitro and effective against cerebral ischemia-reperfusion injury in vivo [52]. Since impaired NO release in diseased vessels contributes to thrombus formation, NO donors display antiplatelet, antithrombotic, anti-inflammatory, and blood pressure-lowering activities. Indeed, 3-n-Butylphthalalde (NBP) has

![Fig. 2. The chemical structures of endogenous gasotransmitters prodrug donors. (A) NO donors. (B) CO donors. (C) H$_2$S donors. (D) CO$_2$ donors. (E) SO$_2$ donors.](image-url)
been utilized as a parent scaffold to develop novel antithrombotic molecules, leading to a four-carbon linker and a diethylamino side chain-fused NBP derivative compound 10 and its isosteric substituted analog 11, both of which showed an enhanced antithrombotic activity compared to that of NBP and aspirin [53]. Moreover, these compounds can be hydrolyzed into NBP and ferulic acid, a hydroxycinnamic acid (HCA) with potent antioxidant and cardioprotective properties [54,55]. Salicylic acid’s nitroxyethyl derivative 12 was shown to be an irreversible COX-1 inhibitor, while its analog 13, which bears a longer carbon chain, was selective to COX-2 [56]. Besides, aspirin-derived compound 14 that bears both an NO donor and H2S releasing moieties displayed anti-inflammatory activity and inhibited the proliferation of a panel of human cancer cell lines [57].

The use of NO donors in cancer has been regarded as a promising strategy since excessive and unregulated NO production has been implicated as a causal or contributing factor to several types of cancer. In addition to the abovementioned aspirin-derived compound 14, molecules derived from other scaffolds were also developed. Amine-based diazeniumdiolates, also called NONOates, hold the advantage of a spontaneous NO release in physiological media [58]. 5-fluorouracil (5-FU)-NONOate hybrids 15 and 16 displayed enhanced cytotoxicity on human cancer cell lines HeLa and DU145, while NONOate derivative DETA/NO(compound 17) increase pulmonary vasodilatation [59]. Curcumin and its derivatives 18–21 significantly increased nitrite production in human monocytic leukemia (THP-1) cells and showed anticancer and anti-inflammatory activities [60]. The tetracyclic diterpenoid isosteviol analog 22 displayed antiproliferative activity on B16F10 cells [61].

Besides, NO-releasing derivatives 23–25 based on ferulic acid containing a phenylsulfonylferoxan moiety were identified as compounds with a potent and broad-spectrum anti-tumor activity [62]. The ferulic acid scaffold has also been used for the development of drugs to decrease neuroinflammation [63]. Its 4-nitroxybutyl-ester derivative 26 was identified as a potent neuroprotective agent due to the inhibition of iNOS [64]. Finally, the NO-releasing neuroprotective ester 27 was derived from the nonsteroid anti-inflammatory drug (NSAID) and potent COX inhibitor Flurbiprofen [65].

CO

To break through serious obstacles of CO gas administration such as well-known toxicity, CO-releasing molecules (CO-RMs) have been designed as donors to monitor CO in cellular environments, including encapsulated CO-RMs, metal-organic framework (MOF) based CO-RMs, CO dissolved in a liquid and photosensitive metal-free CO-RMs. Selected small CO-RMs are depicted in Fig. 2B.

Organic CO donors are another type of CO prodrugs that are metal-free and light is unnecessary for CO release under physiological conditions. Norbornadien-7-ones 28, which can extrude CO via a facile chelotropic reaction with mild conditions, have been described as stable CO produg donors (Fig. 2B). Therefore, the development of strategies based on “click and release” methods and β-elimination reactions are crucial for the precursors of norbornadien-7-ones. In this context, an intramolecular reaction of tetracyclicpentapentadiones and bicyclo[6.1.0]nonyne (BCNs) has been demonstrated as an effective “click and release” way to generate norbornadien-7-ones [66]. Additionally, an intramolecular system has been found significant due to an entropic advantage. As a consequence, unimolecular CO produg donors bearing scaffolds 29 and 30, which are stable at room temperature, have been synthesized for CO release using intramolecular Diels. Furthermore, an esterase-sensitive cleavable linker was introduced as a conformational constraint to keep the alkyne group away from the cyclopentadienone group, preventing the cycloaddition until the restriction is released. As a result, two CO produg donors, which release CO when porcine liver esterase (PLE) is present, were obtained to illustrate that cleavable linkers (-Y – X-) are essential [67].

