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REVIEW ARTICLE

# Hydrogen sulfide and dermatological diseases

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Skin diseases constitute a major health problem affecting a high proportion of the population every day and have different aetiologies that include inflammation, infections, and tumours. Hydrogen sulfide ($H_2S$) is a gaseous signalling molecule recognized as a gasotransmitter together with NO and carbon monoxide. Under physiological conditions, $H_2S$ is produced in the skin by enzymic pathways and plays a physiological role in a variety of functions, such as vasodilatation, cell proliferation, apoptosis, and inflammation. Alterations of $H_2S$ production are implicated in a variety of dermatological diseases, such as psoriasis, melanoma, and other dermatoses. On the other hand, $H_2S$-releasing-based therapies based on $H_2S$ donor compounds are being developed to treat some of these situations. In this review, we provide an up-to-date overview of the role of $H_2S$ in the normal skin and its clinical and pathological significance, as well as the therapeutic potential of different $H_2S$ donors for treatment of skin diseases.

**LINKED ARTICLES:** This article is part of a themed section on Hydrogen Sulfide in Biology & Medicine. To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v177.4/issuetoc

## 1 | INTRODUCTION

For many years, **hydrogen sulfide** ($H_2S$) was simply considered as a toxic gas and an ambient pollutant (Smith & Gosselin, 1979). However, since the detection of its presence and the characterization of its enzymic production in mammals (Stipanuk & Beck, 1982), and the later discovery of its role as an endogenous neuromodulator (Abe & Kimura, 1996), $H_2S$ has emerged as a relevant signalling molecule in biological systems, recognized as a member of the gasotransmitter family, along with **NO** and **carbon monoxide**. $H_2S$ plays major roles in the different physiological regulatory systems. Particularly in the skin, emerging evidence has suggested that endogenous $H_2S$ regulates important functions and changes in $H_2S$ generation have been implicated in the pathogenesis of several skin diseases.

In the sections below, we will describe the role of $H_2S$ in physiological and pathological skin conditions, as well as the potential therapeutic use of the different $H_2S$ donors. The chemical structures of some of these compounds are shown in Figure 1.

## 2 | $H_2S$ PRODUCTION AND METABOLISM IN THE SKIN

The endogenous production of $H_2S$ in mammals involves at least three different enzymic systems involved in the metabolism of the amino acid **L-cysteine**. The major systems are the two pyridoxal 5′-phosphate-dependent enzymes, **cystathionine β-synthase (CBS)** and **cystathionine γ-lyase (CSE)**. While CBS uses L-cysteine and **homocysteine** to produce $H_2S$ (Chen, Jhee, & Kruger, 2004; Singh, Padovani, Leslie, Chiku, & Banerjee, 2009), CSE mainly catalyses **cystathionine** cleavage

**Abbreviations:** 3MST, 3-mercaptopyruvate sulfurtransferase; AD, atopic dermatitis; ATB-346, $H_2S$-releasing naproxen derivative/6-methoxy-α-methyl-2-naphthaleneacetic acid, 4-(aminothioxomethyl)phenyl ester; CBS, cystathionine β-synthase; CSE, cystathionine γ-lyase; DATS, diallyl trisulfide; GYY-4137, (*p*-methoxyphenyl)morpholino-phosphinodithioic acid; $H_2S$, hydrogen sulfide; HBTA, 4-hydroxybenzodithioate; $Na_2S$, sodium sulfide; NaHS, sodium hydrosulfide; NET, neutrophil extracellular traps; NSHD-1, *N*-(benzoylthio) benzamide; TWFULB, thermal waters from Uriage-les Bains

  

