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Recent advances on endogenous gasotransmitters in inflammatory dermatological disorders

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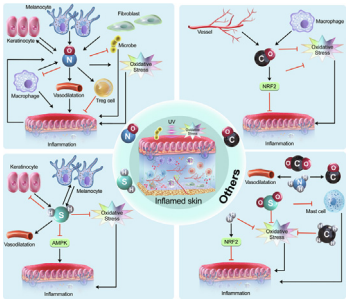
HIGHLIGHTS

- Endogenous gasotransmitters nitric oxide (NO), carbon monoxide (CO), hydrogen sulfide (H_2S), and potential candidates sulfur dioxide (SO_2), methane (CH_4), hydrogen gas (H_2), ammonia (NH_3) and carbon dioxide (CO_2), 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.

GRAPHICAL ABSTRACT



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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.

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Keywords:
Endogenous gasotransmitters
Nitric oxide
Carbon monoxide
Hydrogen sulfide
Dermatological disorder
Inflammation

Aim of review: This review discusses the recent progress and will provide perspectives on endogenous gasotransmitters in the context of inflammatory dermatological disorders.
Key scientific concepts of review: Endogenous gasotransmitters nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H_2S) are signaling molecules that regulate several physiological and pathological processes. In addition, sulfur dioxide (SO), methane (CH_4), hydrogen gas (H_2), ammonia (NH_3), and carbon dioxide (CO_2) can also be generated endogenously and may take part in physiological and pathological processes. These signaling molecules regulate inflammation, vasodilation, and oxidative stress, offering therapeutic potential and attracting interest in the field of inflammatory dermatological disorders including psoriasis, atopic dermatitis, acne, rosacea, and chronic skin ulcers. The development of effective gas donors and inhibitors is a promising alternative to treat inflammatory dermatological disorders with controllable and precise delivery in the future.
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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 (H_2S) are three classical gasotransmitters, implicated in signaling pathways [2]. Other molecules such as sulfur dioxide (SO_2), methane (CH_4), hydrogen gas (H_2), ammonia (NH_3) as well as carbon dioxide (CO_2), 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 H_2S 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 H_2S to be used in inflammatory dermatological disorders. Furthermore, we also describe the possible roles for SO_2, CH_4, H_2, NH_3, and CO_2 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 derivates 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 enzymes (NOSs) 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 Nω-hydroxy-L-arginine, which is further oxidized to L-citrulline and NO, the final product for the effects and actions of NOSs. Usually, nNOS are constitutively expressed in the nervous system and produce 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.

H_2S

H_2S, the third endogenous gasotransmitter after NO and CO, is also a potential biologically active mediator and is generated by

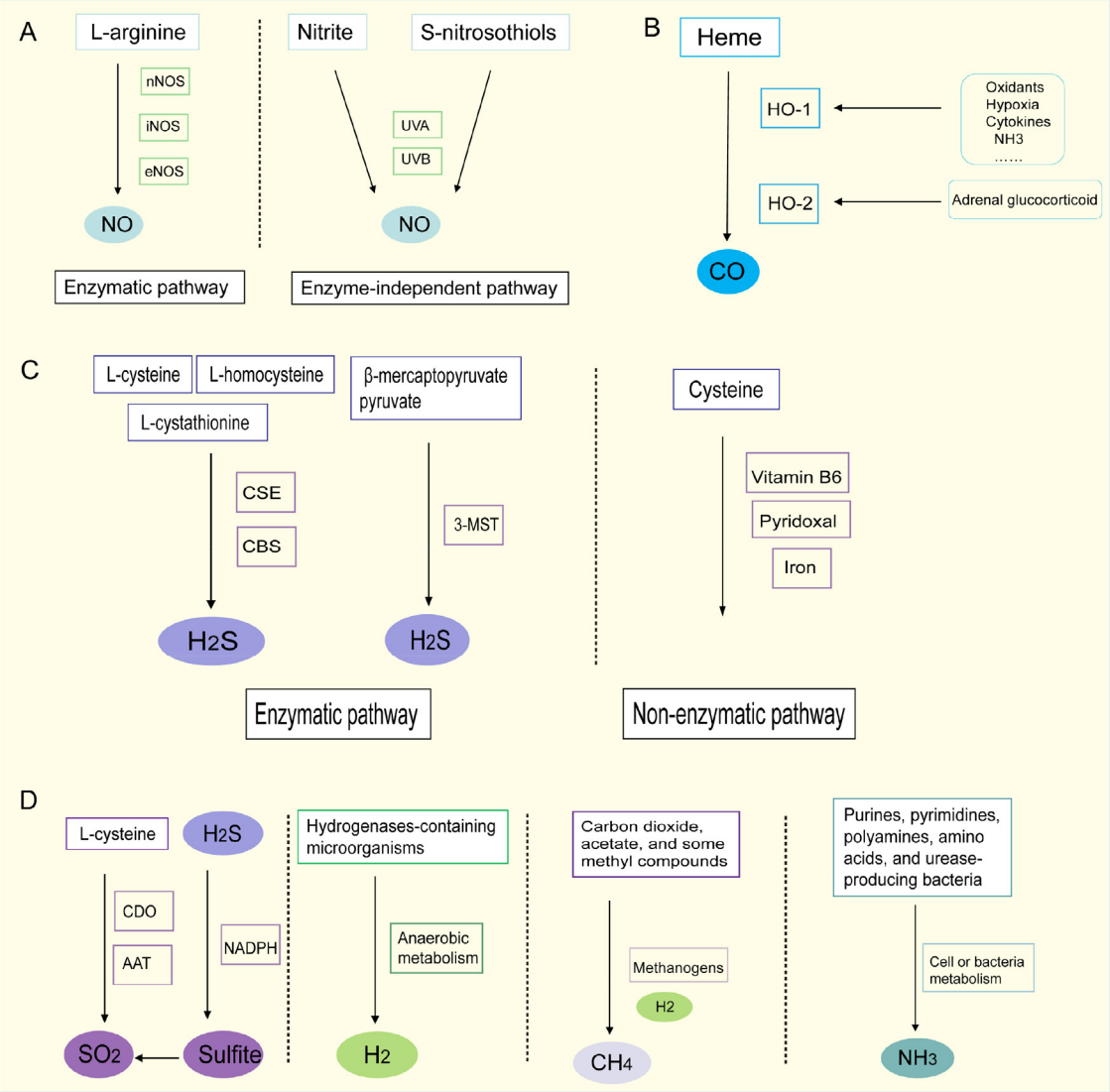

Fig. 1. The main biologic production process of endogenous gasotransmitters. (A) In enzymatic pathway, NO is formed through the decomposition of L-arginine, based on the action of nitric oxide synthase enzymes (NOSs) including neuronal NOS (nNOS), inducible NOS (iNOS), and endothelial NOS (eNOS). In enzymatice-independent pathway, when the skin is exposed to ultraviolet (UV) light, with the photodecomposition of nitrite and *S*-nitrosothiols, NO is formed. (B) The formation of CO is dependent on the degradation of heme catalyzed by heme oxygenase (HO) enzymes (HO-1 and HO-2). With stress events, such as oxidants, hypoxia, cytokines, and NH_3, HO-1 is transcriptionally inducible. HO-2 is mainly expressed in endothelial cells and neurons and can be induced by adrenal glucocorticoid. (C) The production of H_2S is based on enzymatic pathway and non-enzymatic pathway. The enzymatic pathway is mainly attributed to L-cysteine, L-cystathionine, L-homocysteine, and β-mercaptopyruvate pyruvate, with the catalysis of cystathionine-γ-lyase (CSE), cystathionine-β-synthase (CBS), and 3-mercaptopyruvate sulfur transferase (3-MST). In non-enzymatic production of H_2S is derived from cysteine, with the presence of Vitamin B6, pyridoxal (phosphate), and iron. (D) SO_2 is mainly produced via the metabolism of L-cysteine, with the catalysis of cysteine dioxygenase (CDO) and aspartate aminotransferase (AAT). H_2S catalyzed by NADPH oxidases can produce sulfite, the hydrated form of SO_2. H_2 is primarily generated by hydrogenases-containing microorganisms. With the presence of H_2, methanogens reduce carbon dioxide, acetate, and some methyl compounds into CH_4·NH_3 is mainly produced from the breakdown of purines, pyrimidines, polyamines, amino acids and urease-producing bacteria during cell metabolism.

either enzymatic or non-enzymatic processes [26–28]. In mammals, the enzymatic pathway is mainly attributed to L-cysteine, L-cystathionine and L-homocysteine, with the catalysis of cystathionine-γ-lyase (CSE) and cystathionine-β-synthase (CBS). Furthermore, with the substrate β-mercaptopyruvate pyruvate, 3-mercaptopyruvate sulfur transferase (3-MST) can synthesize H_2S in mitochondria. The non-enzymatic pathway for the H_2S production is mainly dependent on sulfur-containing amino acids cysteine, requiring coordinated catalysis by Vitamin B_6, pyridoxal (phosphate), and iron [29]. Besides, H_2S is a volatile gas and might also exist in different forms, such as a reducible form, an acid labile pool and a bound sulfane Sulphur, which can produce free hydrogen sulfide under the physiological stimuli in biological systems [30,31]. In parallel, with the presence of endogenous reductants, gastrointestinal (GI) bacteria can produce H_2S, while the extent to which bacteria-derived H_2S could modulate human function remains unclear [32]. A number of skin cells including melanocytes and keratinocytes can produce H_2S and for more detailed reviews on the production of H_2S, please refer to M. Xu *et al.* [14] and H.-J. Sun *et al.* [33]. The production process of H_2S is shown in Fig. 1C.