In addition to the abovementioned examples of inter or intramolecular “click and release” strategies that demonstrate that norbornadien-7-ones are the key intermediate for CO release, efforts have been made to modify the norbornadien-7-one structure to acquire more stable compounds that release CO via β-elimination. Two norborn-2-en-7-ones, 33 and 34 display outstanding stability and could release CO inside LPS-challenged RAW 264.7 cells and suppress the expression of tumor necrosis factor (TNF) [68]. Compounds 33 and 34 have an aldehyde at the C5 position and a leaving group at C6 that can be eliminated to provide a double bond between the C5 and C6 under physiological conditions. Similarly, using amide and bromide as the electron withdrawing and leaving group, respectively, organic CO produg donors 35 and 36 were designed and showed therapeutic effects both in vivo and in vitro [69]. Also, based on the fact that the increase of ROS levels could be observed in patients with conditions such as infection, cancer and inflammation, ROS-sensitive CO produg donors 37 and 38 bearing a phenylselenenium group at the C5 position were developed [70]. However, these two molecules can only release CO in cells with elevated ROS levels, becoming a potential treatment option for diseases correlated with increased ROS levels.

H2S

H2S is a relevant endogenous gasotransmitter and its potential therapeutic role led to the use of H2S on direct inhalation and simple administration of inorganic sulfide salts, such as Na2S, NaHS, CaS, recognized as fast-releasing H2S donors. In addition, some naturally occurring compounds including diallyl disulfide (DADS) diallyl trisulfide (DATS), and mixture SG1002 have been reported [71–73]. Several small synthetic H2S donors or carbonyl sulfide (COS)-based H2S donors are depicted in Fig. 2C [74].

Other endogenous gases

In addition to NO, CO and H2S, other gas molecules such as CO2 and SO2 have been recently recognized as important biological signaling molecules with implications in a wide variety of processes [75]. This led to an interest in developing donors of these gases as both research tools and potential therapeutic agents. Therefore, produg donors that release CO2 and SO2 are depicted in Fig. 2D and Fig. 2E.

Implications of endogenous gasotransmitters, prodrugs, and inhibitors in cutaneous biology and its inflammatory diseases

NO

NO is a ubiquitous cellular messenger in human skin homeostasis and can be produced by several human cell types, including keratinocytes and macrophages. Its biological function can be categorized as cyclic GMP(cGMP)-dependent signaling and cGMP-independent signaling. cGMP-dependent or classical signaling mainly involves producing the second messenger cGMP and the subsequent activation of specific downstream protein kinases G, channels, or phosphodiesterases [76]. On the other hand, when the NO concentration is higher, the cGMP-independent or non-classical signaling initiates through a covalent post-translational modification of specific proteins, i.e., cysteine and tyrosine residues in proteins, causing nitrosative stress, analogous to oxidative stress.
These functions facilitate NO taking part in several physiologic processes, such as vasodilation, antimicrobial barrier, regulation of inflammation (pro- and anti-inflammatory), autophagy, wound healing, and others [78–80]. To date, an increasing number of researchers have described the role of NO in skin diseases and suggest that NO may be regarded as a potential therapeutic target for inflammatory dermatological disorders. Table 1 depict the potential role of NO in inflammatory dermatological disorders.

**Psoriasis**

Psoriasis is a chronic, immune-mediated disease with complex pathogenesis. Genetic and environmental factors, such as immune system dysfunction, contribute to its development [81]. The proliferation of keratinocytes, increased levels of angiogenic and inflammatory mediators, and infiltration of immune cells are often found in the psoriatic skin [82]. Abeyakirthi S et al. found that arginase is overactive in lesional skin, causing increased arginine consumption while the production of NOS-derived NO is relatively decreased in psoriasis. Furthermore, compared to a vehicle control gel group, the topical application of NO donors improved the plaque in four patients with psoriasis after seven weeks [83]. However, this study included few patients and several authors report a negative and pro-inflammatory effect of NO in the pathogenesis of psoriasis.