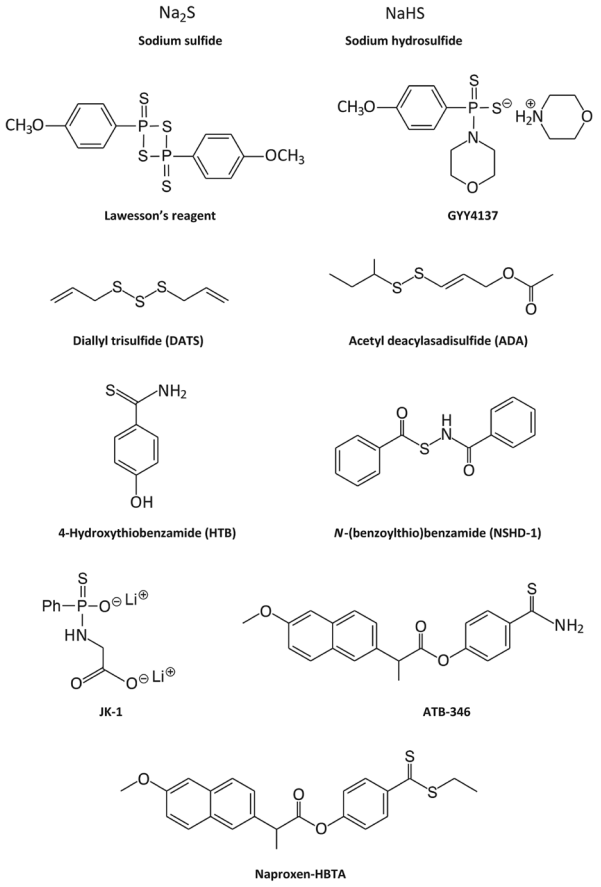


**FIGURE 1** Chemical structures of the $H_2S$ donors cited throughout the text

reaction to provide L-cysteine, ammonia, and α-ketobutyrate (Aitken & Kirsch, 2005). In addition, CSE also catalyses other reactions leading to $H_2S$ production by using L-cysteine and/or homocysteine as substrate (Chiku et al., 2009). The third pathway involves the enzyme **cysteine aminotransferase**, by catalysing the production of **3-mercaptopyruvate**, from L-cysteine and α-ketoglutarate in the presence of reductants, and the enzyme 3-mercaptopyruvate sulfurtransferase (3MST) acting on this substrate to produce $H_2S$ (Nagahara, Yoshii, Abe, & Matsumura, 2007; Shibuya et al., 2009). More recently, another pathway has been described involving the enzymes D-amino-oxidase and 3MST to produce $H_2S$ from the amino acid **D-cysteine** (Shibuya et al., 2013).

All these enzymes are expressed in a wide range of tissues in humans and rodents. However, the enzymes CBS and D-amino-oxidase are primarily expressed in the nervous system, brain, and kidneys (Kabil, Vitvitsky, Xie, & Banerjee, 2011; Moore, Bhatia, & Moochhala, 2003; Shibuya et al., 2013), while CSE is predominantly expressed in the cardiovascular system, liver, small intestine, and stomach (Ishii et al., 2004; Kabil et al., 2011), and the 3MST/cysteine aminotransferase system is localized in the neurons, heart, vascular endothelium, liver, kidney, and smooth muscle (Nagahara, Ito, Kitamura, & Nishino, 1998; Shibuya, Mikami, Kimura, Nagahara, & Kimura, 2009).

In homogenates of human cutaneous tissue, the expression of both CSE and 3MST enzymes was demonstrated by Western blot analysis (Greaney et al., 2017; Kutz, Greaney, Santhanam, & Alexander, 2015; Liu et al., 2014). The study from Lee et al. (2016) reports both mRNA and protein expression of the enzymes CSE and CBS in normal human keratinocytes. Panza et al. (2015) showed that very low gene expression levels for the enzymes CSE, CBS, and 3MST occur in normal human epidermal melanocytes. However, the precise localization of the $H_2S$-generating enzymes in the different cell types of the skin has not yet been determined.