Other endogenous molecules

Other molecules such as SO_2, H_2, CH_4, and NH_3 can also be generated endogenously in mammals and the detailed production and biological function of these gases are reviewed below.

SO_2 has been identified as a possible endogenous gasotransmitter and is mainly produced via the metabolism of sulfur-containing

amino acids L-cysteine, with the catalysis of cysteine dioxygenase (CDO) and aspartate aminotransferase (AAT) [34]. In addition, H_2S catalyzed by NADPH oxidases can produce sulfite [35], the hydrated form of SO_2.

In humans, endogenous H_2, 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 H2 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-butylphthalide (NBP), ferulic acid, salicylic acid, flurbiprofen, curcumin and isosteviol 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 hydroxyl 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-Butylphthalide (NBP) has

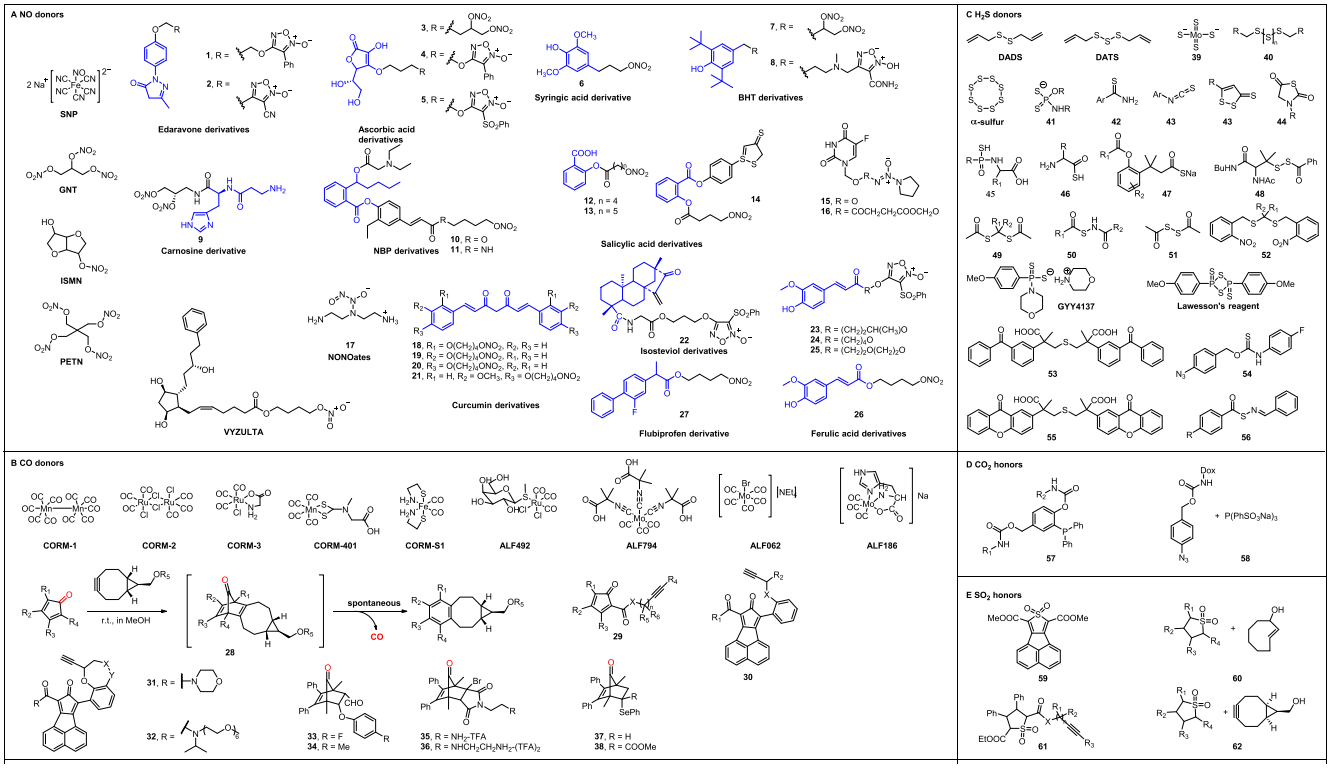

Fig. 2. The chemical structures of endogenous gasotransmitters prodrug donors. (A) NO donors. (B) CO donors. (C) H_2S donors. (D) CO_2 donors. (E) SO_2 donors.

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 NPB and ferulic acid, a hydroxycinnamic acid (HCA) with potent antioxidant and cardioprotective properties [54,55]. Salicylic acid's nitrooxyacyl 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 H_2S 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 vasodilation [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 phenylsulfonylfuroxan 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-nitrooxybutyl-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 aswell-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 cheletropic reaction with mild conditions, have been described as stable CO prodrug 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 intermolecular reaction of teteraphenylcyclopentadienones 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 prodrug 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 prodrug 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 prodrug 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 prodrug donors 37 and 38 bearing a phenyselenium 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.

H_2S

H_2S is a relevant endogenous gasotransmitter and its potential therapeutic role led to the use of H_2S on direct inhalation and simple administration of inorganic sulfide salts, such as Na_2S, NaHS, CaS, recognized as fast-releasing H_2S 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 H_2S donors or carbonyl sulfide (COS)-based H_2S donors are depicted in Fig. 2C [74].

Other endogenous gases

In addition to NO, CO and H_2S, other gas molecules such as CO_2 and SO_2 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, prodrug donors that release CO_2 and SO_2 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

[77]. 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 IFNγ-stimulated monocyte subsets from psoriatic arthritis (PsA) patients compared to those of healthy controls. Furthermore, 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 NOS 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 NOS 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 synthases[86]; eNOS gene polymorphism may be risk factors for the developing of psoriasis[88]; Muramyl peptide is helpful for plaque psoriasis because of its ability to normalize the balance of NO[90].
Atopic dermatitis(AD)	SB414, a NO donor, is a potential treatment for AD because of the 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].	NO may be involved in the pathogenesis of vasodilation and erythema in AD skin[95]; iNOS-derived NO induces the production of α-melanocyte-stimulating hormone, exacerbating the symptoms in an AD animal model[97];Vitamin B(12) cream, a NO synthase inhibitor and NO scavenger, improves pruritus and erythema in AD patients[98].
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[113].	
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 wounds healings via activating Wnt/β-catenin signaling pathway in skin ulcers[124,125].	–

rier, 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 berdazimer sodium, composed of a polysiloxane backbone with covalently bound N-diazeniumdiolate 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 Treg 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, papulopustules, telangiectasia and even phymatous 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 pathophysiological 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/β-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 O_2 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].

Besides, HO-1 and CO can modulate the mitochondria since overexpression of HO-1 and high levels of CO inhibit mitochondrial respiration, resulting in changes in mitochondrial membrane potential, ROS production and autophagy [128,129]. Furthermore, CO can also target immune responses by regulating T cell proliferation and differentiation [130]. Also, CO has been reported to be a potential messenger with communication from host to bacteria in human, especially in GI tract [131]. Hence, CO plays critical roles in biological processes, such as chronic pain, mitochondrial biogenesis, cellular proliferation, inflammation, and immune responses [127,132]. Recently, CO has been proposed as a promising therapeutic mediator due to its demonstrated cytoprotective, anti-inflammatory, anti-oxidative, and immunomodulatory effects [133]. Table 2 summarize the potential role of CO in inflammatory dermatological disorders.

Psoriasis

Previous literature suggests a protective role for HO-1/CO in inflammatory conditions via anti-inflammatory and anti-oxidative 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 ultradeformable 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*. Furhermore, 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
The potential role of CO in inflammatory cutaneous diseases.

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 [135]; 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].
Acute skin inflammation	CO-RM-2-entrapped ultradeformable 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].

H_2S

H_2S, initially considered a poisonous gas, is now perceived to play important roles in a series of physiological and pathological conditions. H_2S acts as a signaling molecule, directly interacting with intracellular biomolecules and improving vascular remodeling through PPARδ/SOCS3 signaling [144,145]. H_2S 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, H_2S protects against cell damage via PI3K/Akt/Nrf2 signaling and promotes melanocytes proliferation and melanin synthesis [147,148]. Also, H_2S is an important mediator for mucosal defense and repair, affecting bacterial-epithelial interactions, and microbiota also appears to be an important target of H_2S in GI tract. Moreover, H_2S 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.