NO levels in serum and plasma from psoriasis patients are significantly higher than those from healthy subjects [84,85]. However, the serum levels of NO were shown to decrease after therapy with methotrexate, and displayed a positive correlation with the severity of disease [85]. Besides, Zhong J et al. revealed that the expression levels of NOS2 were up-regulated in LPS- and mannan-induced psoriasis and PsA (MIP) could be suppressed by either deletion of NOS2 or inhibition of NO synthases, and NOS2-derived NO by tissue macrophages promoted MIP [86]. More recently, Skutnik-Radziszewska A et al. showed that the dysregulation of salivary glands in psoriasis patients is due to inflammation and nitrosative stress, with elevated NO concentration in the saliva and plasma. Indeed, NO is an oxidatively active molecule that regulates inflammation due to its interaction with superoxide anions to form peroxynitrite and other free radicals, suggesting a potential role in psoriasis [87].

NO is a potent regulator of keratinocyte growth and differentiation and a vasodilator and inflammatory mediator involved in skin inflammation, facilitating the development of psoriasis. Coto-Segura P et al. found that eNOS gene polymorphisms may be risk factors for developing psoriasis [88]. Alba BK et al. revealed that NO bioavailability is reduced in individuals with psoriasis, resulting in systemic microvascular dysfunction and impaired endothelium-dependent vasodilation [89]. Furthermore, the degree of psoriatic symptoms is directly related to reductions in NO-dependent vasodilation [89]. Guryanova S et al. revealed that muramyl peptide, a ligand of innate immunity receptors, improves plaque psoriasis, with the ability to normalize the balance of immunocompetent cells and NO [90]. This evidence indicates a possible use of NO inhibitors and potential targets for improving NO bioavailability in the treatment of psoriasis. However, as reported by Dao VT et al., all clinical attempts to inhibit NO seem to have failed even though with positive results in preclinical models [91]. More scientific studies may be needed to explore the efficiency of these NO inhibitors.

**Atopic dermatitis**

Atopic dermatitis (AD) or eczema is a common inflammatory skin disorder characterized by intense itching and recurrent eczematous lesions. The complex and multifactorial causes, such as genetic background, skin microbiome abnormalities, skin bar-

| Table 1 | The potential role of NO in inflammatory cutaneous diseases. |
|---------|-------------------------------------------------------------|
| Inflammatory cutaneous disease | Protective role of NO | Negative role of NO |
| Psoriasis | Arginase is overactive and NOS-derived NO production is relatively decreased in psoriatic skin [83]; An aqueous NO donor gel improves the plaque in four psoriasis patients [83]. | NO levels in saliva, serum, and plasma from psoriasis patients are significantly higher [84,85,87]; Mannan-induced psoriasis can be suppressed by either deletion of NOS2 or inhibition of NO synthase [86]; eNOS gene polymorphism may be risk factors for the development of psoriasis [88]; Muramyl peptide is helpful for plaque psoriasis because of its ability to normalize the balance of NO [90]; NO may be involved in the pathogenesis of vasodilation and erythema in AD skin [95]; iNOS-derived NO induces the production of TNF-α, a melanocyte-stimulating hormone, exacerbating the symptoms in an AD animal model [97]; Vitamin B12 cream, a NO synthase inhibitor and NO scavenger, improves pruritus and erythema in AD patients [98]. |
| Atopic dermatitis (AD) | SB414, a NO donor, is a potential treatment for AD because of its antimicrobial and anti-inflammatory activity [93]; NO released during phototherapy for AD may restore/ enhance suppressive function and Treg cell migration to the skin to dampen localized inflammation [94]. | |
| Acne | C. acnes may cause oxidative damage with increased iNOS/NO and other radicals, initiating degenerative processes of cells [101–103]; NO can be used as a therapy due to antimicrobial properties and suppression of IL-1β by the NLRP3 inflammasome [105,106]; Topical gel SB204, a NO donor, significantly decreases the percentage of both non-inflammatory and inflammatory lesions in acne vulgaris patients [107]. | |
| Allergic contact dermatitis (ACD) | Nitro-oleic acid, a electrophilic nitro-fatty acid from reactions between NO, nitrite, and unsaturated fatty acids, significantly inhibits inflammatory cell infiltration and the production of inflammatory cytokines in the ACD mice skin [111]. | |
| Alopecia areata (AA) | – | eNOS polymorphism is significantly associated to AA; [72] NO modifies erythrocytes superoxide dismutase, an important regulator of oxidative/nitrosative stress, initiating or progressing AA [116]. |
| Chronic skin ulcers or wounds | NO alleviates the inflammatory reaction, increases peri-wound cutaneous blood flow, and promotes wound healing via activating Wnt/β-catenin signaling pathway in skin ulcers [124,125]. | – |
rrier, and a predominant type-2 immune dysregulation, contribute to the form and development of AD [92]. Furthermore, increased levels of iNOS are implicated in AD skin, resulting in NO release from endothelial cells, keratinocytes, Langerhans cells and macrophages. Since NO exerts both pro- and anti-inflammatory activities, the exact role of NO in AD remains unclear. Some authors have shown that SB414, a cream containing berdazomer sodium, composed of a polysiloxane backbone with covalently bound N-diazoniumdiolate NO donors, is effective against AD due to its antimicrobial and anti-inflammatory activities [93]. In addition, Yu C et al. found that phototherapy releases NO, which may restore or enhance T cell migration and restrain localized inflammation, thus playing a therapeutic role in AD treatment [94].