In addition to the enzymic pathways, the endogenous production of $H_2S$ can also occur via non-enzymic processes, although these pathways have not been described in the skin, to date. $H_2S$ can be generated by reduction of elemental sulfur by **GSH** involving NADH or NADPH as electron donors provided through glycolysis (Searcy & Lee, 1998). In the presence of GSH as a reducing agent, $H_2S$ can be formed from bound sulfur (Ishigami et al., 2009). $H_2S$ can also be released from iron–sulfur proteins containing $Fe_2S_2$, $Fe_3S_4$, or $Fe_4S_4$ clusters, such as ferredoxins and Rieske proteins, which can undergo oxidation–reduction reactions (Beinert, Holm, & Münck, 1997). Thiosulfate anions ($S_2O_3^{2-}$) can also form $H_2S$ in a reductive reaction involving pyruvate as a hydrogen donor (Kolluru, Shen, Bir, & Kevil, 2013).

After its enzymic synthesis, $H_2S$ can be either immediately released or stored and subsequently released, in response to a physiological signal. Two forms of cell sulfur stores have been identified: acid-labile sulfur ($H_2S$ is released under acidic conditions) and, as mentioned above, bound sulfane sulfur ($H_2S$ is released under reducing conditions; Ishigami et al., 2009; Ogasawara, Isoda, & Tanabe, 1994). More recent studies have also revealed that bound sulfur species (polysulfides and persulfides) have various physiological roles in mammalian cells, including protection from oxidative stress and activation of **TRPA1 channels** (Kimura, 2015; Koike, Nishimoto, & Ogasawara, 2017).

The metabolic fate of $H_2S$ in skin cells is not yet fully elucidated. In human skin fibroblasts, it has been proposed that the main catabolic pathway of $H_2S$ takes place in the mitochondria and consists of a series of oxidative reactions starting with sulfide-quinone oxidoreductase, which sequentially catalyses the oxidation of the sulfide species $S^{2-}/HS^-$ to $SO_4^{2-}$ (sulfate anion) involving the participation of coenzyme Q-10 (Ziosi et al., 2017).

## 3 | $H_2S$ AND SKIN PATHOPHYSIOLOGY

In the skin, endogenous $H_2S$ has been shown to participate in the regulation of important functions such as vasodilatation (Kutz et al., 2015), cell proliferation (Xie et al., 2016), apoptosis (Gobbi et al., 2009), and inflammation (Lee et al., 2016). Evidence for a functional vasodilatory role for $H_2S$ in the human cutaneous microvasculature has been demonstrated. Kutz et al. (2015) found that exogenous $H_2S$ elicits cutaneous vasodilatation, which is partly mediated by tetraethylammonium-sensitive **calcium-activated potassium channels**, in addition to functional interactions with both NO and **COX**-mediated signalling pathways.

Moreover, Xie et al. (2016) reported that the exogenous supplementation of $H_2S$ (using **sodium hydrosulfide [NaHS]**) in a human keratinocyte cell line (HaCaT) results in increased viability, stimulates

differentiation, and enhances autophagic activity in a concentration-dependent manner, with no significant effect on apoptosis, even at a high concentration (1 mM). In contrast, Gobbi et al. (2009) observed that NaHS (at 2 mM) reduces clonal growth, cell proliferation, and cell adhesion of NCTC 2544 human keratinocytes by limiting the stem cell subpopulation in culture. These effects were mediated by inactivation of the Raf/**MAPK/ERK** signalling pathway, and the reduced adhesion of sulfide-treated cells was associated to down-regulation of the expression of **$\beta_4$**, **$\alpha_2$**, and **$\alpha_6$ integrins** (necessary to promote cell adhesion as well as anti-apoptotic and proliferative signalling in normal keratinocytes).