Psoriasis

Psoriasis is characterized by hyper-proliferative keratinocytes and auto-reactive immune cells [150]. It is indicated that psoriatic keratinocytes generate excessive polyamine that upon cellular turnover activate dendritic cells, which amplify inflammation [151]. Indeed, many studies have focused on the regulation of keratinocyte proliferation, apoptosis and inflammation to improve

Table 3
The potential role of H_2S in inflammatory cutaneous diseases.

Inflammatory cutaneous disease	Protective role of H_2S
Psoriasis	H_2S level in psoriasis patients are significantly lower than those of healthy controls [155]; H_2S inhibits keratinocytes growth, adhesion and IL-8 expression through inhibiting mitogen-activated protein kinase(MAPK) signaling [156,157]; H_2S donors NaHS and GYY4137 significantly enhance iNOS, resulting in the increase of NO, which down-regulates ERK1/2 activation [158].
Itching-related inflammatory diseases	H_2S donors GYY4137and NaHS significantly reduce pruritus secondary to type-2 protease activated receptors (PAR-2) activation in mice [161].
Chronic skin ulcers or wounds	H_2S 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 H_2S 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]. H_2S inhibits keratinocyte growth, adhesion and IL-8 expression by inhibiting the mitogen-activated protein kinase (MAPK) signaling [156,157]. In addition, H_2S 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, H_2S-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 H_2S level in AD patients is also significantly higher compared to healthy controls [160]. Although it is unclear whether H_2S plays a role in the development of rosacea and AD, increased H_2S levels may represent a generalized response to tissue inflammation.

In addition, Coavoy-Sánchez SA *et al.* indicate that both H_2S 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], H_2S donors may be promising candidates to treat itching-related inflammatory diseases. Furthermore, like NO and CO mediator, H_2S also plays 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 H_2S donors in skin wound healing.

The possible roles of other endogenous gasotransmitters in inflammatory dermatological disorders

With a low concentration, SO_2 has been found to induce vasorelaxation [165]. Furthermore, SO_2 has an anti-oxidant effect due to its propensity to be oxidized and anti-inflammatory effect via the NLRP3 inflammasome signaling pathway [166]. Recently, a study has shown that SO_2 can also inhibit mast cell degranulation by the upregulation of the cAMP pathway under hypoxia [167]. Furthermore, a GSH-responsive SO_2 prodrug donor has been successfully used in the therapy of subcutaneous and metastatic melanoma therapy [168]. Meanwhile, CH_4 is inherently nontoxic and protective against apoptosis, oxidative stress, and inflammation [169,170]. Although the roles of SO_2 and CH_4 in skin inflammatory disorders are unclear, we believe that these mechanisms make them promising gases to be used in the treatment of several inflammatory dermatological disorders.

H_2 is beneficial due to its neuroprotective, anti-oxidant, anti-apoptotic and anti-inflammatory properties [36,171]. H_2 can upregulate Nrf-2 and HO-1, and downregulate the TNF-α, IL-1β, IL-6 and IL-8 [172,173]. Fang W *et al.* reveal that H_2 inhalation remarkably decreases ROS accumulation and inhibits the infiltration of inflammatory cells and pro-inflammatory cytokines (TNF-α, IL-1, IL-6 and IL-8), thus suppressing the formation of pressure ulcers in a mouse model [174]. NH_3 is a potentially important signaling mediator in the vasculature that facilitates endothelial cell survival and has cytoprotective properties via indirectly generating HO-1 and CO [25]. Endogenous stimuli-responsive CO_2 delivery is primarily used in anticancer treatment because it can be loaded with anticancer drug [175]. Besides, CO_2 therapies improves the microvasular function in diabetic skin ulcers [176]. However, the possible application of NH_3 and CO_2 still needs further exploration. Table 4 summarizes the potential roles of these mediators in inflammatory dermatological disorders.

Table 4
The potential role of SO_2, CH_4, H_2, and NH_3 in inflammatory cutaneous diseases.

Signaling gas	Potential role in inflammatory cutaneous disease
SO_2	SO_2 has anti-oxidant effect due to its propensity to get oxidized and anti-inflammation effect via NLRP3 inflammasome signaling pathway [166]. inhibit mast cell degranulation by upregulating the cAMP pathway under hypoxic circumstance [167].
CH_4	CH_4 is inherently nontoxic and protects the organ against injury through anti-apoptotic, anti-oxidative, and anti-inflammatory actions [169,170].
H_2	H_2 has a number of advantages, including neuroprotection, anti-oxidant, anti-apoptotic and anti-inflammatory properties [36,171]. H_2 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].
NH_3	NH_3 promotes endothelial cell survival and has cytoprotective action via indirectly generating HO-1 and CO [25].

Conclusions and future perspectives

Endogenous gasotransmitters NO, CO and H_2S regulate both physiological and pathological processes and are important signaling molecules in mammalian tissues. Furthermore, SO_2, CH_4, H_2, and NH_3 can also be generated endogenously and may partcipate in physiological processes. Inflammatory skin disorders cause major problems in dermatology due to their complex pathophysiology 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 H_2S donors are also potential therapeutic gases for inflammatory skin disorders due to their antioxidant, anti-inflammatory and cytoprotective activities. Although the roles of SO_2, CH_4, H_2, and NH_3 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 H_2S 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 participant in both the innate and adaptive responses of the cutaneous immune system [178]. In fact, studies have revealed that the unbalanced skin and gut microorganisms 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 microbiome are scarce, the possible role of CO and H_2S 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