However, other studies indicate that increased levels of NO may be involved in the pathogenesis of vasodilation and erythema in AD skin [95]. As a potent vasodilator, NO regulates the vascular tone and responses to histamine and prostaglandin E2 (PGE2), modulating airway inflammation, the immune system, and oxidative damage [96]. Besides, it was reported that iNOS-derived NO induces the production of α-melanocyte-stimulating hormone (α-MSH), affecting cytokine production and mediator release, which exacerbates the symptoms of an AD animal model caused by epicutaneous sensitization [97]. These studies provide new insights for therapies targeting the NO pathway to treat AD. Indeed, Stücker M et al. examined the efficacy of a vitamin B (12) cream, an NO synthase inhibitor and NO scavenger in a phase III multicentre trial, and they concluded that there is a significant improvement in the use of vitamin B (12) compared to placebo in AD patients [98].

Taken together, an imbalanced expression of NO is involved in AD development. However, the protective or negative roles for NO in this disease are controversial and further research is needed to uncover their clinical implications.

Acne and rosacea

Acne is a multifactorial inflammatory skin disease that affects the pilosebaceous follicles, with pathogenic factors such as microbial colonization with Cutibacterium acnes (C. acnes, also named Propionibacterium acnes, P. acnes), sebum production, and complex inflammatory pathways [99,100]. Inflammation induced by P. acnes plays a significant role in the pathogenesis of acne, with the activation of a nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasome, increased interleukin-1β (IL-1β) and TNF-α. In parallel, C. acnes may cause oxidative damage with increased iNOS, superoxide dismutase (SOD) and other radicals, initiating degenerative processes in skin cells [101-103]. Although oxidative damage aggravates inflammation, NO can be beneficial due to its antimicrobial properties and suppression of inflammatory cytokines [104]. Besides, NO can also suppress the continual production of IL-1β by the NLRP3 inflammasome [105]. Indeed, Qin M et al. provided evidence that NO-releasing nanoparticles prevent inflammation caused by P. acnes via the inhibition of microbial stimulation of the innate immune response [106]. Furthermore, another phase II study indicated that the topical gel SB204, an NO donor, significantly decreased the percentage of non-inflammatory and inflammatory lesions in acne vulgaris patients [107]. Importantly, this molecule may eliminate a clinical concern regarding the excessive use of antibiotics and bacterial resistance.