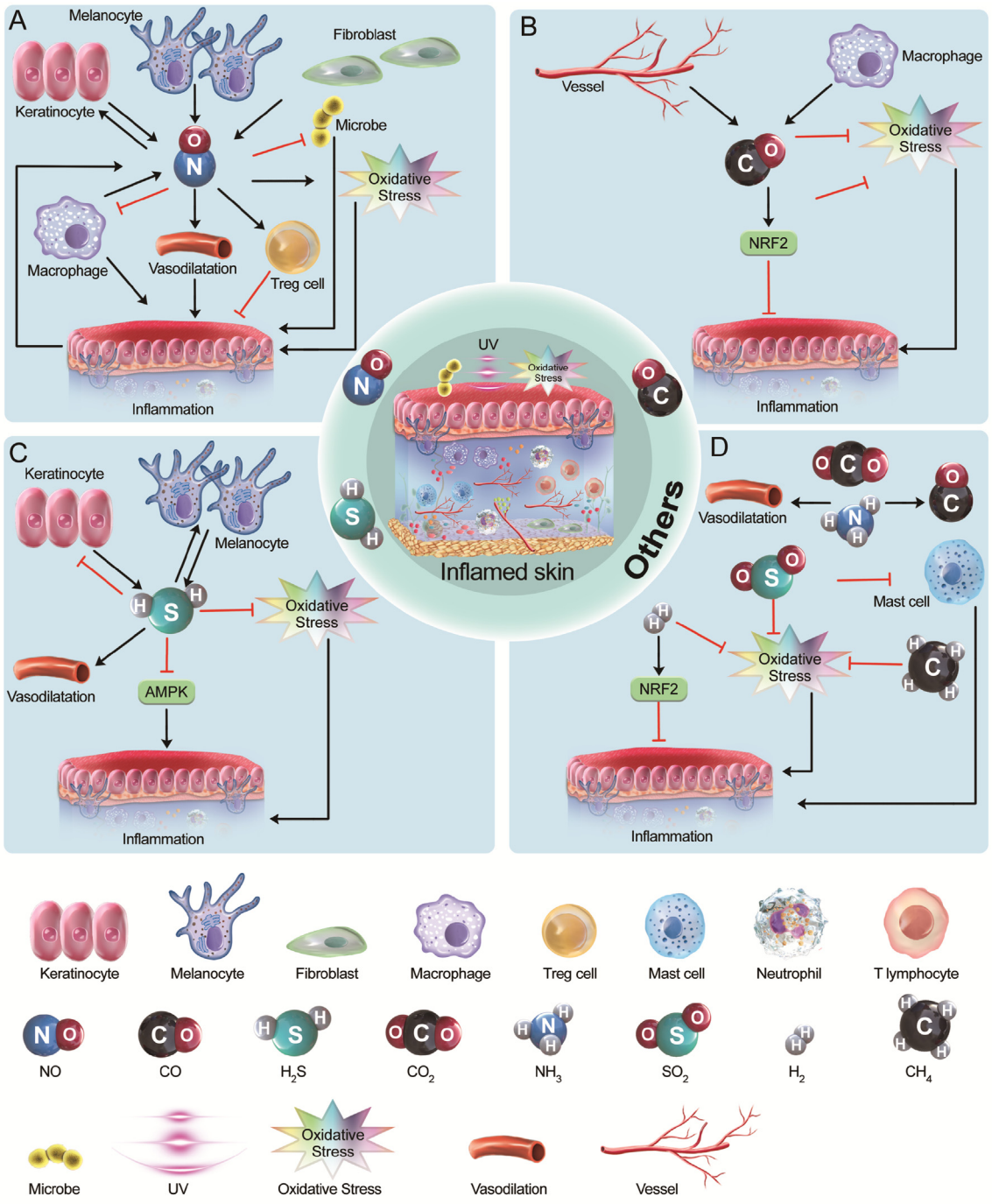

Fig. 3. The potential roles of endogenous gasotransmitters in skin inflammation. (A) Keratinocyte, melanocyte, fibroblast and macrophage produce NO, which facilitates the production of keratinocyte, regulatory T cell(Treg cell), vasodilation, and oxidative stress, while inhibits macrophage and microbe. Furthermore, Treg cell inhibits the production of inflammation, while vasodilation, macrophage, microbe and oxidative stress can cause inflammtion, which further increases the production of NO. (B) The vessel and macrophage can produce CO, which inhibit inflammtion via inhibiting oxidative stress and facilitating the production of NRF2. Oxidative stress causes skin inflammtion, but NRF2 inhibit inflammtion. (C) Keratinocyte and melanocyte produce H_2S, which facilitates the production of melanocyte but inhibts the production of keratinocyte. H_2S can inhibit inflammtion via inhibiting AMPK and oxidative stress. H_2S can also cause vasodilation. (D) CO_2 and NH_3 facilitate vasodilation and the production of CO. SO_2 can inhibit skin inflammtion with the mast cell and oxidative stress inhibition. H_2 and CH_4 also inhibit skin inflammtion through the inhibition of oxidative stress. Furthermore, H_2 facilitates the production of NRF2 to inhibit inflammtion.

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 outmost 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, Funding acquisition. **Wei Huang:** Formal analysis, Software, Data curation. **Xian Jiang:** Software, Writing – review & editing, Funding acquisition. **Gu He:** Conceptualization, Writing – review & editing, Funding 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.

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References

[1] Wang R. Gasotransmitters: growing pains and joys. Trends Biochem Sci 2014;39:227–32.
[2] Mustafa AK, Gadalla MM, Snyder SH. Signaling by gasotransmitters. Sci Signal 2009;2. re2.
[3] Schraufnagel DE, Balmes JR, Cowl CT, De Matteis S, Jung SH, Mortimer K, et al. Air Pollution and Noncommunicable Diseases: A Review by the Forum of International Respiratory Societies' Environmental Committee, Part 2: Air Pollution and Organ Systems. Chest 2019;155:417–26.
[4] Mancebo SE, Wang SQ. Recognizing the impact of ambient air pollution on skin health. J Eur Acad Dermatol Venereol 2015;29:2326–32.
[5] Farag MA, Abdelwareth A, Sallam IE, el Shorbagi M, Jehmlich N, Fritz-Wallace K, et al. Metabolomics reveals impact of seven functional foods on metabolic pathways in a gut microbiota model. J Adv Res 2020;23:47–59.
[6] Farag MA, El-Kersh DM. Volatiles profiling in Ceratonia siliqua (Carob bean) from Egypt and in response to roasting as analyzed via solid-phase microextraction coupled to chemometrics. J Adv Res 2017;8:379–85.
[7] Farag MA, Hegazi N, Dokhalahy E, Khattab AR. Chemometrics based GC-MS aroma profiling for revealing freshness, origin and roasting indices in saffron spice and its adulteration. Food Chem 2020;331.
[8] Korbut E, Brzozowski T, Magierowski M. Carbon Monoxide Being Hydrogen Sulfide and Nitric Oxide Molecular Sibling, as Endogenous and Exogenous Modulator of Oxidative Stress and Antioxidative Mechanisms in the Digestive System. Oxid Med Cell Longev 2020;2020:5083876.
[9] Lv B, Chen S, Tang C, Jin H, Du J, Huang Y. Hydrogen sulfide and vascular regulation - An update. J Adv Res 2021;27:85–97.
[10] Pieretti JC, Junho CVC, Carneiro-Ramos MS, Seabra AB. H(2)S- and NO-releasing gasotransmitter platform: A crosstalk signaling pathway in the treatment of acute kidney injury. Pharmacol Res 2020;161:105121.
[11] Li Z, Polhemus DJ, Lefer DJ. Evolution of Hydrogen Sulfide Therapeutics to Treat Cardiovascular Disease. Circ Res 2018;123:590–600.
[12] Szabo C. Gasotransmitters in cancer: from pathophysiology to experimental therapy. Nat Rev Drug Discov 2016;15:185–203.
[13] Guan SP, Seet RCS, Kennedy BK. Does eNOS derived nitric oxide protect the young from severe COVID-19 complications? Ageing Res Rev 2020;64:101201.
[14] Xu M, Zhang L, Song S, Pan L, Muhammad Arslan I, Chen Y, et al. Hydrogen sulfide: Recent progress and perspectives for the treatment of dermatological diseases. J Adv Res 2021;27:11–7.
[15] Ferreira CA, Ni D, Rosenkrans ZT, Cai W. Scavenging of reactive oxygen and nitrogen species with nanomaterials. Nano Res 2018;11:4955–84.
[16] Opländer C, Volkmar CM, Paunel-Görgülü A, van Faassen EE, Heiss C, Kelm M, et al. Whole body UVA irradiation lowers systemic blood pressure by release of nitric oxide from intracutaneous photolabile nitric oxide derivates. Circ Res 2009;105:1031–40.
[17] Pelegrino MT, Paganotti A, Seabra AB, Weller RB. Photochemistry of nitric oxide and S-nitrosothiols in human skin. Histochem Cell Biol 2020;153:431–41.
[18] Förstermann U, Sessa WC. Nitric oxide synthases: regulation and function. Eur Heart J 2012;33:829-37, 37a-37d.
[19] McNamara TC, Keen JT, Simmons GH, Alexander LM, Wong BJ. Endothelial nitric oxide synthase mediates the nitric oxide component of reflex cutaneous vasodilatation during dynamic exercise in humans. J Physiol 2014;592:5317–26.
[20] Cinelli MA, Do HT, Miley GP, Silverman RB. Inducible nitric oxide synthase: Regulation, structure, and inhibition. Med Res Rev 2020;40:158–89.
[21] Chong SZ, Tan KW, Wong FHS, Chua YL, Tang Y, Ng LG, et al. CD8 T cells regulate allergic contact dermatitis by modulating CCR2-dependent TNF/iNOS-expressing Ly6C+ CD11b+ monocytic cells. J Invest Dermatol 2014;134:666–76.
[22] Medina MV, Sapochnik D, Garcia Solá M, Coso O. Regulation of the Expression of Heme Oxygenase-1: Signal Transduction, Gene Promoter Activation, and Beyond. Antioxid Redox Signal 2020;32:1033–44.
[23] Fleischhacker AS, Carter EL, Ragsdale SW. Redox Regulation of Heme Oxygenase-2 and the Transcription Factor, Rev-Erb, Through Heme Regulatory Motifs. Antioxid Redox Signal 2018;29:1841–57.
[24] Zakhary R, Gaine SP, Dinerman JL, Ruat M, Flavahan NA, Snyder SH. Heme oxygenase 2: endothelial and neuronal localization and role in endothelium-dependent relaxation. Proc Natl Acad Sci U S A 1996;93:795–8.
[25] Liu XM, Peyton KJ, Durante W. Ammonia promotes endothelial cell survival via the heme oxygenase-1-mediated release of carbon monoxide. Free Radic Biol Med 2017;102:37–46.
[26] Singh S, Banerjee R. PLP-dependent H(2)S biogenesis. Biochim Biophys Acta 2011;1814:1518–27.
[27] Ibrahim H, Serag A, Farag MA. Emerging analytical tools for the detection of the third gasotransmitter H2S, a comprehensive review. J Adv Res 2021;27:137–53.
[28] Khalil MNA, Fekry MI, Farag MA. Metabolome based volatiles profiling in 13 date palm fruit varieties from Egypt via SPME GC-MS and chemometrics. Food Chem 2017;217:171–81.
[29] Yang J, Minkler P, Grove D, Wang R, Willard B, Dweik R, et al. Non-enzymatic hydrogen sulfide production from cysteine in blood is catalyzed by iron and vitamin B(6). Commun Biol 2019;2:194.
[30] Shen X, Peter EA, Bir S, Wang R, Kevil CG. Analytical measurement of discrete hydrogen sulfide pools in biological specimens. Free Radic Biol Med 2012;52:2276–83.
[31] Nagy P, Pálinkás Z, Nagy A, Budai B, Tóth I, Vasas A. Chemical aspects of hydrogen sulfide measurements in physiological samples. Biochim Biophys Acta 2014;1840:876–91.
[32] Flannigan KL, McCoy KD, Wallace JL. Eukaryotic and prokaryotic contributions to colonic hydrogen sulfide synthesis. Am J Physiol Gastrointest Liver Physiol 2011;301:G188–93.
[33] Sun HJ, Wu ZY, Nie XW, Wang XY, Bian JS. Implications of hydrogen sulfide in liver pathophysiology: Mechanistic insights and therapeutic potential. J Adv Res 2021;27:127–35.
[34] Singer TP, Kearney EB. Intermediary metabolism of L-cysteinesulfinic acid in animal tissues. Arch Biochem Biophys 1956;61:397–409.
[35] Mitsuhashi H, Yamashita S, Ikeuchi H, Kuroiwa T, Kaneko Y, Hiromura K, et al. Oxidative stress-dependent conversion of hydrogen sulfide to sulfite by activated neutrophils. Shock 2005;24:529–34.
[36] Ohta S. Molecular hydrogen as a preventive and therapeutic medical gas: initiation, development and potential of hydrogen medicine. Pharmacol Ther 2014;144:1–11.
[37] Ostojic SM. Non-gut microbiota as a source of bioactive hydrogen. Postgrad Med J 2017;93:170.
[38] Roberge MT, Finley JW, Lukaski HC, Borgerding AJ. Evaluation of the pulsed discharge helium ionization detector for the analysis of hydrogen and methane in breath. J Chromatogr A 2004;1027:19–23.
[39] Nose K, Nunome Y, Kondo T, Araki S, Tsuda T. Identification of gas emanated from human skin: methane, ethylene, and ethane. Anal Sci 2005;21:625–8.
[40] Chaudhary PP, Conway PL, Schlundt J. Methanogens in humans: potentially beneficial or harmful for health. Appl Microbiol Biotechnol 2018;102:3095–104.
[41] Aoyagi T, Engstrom GW, Evans WB, Summerskill WH. Gastrointestinal urease in man. I. Activity of mucosal urease. Gut 1966;7:631–5.
[42] Hottinger DG, Beebe DS, Kozhimannil T, Prielipp RC, Belani KG. Sodium nitroprusside in 2014: A clinical concepts review. J Anaesthesiol Clin Pharmacol 2014;30:462–71.
[43] Tan Z, Shang X, Li L, Tian L, Ma Y, Peng Y, et al. Clinical study of isosorbide mononitrate treatment for angina pectoris in coronary heart disease. Exp Ther Med 2013;5:1133–6.
[44] Barst RJ, Channick R, Ivy D, Goldstein B. Clinical perspectives with long-term pulsed inhaled nitric oxide for the treatment of pulmonary arterial hypertension. Pulm Circ 2012;2:139–47.