Rosacea is also a chronic inflammatory dermatosis, with recurrent flushing, persistent erythema of the central face, papulespules, telangiectasia and even phymatos changes [108]. Genetic susceptibility with dysregulation of immune and neurocutaneous pathways contribute to the pathogenesis of rosacea. Among these mechanisms, the activation of keratinocyte-derived toll-like receptor 2 (TLR2), induced by an extracellular pathogen- or damage-associated molecular patterns, such as microbes, is the classical inflammatory pathway. This facilitates the expression of the antimicrobial peptide cathelicidin and activation of the NLRP3 inflammasome [109]. The possible role of NO in the pathogenesis of rosacea is still unclear and data gathered are still limited. A study by Mehmet Ali Gürer et al. that included thirty-three rosacea patients has shown a normal serum nitrate level [110]. However, Moura AKA et al. found that the expression of iNOS is increased in rosacea lesions [111]. Since there are similar pathogenesis mechanisms between acne and rosacea, such as increased cytokines and activation of the NLRP3, NO may be a possible candidate compound to treat rosacea. However, further research is needed to explore the correlation between NO and rosacea.

Other inflammatory dermatological disorders

A few studies have focused on the association between NO and other skin diseases. Allergic contact dermatitis (ACD) is a common inflammatory dermatosis, mainly mediated by antigen-specific T cells. It is suggested that low NO levels facilitate the attraction of neutrophils, while high levels of NO are anti-inflammatory [112]. Mathers AR et al. revealed that nitro-oleic acid, an electrophilic nitro-fatty acid obtained from reactions between NO, nitrite, and unsaturated fatty acids, significantly inhibits the infiltration of inflammatory cells and the production of inflammatory cytokines in the skin of ACD mice [113].

Alopecia areata is a common inflammatory and nonscarring type of hair loss with complex pathogenesis that involves genetic, innate and adaptive immune pathways (T-cell involvement), as well as oxidative stress [114]. It has been shown that eNOS polymorphism is significantly associated with AA [115]. In addition, a previous study indicated that NO modifies SOD in erythrocytes, which is an important regulator of oxidative/nitrosative stress, thus contributing to the development of AA [116].

Besides, chronic skin ulcers or wounds are non-healed wounds caused by the inflammation of the epidermis up to the dermis, mainly associated with systemic diseases or mechanical damage, such as diabetic skin wounds, and pressure ulcers [117]. Moreover, skin and GI mucosa share some important characteristics, such as being physical protective barriers and richly vascularized in the histologic structures, and both of them are complex immune organs that play critical roles in the overall immune systems and homeostasis [118,119]. It was reported that NO antagonized the gastric ulceration through a cytoprotective way [120]. Also, previous research revealed that NO donors, such as glyceryl trinitrate (GTN), isosorbide dinitrate (IDN) and molsidomine (MOL) had protective effect on the gastric electrolyte barrier [121]. Furthermore, since there are similar pathophysiologic healing processes between skin wounds and gastric ulcers, with inflammation, proliferation, and remodeling [122,123], thus they may have similar treatment methods. In fact, several studies have found that NO can alleviate the inflammatory reaction, increasing peri-wound cutaneous blood flow and promoting wound healing via the activation of the Wnt/ji-catenin signaling pathway [124,125]. Taken together, these data support that NO donors are a promising treatment strategy for skin ulcers.

CO

CO has traditionally been considered a poison due to its high affinity for hemoglobin (Hb) and O2 transport and delivery inhibition. However, CO also serves as a therapeutic molecule for neural and vascular systems because of its protective effects, similar to HO-1 [126]. CO can bind to heme iron and activate the hemoprotein guanylate cyclase, which inhibits cellular signaling molecules, such as p38 MAPK, NF-κB and NLRP3 inflammasome, all of which are relevant during inflammation and neuropathic pain [127,128].
The potential role of CO in inflammatory cutaneous diseases.

**Psoriasis**

Previous literature suggests a protective role for HO-1/CO in inflammatory conditions via anti-inflammatory and antioxidative mechanisms, and several researchers have shown a possible role of HO and CO in psoriasis. Increased expression of HO-1 is found in psoriatic skin and may protect from the toxic effects of ROS. Meanwhile, pharmacologic up-regulation of HO-1 was shown to improve psoriasiform lesions in guinea pigs [134,135]. As the main product of HO-1, CO seems to be the active compound responsible for improving psoriasis. Indeed, in a psoriasis mouse model induced by imiquimod, psoriasis-mediated inflammation was reduced by hybrid molecules, consisting of CO-RMs or CO donors, known to activate nuclear factor-2 erythroid factor-2 (Nrf2) and HO-1 [136]. Nrf2 is involved in the defense of tissues against oxidative and inflammatory stress given that activated Nrf2 contributes to the inhibition of NF-κB and STAT3 in psoriasis [137].