[45] Chen SH, Chen LK, Teng TH, Chou WH. Comparison of inhaled nitric oxide with aerosolized prostacyclin or analogues for the postoperative management of pulmonary hypertension: a systematic review and meta-analysis. Ann Med 2020;52:120–30.
[46] Kaufman MB. Pharmaceutical Approval Update. P t 2018;43:22–60.
[47] Hoy SM. Latanoprostene Bunod Ophthalmic Solution 0.024%: A Review in Open-Angle Glaucoma and Ocular Hypertension. Drugs 2018;78:773–80.
[48] Oliveira C, Benfeito S, Fernandes C, Cagide F, Silva T, Borges F. NO and HNO donors, nitrones, and nitroxides: Past, present, and future. Med Res Rev 2018;38:1159–87.
[49] Chegaev K, Cena C, Giorgis M, Rolando B, Tosco P, Bertinaria M, et al. Edaravone derivatives containing NO-donor functions. J Med Chem 2009;52:574–8.
[50] Cena C, Chegaev K, Balbo S, Lazzarato L, Rolando B, Giorgis M, et al. Novel antioxidant agents deriving from molecular combination of Vitamin C and NO-donor moieties. Bioorg Med Chem 2008;16:5199–206.
[51] Boschi D, Tron GC, Lazzarato L, Chegaev K, Cena C, Di Stilo A, et al. NO-donor phenols: a new class of products endowed with antioxidant and vasodilator properties. J Med Chem 2006;49:2886–97.
[52] Bertinaria M, Rolando B, Giorgis M, Montanaro G, Marini E, Collino M, et al. Carnosine analogues containing NO-donor substructures: synthesis, physico-chemical characterization and preliminary pharmacological profile. Eur J Med Chem 2012;54:103–12.
[53] Li Y, Wang X, Fu R, Yu W, Wang X, Lai Y, et al. Synthesis and evaluation of nitric oxide-releasing derivatives of 3-n-butylphthalide as anti-platelet agents. Bioorg Med Chem Lett 2011;21:4210–4.
[54] Wang B, Ouyang J, Liu Y, Yang J, Wei L, Li K, et al. Sodium ferulate inhibits atherosclerogenesis in hyperlipidemia rabbits. J Cardiovasc Pharmacol 2004;43:549–54.
[55] Wang BH, Ou-Yang JP. Pharmacological actions of sodium ferulate in cardiovascular system. Cardiovasc Drug Rev 2005;23:161–72.
[56] Cena C, Tosco P, Marini E, Lazzarato L, Piccinini M, Ramondetti C, et al. Nitrooxyacyl derivatives of salicylic acid: aspirin-like molecules that covalently inactivate cyclooxygenase-1. ChemMedChem 2011;6:523–30.
[57] Kodela R, Chattopadhyay M, Kashfi K. NOSH-Aspirin: A Novel Nitric Oxide-Hydrogen Sulfide-Releasing Hybrid: A New Class of Anti-inflammatory Pharmaceuticals. ACS Med Chem Lett 2012;3:257–62.
[58] Lam CF, Van Heerden PV, Blott J, Roberts B, Ilett KF. The selective pulmonary vasodilatory effect of inhaled DETA/NO, a novel nitric oxide donor, in ARDS-a pilot human trial. J Crit Care 2004;19:48–53.
[59] Cai TB, Tang X, Nagorski J, Brauschweiger PG, Wang PG. Synthesis and cytotoxicity of 5-fluorouracil/diazeniumdiolate conjugates. Bioorg Med Chem 2003;11:4971–5.
[60] Ahmed MM, Khan MA, Rainsford KD. Synthesis of thiophene and NO-curcuminoids for antiinflammatory and anti-cancer activities. Molecules 2013;18:1483–501.
[61] Wang TT, Liu Y, Chen L. Synthesis and cytotoxic activity of nitric oxide-releasing isosteviol derivatives. Bioorg Med Chem Lett 2014;24:2202–5.
[62] Li W, Li N, Tang Y, Li B, Liu L, Zhang X, et al. Biological activity evaluation and structure-activity relationships analysis of ferulic acid and caffeic acid derivatives for anticancer. Bioorg Med Chem Lett 2012;22:6085–8.
[63] Wenk GL, McGann-Gramling K, Hauss-Wegrzyniak B, Ronchetti D, Maucci R, Rosi S, et al. Attenuation of chronic neuroinflammation by a nitric oxide-releasing derivative of the antioxidant ferulic acid. J Neurochem 2004;89:484–93.
[64] Ronchetti D, Impagnatiello F, Guzzetta M, Gasparini L, Borgatti M, Gambari R, et al. Modulation of iNOS expression by a nitric oxide-releasing derivative of the natural antioxidant ferulic acid in activated RAW 264.7 macrophages. Eur J Pharmacol 2006;532:162–9.
[65] Armour KJ, van't Hof RJ, Armour KE, Torbergsen AC, Del Soldato P, Ralston SH. Inhibition of bone resorption in vitro and prevention of ovariectomy-induced bone loss in vivo by flurbiprofen nitroxybutylester (HCT1026). Arthritis Rheum 2001;44:2185-92.
[66] Chen W, Wang D, Dai C, Hamelberg D, Wang B. Clicking 1,2,4,5-tetrazine and cyclooctynes with tunable reaction rates. Chem Commun (Camb) 2012;48:1736–8.
[67] Ji X, Ji K, Chittavong V, Yu B, Pan Z, Wang B. An esterase-activated click and release approach to metal-free CO-prodrugs. Chem Commun (Camb) 2017;53:8296–9.
[68] Ji X, De La Cruz LKC, Pan Z, Chittavong V, Wang B. pH-Sensitive metal-free carbon monoxide prodrugs with tunable and predictable release rates. Chem Commun (Camb) 2017;53:9628–31.
[69] Kueh JTB, Stanley NJ, Hewitt RJ, Woods LM, Larsen L, Harrison JC, et al. Norborn-2-en-7-ones as physiologically-triggered carbon monoxide-releasing prodrugs. Chem Sci 2017;8:5454–9.
[70] Pan Z, Zhang J, Ji K, Chittavong V, Ji X, Wang B. Organic CO Prodrugs Activated by Endogenous ROS. Org Lett 2018;20:8–11.
[71] Liang D, Wu H, Wong MW, Huang D. Diallyl Trisulfide Is a Fast H2S Donor, but Diallyl Disulfide Is a Slow One: The Reaction Pathways and Intermediates of Glutathione with Polysulfides. Org Lett 2015;17:4196–9.
[72] Predmore BL, Kondo K, Bhushan S, Zlatopolsky MA, King AL, Aragon JP, et al. The polysulfide diallyl trisulfide protects the ischemic myocardium by preservation of endogenous hydrogen sulfide and increasing nitric oxide bioavailability. Am J Physiol Heart Circ Physiol 2012;302:H2410–8.
[73] Kondo K, Bhushan S, King AL, Prabhu SD, Hamid T, Koenig S, et al. H_2S protects against pressure overload-induced heart failure via upregulation of endothelial nitric oxide synthase. Circulation 2013;127:1116–27.
[74] Zheng Y, Yu B, De La Cruz LK, Roy Choudhury M, Anifowose A, Wang B. Toward Hydrogen Sulfide Based Therapeutics: Critical Drug Delivery and Developability Issues. Med Res Rev 2018;38:57–100.
[75] Ji X, Pan Z, Yu B, De La Cruz LK, Zheng Y, Ke B, et al. Click and release: bioorthogonal approaches to "on-demand" activation of prodrugs. Chem Soc Rev 2019;48:1077–94.
[76] Rodríguez-Juárez F, Aguirre E, Cadenas S. Relative sensitivity of soluble guanylate cyclase and mitochondrial respiration to endogenous nitric oxide at physiological oxygen concentration. Biochem J 2007;405:223–31.
[77] White TA, Walseth TF, Kannan MS. Nitric oxide inhibits ADP-ribosyl cyclase through a cGMP-independent pathway in airway smooth muscle. Am J Physiol Lung Cell Mol Physiol 2002;283:L1065–71.
[78] Yu CH, Suh B, Shin I, Kim EH, Kim D, Shin YJ, et al. Inhibitory Effects of a Novel Chrysin-Derivative, CPD 6, on Acute and Chronic Skin Inflammation. Int J Mol Sci 2019;20.
[79] Li X, Shang B, Li YN, Shi Y, Shao C. IFNγ and TNFα synergistically induce apoptosis of mesenchymal stem/stromal cells via the induction of nitric oxide. Stem Cell Res Ther 2019;10:18.
[80] Bogdan C. Nitric oxide and the immune response. Nat Immunol 2001;2:907–16.
[81] Armstrong AW, Read C. Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review. JAMA 2020;323:1945–60.
[82] Greb JE, Goldminz AM, Elder JT, Lebwohl MG, Gladman DD, Wu JJ, et al. Psoriasis. Nat Rev Dis Primers 2016;2:16082.
[83] Abeyakirthi S, Mowbray M, Bredenkamp N, van Overloop L, Declercq L, Davis PJ, et al. Arginase is overactive in psoriatic skin. Br J Dermatol 2010;163:193–6.
[84] Sikar Aktürk A, Özdoğan HK, Bayramgürler D, Çekmen MB, Bilen N, Kıran R. Nitric oxide and malondialdehyde levels in plasma and tissue of psoriasis patients. J Eur Acad Dermatol Venereol 2012;26:833–7.
[85] Tekin NS, Ilter N, Sancak B, Ozden MG, Gurer MA. Nitric oxide levels in patients with psoriasis treated with methotrexate. Mediators Inflamm 2006;2006:16043.
[86] Zhong J, Scholz T, Yau ACY, Guerard S, Hüffmeier U, Burkhardt H, et al. Mannan-induced Nos2 in macrophages enhances IL-17-driven psoriatic arthritis by innate lymphocytes. Sci Adv 2018;4:eaas9864.
[87] Skutnik-Radziszewska A, Maciejczyk M, Flisiak I, Kołodziej JKU, Kotowska-Rodziewicz A, Klimiuk A, et al. Enhanced Inflammation and Nitrosative Stress in the Saliva and Plasma of Patients with Plaque Psoriasis. J Clin Med 2020;9.
[88] Coto-Segura P, Coto E, Mas-Vidal A, Morales B, Alvarez V, Díaz M, et al. Influence of endothelial nitric oxide synthase polymorphisms in psoriasis risk. Arch Dermatol Res 2011;303:445–9.
[89] Alba BK, Greaney JL, Ferguson SB, Alexander LM. Endothelial function is impaired in the cutaneous microcirculation of adults with psoriasis through reductions in nitric oxide-dependent vasodilation. Am J Physiol Heart Circ Physiol 2018;314:H343–9.
[90] Guryanova S, Udzhukhu V, Kubylinsky A. Pathogenetic Therapy of Psoriasis by Muramyl Peptide. Front Immunol 2019;10:1275.
[91] Dao VT, Elbatreek MH, Fuchß T, Grädler U, Schmidt H, Shah AM, et al. Nitric Oxide Synthase Inhibitors into the Clinic at Last. Handb Exp Pharmacol 2021;264:169–204.
[92] Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. Lancet 2020;396:345–60.
[93] Guttman-Yassky E, Gallo RL, Pavel AB, Nakatsuji T, Li R, Zhang N, et al. A Nitric Oxide-Releasing Topical Medication as a Potential Treatment Option for Atopic Dermatitis through Antimicrobial and Anti-Inflammatory Activity. J Invest Dermatol 2020;140:2531-5.e2.
[94] Yu C, Fitzpatrick A, Cong D, Yao C, Yoo J, Turnbull A, et al. Nitric oxide induces human CLA(+)CD25(+)Foxp3(+) regulatory T cells with skin-homing potential. J Allergy Clin Immunol 2017;140:1441-4.e6.
[95] Taniuchi S, Kojima T, Hara Mt K, Yamamoto A, Sasai M, Takahashi H, et al. Increased serum nitrate levels in infants with atopic dermatitis. Allergy 2001;56:693–5.
[96] Steinhoff M, Steinhoff A, Homey B, Luger TA, Schneider SW. Role of vasculature in atopic dermatitis. J Allergy Clin Immunol 2006;118:190–7.
[97] Orita K, Hiramoto K, Kobayashi H, Ishii M, Sekiyama A, Inoue M. Inducible nitric oxide synthase (iNOS) and α-melanocyte-stimulating hormones of iNOS origin play important roles in the allergic reactions of atopic dermatitis in mice. Exp Dermatol 2011;20:911–4.
[98] Stücker M, Pieck C, Stoerb C, Niedner R, Hartung J, Altmeyer P. Topical vitamin B12–a new therapeutic approach in atopic dermatitis-evaluation of efficacy and tolerability in a randomized placebo-controlled multicentre clinical trial. Br J Dermatol 2004;150:977–83.
[99] Zaenglein AL, Pathy AL, Schlosser BJ, Alikhan A, Baldwin HE, Berson DS, et al. Guidelines of care for the management of acne vulgaris. J Am Acad Dermatol 2016;74:945-73.e33.
[100] Dréno B, Pécastaings S, Corvec S, Veraldi S, Khammari A, Roques C. Cutibacterium acnes (Propionibacterium acnes) and acne vulgaris: a brief look at the latest updates. J Eur Acad Dermatol Venereol 2018;32(Suppl 2):5–14.
[101] Tsai HH, Lee WR, Wang PH, Cheng KT, Chen YC, Shen SC. Propionibacterium acnes-induced iNOS and COX-2 protein expression via ROS-dependent NF-κB and AP-1 activation in macrophages. J Dermatol Sci 2013;69:122–31.

[102] Sarici G, Cinar S, Armutcu F, Altinyazar C, Koca R, Tekin NS. Oxidative stress in acne vulgaris. J Eur Acad Dermatol Venereol 2010;24:763–7.
[103] Qin M, Pirouz A, Kim MH, Krutzik SR, Garbán HJ, Kim J. Propionibacterium acnes Induces IL-1β secretion via the NLRP3 inflammasome in human monocytes. J Invest Dermatol 2014;134:381–8.
[104] Green SJ, Nacy CA, Schreiber RD, Granger DL, Crawford RM, Meltzer MS, et al. Neutralization of gamma interferon and tumor necrosis factor alpha blocks in vivo synthesis of nitrogen oxides from L-arginine and protection against Francisella tularensis infection in Mycobacterium bovis BCG-treated mice. Infect Immun 1993;61:689–98.
[105] Mishra BB, Rathinam VA, Martens GW, Martinot AJ, Kornfeld H, Fitzgerald KA, et al. Nitric oxide controls the immunopathology of tuberculosis by inhibiting NLRP3 inflammasome-dependent processing of IL-1β. Nat Immunol 2013;14:52–60.
[106] Qin M, Landriscina A, Rosen JM, Wei G, Kao S, Olcott W, et al. Nitric Oxide-Releasing Nanoparticles Prevent Propionibacterium acnes-Induced Inflammation by Both Clearing the Organism and Inhibiting Microbial Stimulation of the Innate Immune Response. J Invest Dermatol 2015;135:2723–31.
[107] Baldwin H, Blanco D, McKeever C, Paz N, Vasquez YN, Quiring J, et al. Results of a Phase 2 Efficacy and Safety Study with SB204, an Investigational Topical Nitric Oxide-releasing Drug for the Treatment of Acne Vulgaris. J Clin Aesthet Dermatol 2016;9:12–8.
[108] Gallo RL, Granstein RD, Kang S, Mannis M, Steinhoff M, Tan J, et al. Standard classification and pathophysiology of rosacea: The 2017 update by the National Rosacea Society Expert Committee. J Am Acad Dermatol 2018;78:148–55.
[109] Holmes AD, Steinhoff M. Integrative concepts of rosacea pathophysiology, clinical presentation and new therapeutics. Exp Dermatol 2017;26:659–67.
[110] Gürer MA, Erel A, Erbaş D, Cağlar K, Atahan C. The seroprevalence of Helicobacter pylori and nitric oxide in acne rosacea. Int J Dermatol 2002;41:768–70.
[111] Moura AKA, Guedes F, Rivitti-Machado MC, Sotto MN. Inate immunity in rosacea. Langerhans cells, plasmacytoid dentritic cells, Toll-like receptors and inducible oxide nitric synthase (iNOS) expression in skin specimens: case-control study. Arch Dermatol Res 2018;310:139–46.
[112] Ross R, Reske-Kunz AB. The role of NO in contact hypersensitivity. Int Immunopharmacol 2001;1:1469–78.
[113] Mathers AR, Carey CD, Killeen ME, Diaz-Perez JA, Salvatore SR, Schopfer FJ, et al. Electrophilic nitro-fatty acids suppress allergic contact dermatitis in mice. Allergy 2017;72:656–64.
[114] Strazzulla LC, Wang EHC, Avila L, Lo Sicco K, Brinster N, Christiano AM, et al. Alopecia areata: Disease characteristics, clinical evaluation, and new perspectives on pathogenesis. J Am Acad Dermatol 2018;78:1–12.
[115] Alfadhli S, Kharrat NJ, Al-Tememy B, Nanda A, Rebai A. Susceptible and protective endothelial nitric oxide synthase gene polymorphism in alopecia areata in the Kuwaiti population. Autoimmunity 2008;41:522–5.
[116] Rasheed Z, Alzolibani AA, Al-Shobaili HA, Saif GB, Al Robaee AA. Biochemical and immunological studies on erythrocytes superoxide dismutase modified by nitric oxide in patients with alopecia areata: Implications in alopecia patchy persistent and alopecia universalis. Immunol Lett 2014;160:50–7.
[117] Zhao R, Liang H, Clarke E, Jackson C, Xue M. Inflammation in Chronic Wounds. Int J Mol Sci 2016;17.
[118] O'Neill CA, Monteleone G, McLaughlin JT, Paus R. The gut-skin axis in health and disease: A paradigm with therapeutic implications. BioEssays 2016;38:1167–76.
[119] Allaire JM, Crowley SM, Law HT, Chang SY, Ko HJ, Vallance BA. The Intestinal Epithelium: Central Coordinator of Mucosal Immunity. Trends Immunol 2018;39:677–96.
[120] Qui BS, Mei QB, Liu L, Tchou-Wong KM. Effects of nitric oxide on gastric ulceration induced by nicotine and cold-restraint stress. World J Gastroenterol 2004;10:594–7.
[121] Szlachcic A, Bilski R, Dziaduś-Sokolowska A, Michalski J, Mroczka J. The effect of nitric oxide donors and L-arginine on the gastric electrolyte barrier. J Physiol Pharmacol 2001;52:211–20.
[122] Falanga V. Wound healing and its impairment in the diabetic foot. Lancet 2005;366:1736–43.
[123] Tarnawski AS, Ahluwalia A. Molecular mechanisms of epithelial regeneration and neovascularization during healing of gastric and esophageal ulcers. Curr Med Chem 2012;19:16–27.
[124] Minniti CP, Gorbach AM, Xu D, Hon YY, Delaney KM, Seidel M, et al. Topical sodium nitrite for chronic leg ulcers in patients with sickle cell anaemia: a phase 1 dose-finding safety and tolerability trial. Lancet Haematol 2014;1:e95–e103.
[125] Nie X, Zhang H, Shi X, Zhao J, Chen Y, Wu F, et al. Asiaticoside nitric oxide gel accelerates diabetic cutaneous ulcers healing by activating Wnt/β-catenin signaling pathway. Int Immunopharmacol 2020;79:106109.
[126] Otterbein LE, Soares MP, Yamashita K, Bach FH. Heme oxygenase-1: unleashing the protective properties of heme. Trends Immunol 2003;24:449–55.
[127] Pol O. The role of carbon monoxide, heme oxygenase 1, and the Nrf2 transcription factor in the modulation of chronic pain and their interactions with opioids and cannabinoids. Med Res Rev 2021;41:136–55.
[128] Ryter SW. Heme oxygenase-1/carbon monoxide as modulators of autophagy and inflammation. Arch Biochem Biophys 2019;678:108186.
[129] Stucki D, Stahl W. Carbon monoxide - beyond toxicity? Toxicol Lett 2020;333:251–60.
[130] Ryter SW, Choi AM. Targeting heme oxygenase-1 and carbon monoxide for therapeutic modulation of inflammation. Transl Res 2016;167:7–34.
[131] Hopper CP, De La Cruz LK, Lyles KV, Wareham LK, Gilbert JA, Eichenbaum Z, et al. Role of Carbon Monoxide in Host-Gut Microbiome Communication. Chem Rev 2020;120:13273–311.
[132] Ryter SW, Ma KC, Choi AMK. Carbon monoxide in lung cell physiology and disease. Am J Physiol Cell Physiol 2018;314:C211–27.
[133] Yang X, de Caestecker M, Otterbein LE, Wang B. Carbon monoxide: An emerging therapy for acute kidney injury. Med Res Rev 2020;40:1147–77.
[134] Hanselmann C, Mauch C, Werner S. Haem oxygenase-1: a novel player in cutaneous wound repair and psoriasis? Biochem J 2001;353:459–66.
[135] Ma LJ, You Y, Bai BX, Li YZ. Therapeutic effects of heme oxygenase-1 on psoriasiform skin lesions in guinea pigs. Arch Dermatol Res 2009;301:459–66.
[136] El Ali Z, Ollivier A, Manin S, Rivard M, Motterlini R, Foresti R. Therapeutic effects of CO-releaser/Nrf2 activator hybrids (HYCOs) in the treatment of skin wound, psoriasis and multiple sclerosis. Redox Biol 2020;34:101521.
[137] Lee J, Song K, Hiebert P, Werner S, Kim TG, Kim YS. Tussilagonone Ameliorates Psoriatic Features in Keratinocytes and Imiquimod-Induced Psoriasis-Like Lesions in Mice via NRF2 Activation. J Invest Dermatol 2020;140:1223-32.e4.
[138] Lee GY, Zeb A, Kim EH, Suh B, Shin YJ, Kim D, et al. CORM-2-entrapped ultradeformable liposomes ameliorate acute skin inflammation in an ear edema model via effective CO delivery. Acta Pharm Sin B 2020;10:2362–73.
[139] Klinger-Strobel M, Gläser S, Makarewicz O, Wyrwa R, Weisser J, Pletz MW, et al. Bactericidal Effect of a Photoresponsive Carbon Monoxide-Releasing Nonwoven against Staphylococcus aureus Biofilms. Antimicrob Agents Chemother 2016;60:4037–46.
[140] Kobayashi T, Glatz M, Horiuchi K, Kawasaki H, Akiyama H, Kaplan DH, et al. Dysbiosis and Staphylococcus aureus Colonization Drives Inflammation in Atopic Dermatitis. Immunity 2015;42:756–66.
[141] Takagi T, Naito Y, Uchiyama K, Mizuhima K, Suzuki T, Horie R, et al. Carbon monoxide promotes gastric wound healing in mice via the protein kinase C pathway. Free Radic Res 2016;50:1098–105.
[142] Brzozowski T, Magierowska K, Magierowski M, Ptak-Belowska A, Pajdo R, Kwiecien S, et al. Recent Advances in the Gastric Mucosal Protection Against Stress-induced Gastric Lesions. Importance of Renin-angiotensin Vasoactive Metabolites, Gaseous Mediators and Appetite Peptides. Curr Pharm Des 2017;23:3910–22.
[143] Lin S, Zhang Q, Li S, Zhang T, Wang L, Qin X, et al. Antioxidative and Angiogenesis-Promoting Effects of Tetrahedral Framework Nucleic Acids in Diabetic Wound Healing with Activation of the Akt/Nrf2/HO-1 Pathway. ACS Appl Mater Interfaces 2020;12:11397–408.
[144] Papapetropoulos A, Pyriochou A, Altaany Z, Yang G, Marazioti A, Zhou Z, et al. Hydrogen sulfide is an endogenous stimulator of angiogenesis. Proc Natl Acad Sci USA 2009;106:21972–7.
[145] Tian D, Teng X, Jin S, Chen Y, Xue H, Xiao L, et al. Endogenous hydrogen sulfide improves vascular remodeling through PPARδ/SOCS3 signaling. J Adv Res 2021;27:115–25.
[146] Wu D, Wang H, Teng T, Duan S, Ji A, Li Y. Hydrogen sulfide and autophagy: A double edged sword. Pharmacol Res 2018;131:120–7.
[147] Zhang J, Shi C, Wang H, Gao C, Chang P, Chen X, et al. Hydrogen sulfide protects against cell damage through modulation of PI3K/Akt/Nrf2 signaling. Int J Biochem Cell Biol 2019;117:105636.
[148] Ying J, Wang Q, Jiang M, Wang X, Liu W, Wang X, et al. Hydrogen Sulfide Promotes Cell Proliferation and Melanin Synthesis in Primary Human Epidermal Melanocytes. Skin Pharmacol Physiol 2020;33:61–8.
[149] Dilek N, Papapetropoulos A, Toliver-Kinsky T, Szabo C. Hydrogen sulfide: An endogenous regulator of the immune system. Pharmacol Res 2020;161:105119.
[150] Benhadou F, Mintoff D, Del Marmol V. Psoriasis: Keratinocytes or Immune Cells - Which Is the Trigger? Dermatology 2019;235:91–100.
[151] Lou F, Sun Y, Xu Z, Niu L, Wang Z, Deng S, et al. Excessive Polyamine Generation in Keratinocytes Promotes Self-RNA Sensing by Dendritic Cells in Psoriasis. Immunity 2020;53:204-16.e10.
[152] Weatherhead SC, Farr PM, Jamieson D, Hallinan JS, Lloyd JJ, Wipat A, et al. Keratinocyte apoptosis in epidermal remodeling and clearance of psoriasis induced by UV radiation. J Invest Dermatol 2011;131:1916–26.
[153] Shi HJ, Zhou H, Ma AL, Wang L, Gao Q, Zhang N, et al. Oxymatrine therapy inhibited epidermal cell proliferation and apoptosis in severe plaque psoriasis. Br J Dermatol 2019;181:1028–37.
[154] Thatikonda S, Pooladanda V, Sigalapalli DK, Godugu C. Piperlongumine regulates epigenetic modulation and alleviates psoriasis-like skin inflammation via inhibition of hyperproliferation and inflammation. Cell Death Dis 2020;11:21.
[155] Alshorafa AK, Guo Q, Zeng F, Chen M, Tan G, Tang Z, et al. Psoriasis is associated with low serum levels of hydrogen sulfide, a potential anti-inflammatory molecule. Tohoku J Exp Med 2012;228:325–32.
[156] Gobbi G, Ricci F, Malinverno C, Carubbi C, Pambianco M, Panfilis G, et al. Hydrogen sulfide impairs keratinocyte cell growth and adhesion inhibiting mitogen-activated protein kinase signaling. Lab Invest 2009;89:994–1006.
[157] Mirandola P, Gobbi G, Micheloni C, Vaccarezza M, Di Marcantonio D, Ruscitti F, et al. Hydrogen sulfide inhibits IL-8 expression in human keratinocytes via MAP kinase signaling. Lab Invest 2011;91:1188–94.