**Skin inflammation, AD, and skin wounds**

Skin inflammation, characterized by increased inflammatory cells and pro-inflammatory cytokines in dermal tissues, is a classical expression of inflammatory dermatological diseases. Recently, Lee G Y et al. showed that CO-RM-2-entrapped ultraformable liposomes (CORM-2-UDLs), exogenous counterparts that mimic CO, demonstrated anti-inflammatory properties through a decrease of the production and levels of nitrite and pro-inflammatory cytokines in vitro. Furthermore, this compound could successfully alleviate skin inflammation by reducing ear edema, neutrophil accumulation, and cytokines including IL-6, IL-1β and TNF-α expression in an acute skin inflammation model [138].

On the other hand, another group indicates that CO increases ROS concentration in biofilms, repressing the electron transport chain, displaying an antimicrobial activity against Staphylococcus aureus [139], which is an important pathogenic factor that drives inflammation in AD [140]. Also, researches found that CO could decrease ulcer size and accelerated the gastric ulcer healing [141,142]. Similarly, it was reported that the activation of the Akt/Nrf2/HO-1 pathway protects endothelial cell function, reduces inflammation, and impedes oxidative damage, facilitating the healing of skin wounds [143]. Thus, as a powerful antioxidant, anti-inflammatory and cytoprotective molecule, CO has protective effect in wounds healing and future studies should focus on the effects of CO in dermatology.

### Table 2

| Inflammatory cutaneous disease                  | Protective role of CO                          |
|-----------------------------------------------|-----------------------------------------------|
| Psoriasis                                     | The expression levels of HO-1 is increased in psoriatic skin and may play an importantly protective role from the toxic effects of ROS [134]; Pharmacologic up-regulation of HO-1 contributes to the resolution of psoriasiform skin lesions in guinea pigs [133]; Psoriasis-mediated inflammation in a mouse psoriasis model is reduced by hybrid molecules, consisting of CO-RMs or CO donors, known to activate nuclear factor-2 erythroid factor-2 (Nrf2) and HO-1 [136]. Nrf2 is involved in the defense of tissues against oxidative and inflammatory stress given that activated Nrf2 contributes to the inhibition of NF-κB and STAT3 in psoriasis [137]. |
| Acute skin inflammation                       | CO-RM-2-entrapped ultraformable liposomes (CORM-2-UDLs), mimicking the function of CO, demonstrate anti-inflammatory activity by decreasing nitrite production and pro-inflammatory cytokine levels in vitro [138]; CORM-2-UDLs ameliorate skin inflammation by reducing ear edema, pathological scores, neutrophil accumulation, and inflammatory cytokines including IL-6, IL-1β and TNF-α expression in an acute skin inflammation model [138]. |
| Chronic skin ulcers or wounds                 | The activation of the Akt/Nrf2/HO-1 pathway protects endothelial cell function, reduces inflammation, and impedes oxidative damage, facilitating the skin wounds healings [143]. |

**H2S**

H2S, initially considered a poisonous gas, is now perceived to play important roles in a series of physiological and pathological conditions. H2S acts as a signaling molecule, directly interacting with intracellular biomolecules and improving vascular remodeling through PPARs/SOD3S signaling [144,145]. H2S also mediates autophagy, with both pro- or anti-autophagy effects, which is involved in signaling pathways PI3K/Akt/mTOR, AMPK/mTOR, and others [146]. In addition, H2S protects against cell damage via PI3K/Akt/Nrf2 signaling and promotes melanocytes proliferation and melanin synthesis [147,148]. Also, H2S is an important mediator for mucosal defense and repair, affecting bacterial-epithelial interactions, and microbiota also appears to be an important target of H2S in GI tract. Moreover, H2S can regulate the immune system and is associated with various inflammatory and immune diseases [149]. Table 3 shows the potential role of H2S in inflammatory dermatological disorders.

### Table 3

| Inflammatory cutaneous disease                  | Protective role of H2S                          |
|-----------------------------------------------|-----------------------------------------------|
| Psoriasis                                     | H2S level in psoriasis patients are significantly lower than those of healthy controls [155]; H2S inhibits keratinocytes growth, adhesion and IL-8 expression through inhibiting mitogen-activated protein kinase (MAPK) signaling [156,157]; H2S donors NaHS and GYY4137 significantly enhance iNOS, resulting in the increase of NO, which down-regulates ERK1/2 activation [158]. |
| Itching-related inflammatory diseases Chronic skin ulcers or wounds | H2S donors GYY4137and NaHS significantly reduce pruritus secondary to type-2 protease activated receptors (PAR-2) activation in mice [161]; H2S accelerates wound healing via inhibiting ROS production, ERK1/2 and p38 activation and enhancing VEGF expression [163,164]. |
psoriasis [152–154]. Alshorafa AK et al. revealed that the serum H2S levels in psoriasis patients are significantly lower than those of healthy controls, while serum levels of TNF-α, IL-6 and IL-8 are significantly higher than those of controls [155]. H2S inhibits keratinocyte growth, adhesion and IL-8 expression by inhibiting the mitogen-activated protein kinase (MAPK) signaling [156,157]. In addition, H2S donors NaHS and GYY4137 significantly enhance iNOS levels, increasing NO, which down-regulates ERK1/2 activation in keratinocytes [158]. Based on these pieces of evidence, H2S-releasing agents may be promising agents to treat psoriasis.

**Other inflammatory dermatological disorders**

Studies find that the mean disulfide level is significantly higher in rosacea patients than control [159], and the serum H2S level in AD patients is also significantly higher compared to healthy controls [160]. Although it is unclear whether H2S plays a role in the development of rosacea and AD, increased H2S levels may represent a generalized response to tissue inflammation.

In addition, Coavoy-Sánchez SA et al. indicated that both H2S donors GYY4137 and NaHS significantly reduce pruritus secondary to type-2 protease activated receptors (PAR-2) activation in mice [161]. Since pruritus or itching is an unpleasant sensation relevant to disorders of the skin and other organs [162], H2S donors may be promising candidates to treat itching-related inflammatory diseases. Furthermore, like NO and CO mediator, H2S may play a positive role in the gastric ulcer healing [142] and it accelerates wound healing via the inhibition of ROS production, ERK1/2 and p38 activation and enhancement of VEGF expression [163,164], which further support the positive function of H2S donors in skin wound healing.

The possible roles of other endogenous gasotransmitters in inflammatory dermatological disorders

With a low concentration, SO2 has been found to induce vasorelaxation [165]. Furthermore, SO2 has an anti-oxidant effect due to its propensity to be oxidized and anti-inflammatory effect via the NLPR3 inflammasome signaling pathway [166]. Recently, a study has shown that SO2 can also inhibit mast cell degranulation by upregulating the CAMP pathway under hypoxic circumstance [167]. Furthermore, a GSH-responsive SO2 prodrug donor has shown that SO2 can also inhibit mast cell degranulation by upregulating the cAMP pathway under hypoxic circumstance [167]. In addition, SO2 donors NaHS and GYY4137 significantly enhance iNOS levels, increasing NO, which down-regulates ERK1/2 activation in keratinocytes [158]. Based on these pieces of evidence, H2S-releasing agents may be promising agents to treat psoriasis.