[158] Merighi S, Gessi S, Varani K, Fazzi D, Borea PA. Hydrogen sulfide modulates the release of nitric oxide and VEGF in human keratinocytes. Pharmacol Res 2012;66:428–36.
[159] Sener S, Akbas A, Kilinc F, Baran P, Erel O, Aktas A. Thiol/disulfide homeostasis as a marker of oxidative stress in rosacea: a controlled spectrophotometric study. Cutan Ocul Toxicol 2019;38:55–8.
[160] Moniaga CS, Kamata Y, Ogawa H, Suga Y, Tominaga M, Takamori K. Hydrogen sulfide modulates the expression of axon-guidance molecules in human keratinocytes. J Dermatol Sci 2020;97:232–5.
[161] Coavoy-Sánchez SA, Rodrigues L, Teixeira SA, Soares AG, Torregrossa R, Wood ME, et al. Hydrogen sulfide donors alleviate itch secondary to the activation of type-2 protease activated receptors (PAR-2) in mice. Pharmacol Res 2016;113:686–94.
[162] Cevikbas F, Lerner EA. Physiology and Pathophysiology of Itch. Physiol Rev 2020;100:945–82.
[163] Yang CT, Chen L, Chen WL, Li N, Chen MJ, Li X, et al. Hydrogen sulfide primes diabetic wound to close through inhibition of NETosis. Mol Cell Endocrinol 2019;480:74–82.
[164] Xu M, Hua Y, Qi Y, Meng G, Yang S. Exogenous hydrogen sulphide supplement accelerates skin wound healing via oxidative stress inhibition and vascular endothelial growth factor enhancement. Exp Dermatol 2019;28:776–85.
[165] Zhang Q, Lyu W, Yu M, Niu Y. Sulfur dioxide induces vascular relaxation through PI3K/Akt/eNOS and NO/cGMP signaling pathways in rats. Hum Exp Toxicol 2020;39:1108–17.
[166] Yang L, Zhang H, Chen P. Sulfur dioxide attenuates sepsis-induced cardiac dysfunction via inhibition of NLRP3 inflammasome activation in rats. Nitric Oxide 2018;81:11–20.
[167] Zhang L, Jin H, Song Y, Chen SY, Wang Y, Sun Y, et al. Endogenous sulfur dioxide is a novel inhibitor of hypoxia-induced mast cell degranulation. J Adv Res 2021;29:55–65.
[168] An L, Zhang P, Shen W, Yi X, Yin W, Jiang R, et al. A sulfur dioxide polymer prodrug showing combined effect with doxorubicin in combating subcutaneous and metastatic melanoma. Bioact Mater 2021;6:1365–74.
[169] Sun A, Wang W, Ye X, Wang Y, Yang X, Ye Z, et al. Protective Effects of Methane-Rich Saline on Rats with Lipopolysaccharide-Induced Acute Lung Injury. Oxid Med Cell Longev 2017;2017:7430193.
[170] Song K, Zhang M, Hu J, Liu Y, Liu Y, Wang Y, et al. Methane-rich saline attenuates ischemia/reperfusion injury of abdominal skin flaps in rats via regulating apoptosis level. BMC Surg 2015;15:92.
[171] Ohsawa I, Ishikawa M, Takahashi K, Watanabe M, Nishimaki K, Yamagata K, et al. Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals. Nat Med 2007;13:688–94.
[172] Yang M, Dong Y, He Q, Zhu P, Zhuang Q, Shen J, et al. Hydrogen: A Novel Option in Human Disease Treatment. Oxid Med Cell Longev 2020;2020:8384742.
[173] Nogueira JE, Passaglia P, Mota CMD, Santos BM, Batalhão ME, Carnio EC, et al. Molecular hydrogen reduces acute exercise-induced inflammatory and oxidative stress status. Free Radic Biol Med 2018;129:186–93.
[174] Fang W, Wang G, Tang L, Su H, Chen H, Liao W, et al. Hydrogen gas inhalation protects against cutaneous ischaemia/reperfusion injury in a mouse model of pressure ulcer. J Cell Mol Med 2018;22:4243–52.
[175] Min HS, Son S, You DG, Lee TW, Lee J, Lee S, et al. Chemical gas-generating nanoparticles for tumor-targeted ultrasound imaging and ultrasound-triggered drug delivery. Biomaterials 2016;108:57–70.
[176] Finžgar M, Frangež HB, Cankar K, Frangež I. Transcutaneous application of the gaseous CO(2) for improvement of the microvascular function in patients with diabetic foot ulcers. Microvasc Res 2021;133:104100.
[177] Wallace JL, Motta JP, Buret AG. Hydrogen sulfide: an agent of stability at the microbiome-mucosa interface. Am J Physiol Gastrointest Liver Physiol 2018;314:G143–9.
[178] Byrd AL, Belkaid Y, Segre JA. The human skin microbiome. Nat Rev Microbiol 2018;16:143–55.
[179] Ellis SR, Nguyen M, Vaughn AR, Notay M, Burney WA, Sandhu S, et al. The Skin and Gut Microbiome and Its Role in Common Dermatologic Conditions. Microorganisms 2019;7.
[180] Zhou Y, Yang T, Liang K, Chandrawati R. Metal-organic frameworks for therapeutic gas delivery. Adv Drug Deliv Rev 2021;171:199–214.

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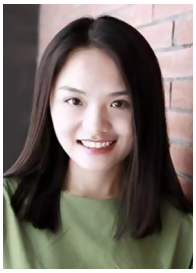

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