**Table 4**

| Signaling gas | Potential role in inflammatory cutaneous disease |
|--------------|-------------------------------------------------|
| SO2          | SO2 has anti-oxidant effect due to its propensity to get oxidized and anti-inflammation effect via NLPR3 inflammasome signaling pathway [166]. Inhibit mast cell degranulation by upregulating the cAMP pathway under hypoxic circumstance [167]. |
| CH4          | CH4 has a number of advantages, including neuroprotection, anti-oxidant, anti-apoptotic and anti-inflammatory properties [36,171]. H2 inhalation remarkably decreases ROS accumulation and inhibit the overexpression of inflammatory cells infiltration and pro-inflammatory cytokines (TNF-α, IL-1, IL-6 and IL-8), suppressing the formation of pressure ulcer in a mouse model [174]. |
| NH3          | NH3 promotes endothelial cell survival and has cytotoxic action via indirectly generating HO-1 and CO [25]. |

**Conclusions and future perspectives**

Endogenous gasotransmitters NO, CO and H2S regulate both physiological and pathological processes and are important signaling molecules in mammalian tissues. Furthermore, SO₂, CH₄, H₂, and NH₃ can also be generated endogenously and may participate in physiological processes. Inflammatory skin disorders cause major problems in dermatology due to their complex pathophysiologic and refractory nature. As the first endogenous gasotransmitter discovered, NO displays anti-inflammatory properties and is protective against cell apoptosis, making NO donors promising compounds to treat psoriasis, AD, acne, and rosacea. However, due to its vasodilation and pro-inflammatory function, NO may be involved in the pathogenesis of psoriasis and AD, and NO inhibitors may be useful under these circumstances. The exact role of NO in these diseases is complex and controversial, and further research is needed to explore the relationship between NO and psoriasis and AD. In addition, CO and H2S donors are also potential therapeutic gases for inflammatory skin disorders due to their antioxidant, anti-inflammatory and cytoprotective activities. Although the roles of SO₂, CH₄, H₂, and NH₃ in inflammatory dermatological disorders are unclear and remain insufficiently explored, studies have increasingly focused on the possible roles of these endogenous molecules to treat these disorders.

In addition, gaseous molecules such as CO and H2S have been reported to be potential messengers in communication in the direction from host to bacteria and microbiota also appears to be an important target of these molecules in human, especially GI tract [131,177]. Similar to microbes in GI tract, the skin is populated with millions of microbes, which participate in both the innate and adaptive responses of the cutaneous immune system [178]. In fact, studies have revealed that the unbalanced skin and gut microbiota were present in diverse inflammatory dermatological disorders, such as psoriasis, AD, acne, and rosacea [179]. Although relevant reports on the relationship between these gaseous mediators and skin microbiota are scarce, the possible role of CO and H2S on the possible modulation of skin microbiome is worth exploring and studying.

In summary, these signaling molecules offer a therapeutic potential and have attracted interest in treating inflammatory dermatological disorders due to their possible roles in skin inflammation (Fig. 3). However, the inherent labile nature of these therapeutic gases makes them challenging to store and deliver [180]. Hence, it is difficult to predict the exact contribution of these
molecules in complex immune and inflammatory processes in vivo. Further research toward developing more effective gas donors and inhibitors with a capacity for organelle-specific accumulation is needed. As the outermost layer of the body, the skin is visible, which makes these donors or inhibitors a promising alternative as controllable and precise delivery drugs in future experimental and clinical therapies against skin diseases. Besides, since topical use of non-steroidal anti-inflammatory drugs is usually used to treat inflammatory dermatological disorders, gaseous molecules-releasing anti-inflammatory drugs probably be potential dominant drugs in the development of skin-pharmacology. Also, there may also be complex interactions among various signaling molecules, further research should focus on the effects of these mediators in inflammatory dermatological disorders.
Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

Credit authorship contribution statement

Lian Wang: Conceptualization, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. Xin Xie: Formal analysis, Validation, Writing – original draft. Bowen Ke: Formal analysis, Data curation, Writing – review & editing. Fundung acquisition. Weihuang: Formal analysis, Software, Data curation. Xian Jang: Software, Writing – review & editing. Fundung acquisition. Gu He: Conceptualization, Writing – review & editing, Fundung acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We are grateful for the financial support from the National Natural Science Foundation of China (grant no. 21772131, 81872535 and 81773685), the 1.3.5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (ZYJC21002 and ZYJC18032), Clinical Research Innovation Project, West China Hospital, Sichuan University (2019XHCCX10), China Postdoctoral Science Foundation (2020M673295, 2020T130273) and the Fundamental Research Funds of Science & Technology Department of Sichuan Province (Grant Nos. 2019YFY0004 and 2017JY0075).

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