It is thus clear that, according to the concentration used, $H_2S$ shows a dual behaviour profile. While, at low concentrations, it stimulates keratinocyte proliferation, at high concentrations, it promotes pro-apoptotic effects. This $H_2S$ behaviour pattern, similar to that observed with NO, has already been observed in several other situations and systems and reflects the wide array of molecular targets that $H_2S$ can interact with (such as protein S-sulfhydration and metal ions) on the basis of the target affinities. Moreover, Lee et al. (2016) showed that both CSE and CBS promote the resolution of cutaneous inflammation. In normal human keratinocytes exposed to sub-cytotoxic formaldehyde concentrations, these enzymes are up-regulated, and the $H_2S$ produced can, in turn, inhibit the up-regulation of pro-inflammatory mediators (such as **MMP-1**, **$PGE_2$**, and **IL-8**) that participate in the early pro-inflammatory response. Merighi, Gessi, Varani, Fazzi, and Borea (2012) have shown that the exogenous application of $H_2S$ on cultured NCTC 2544 human keratinocytes results in significant enhancement of **inducible NOS**-derived NO production which occurs in an **Akt**-dependent manner, and the increased NO can in turn down-regulate ERK1/2 activation, thereby resulting in decreased **VEGF** release.

## 4 | $H_2S$ AND SKIN DISEASES

### 4.1 | Folk medicine and the early evidence based on protein sulfur

Bathing in natural thermal waters containing sulfur (with $H_2S$ concentrations in the range 0.3–8 mM) has been used for centuries as a folk medicine procedure in the search for effective treatment and relief of several conditions including wound healing, acne, rosacea, scabies, atopic dermatitis (AD), psoriasis, and urticaria. Furthermore, over the last two decades, there have been an increasing number of in vitro and in vivo studies providing some insight into the effects of external application of such thermal waters on the skin.

For example, Shani et al. (1997) report the efficacy of Dead Sea sulfurous therapy in 1,408 AD patients, with reduction of pruritus during the first week of treatment and complete elimination of lesions in 90% of patients after 4 to 6 weeks of therapy. In patients with psoriatic plaques, Mazzulla, Nicoletta, Perrotta, De Stefano, and Sesti (2013) point out that bathing treatment in the sulfurous waters of Terme Luigiane (Italy) promotes a significant recovery of the mechanical properties of the skin (i.e., increase of the elasticity parameters). Balneotherapy studies in mice with experimental AD induced by the hapten dinitrochlorobenzene report that treatment with mineral water containing high sulfur, calcium, and chlorine concentrations reduces scratching behaviour, decreases the severity of skin lesions, and reduces serum levels of IgE, **IL-1**, **IL-13**, and **TNF**-α in comparison with the controls (Bajgai et al., 2017).

Joly, Branka, and Lefeuvre (2014) showed that the thermal waters from Uriage-les-Bains (TWFULB), with high concentrations of sulfate anion, showed significant protective effects against oxidative stress induced by exposure of human dermal fibroblasts to **hypoxanthine/xanthine oxidase**, with improved cell viability and reduced lipid peroxidation. TWFULB also showed to have significant SOD-like activity and protective effects on the UVB-stressed DNA in human keratinocytes. In an ex vivo model of human skin explants, TWFULB was able to counterbalance the negative effect of UVB on the intracellular catalase activity and on the cutaneous claudin-6 expression. In the study by Karagülle et al. (2018), incubation of the human keratinocyte cell line HaCaT with two different thermal waters, thermo-mineral BJ1 (Bursa, Turkey) or oligomineral BG (Bolu, Turkey) for 3 days, significantly reduced expression of IL-1α, TNF-α, and VEGF. However, while the antiangiogenic effects of BG water on HaCaT cells might be due to the sulfur contents, the anti-inflammatory effects of the BJ1 waters were attributed to its silica contents.

From these reports, it is clear that the results obtained with natural waters cannot be solely due to the presence of $H_2S$–sulfur and, mainly in relation to the beneficial effects in humans, other variables such as salt contents, osmolarity, pH, temperature, the presence of other potentially active substances, and even a placebo effect must be considered. However, it is a fact that the inappropriate regulation of $H_2S$ production is implicated in several skin pathological conditions. The study of the relative amounts of protein-bound sulfhydryl/thiol and disulfide groups in human epidermis has been the focus of many investigations, particularly since Barrnett and Seligman (1954) published their specific staining method to demonstrate the presence of sulfhydryl and disulfide groups by histochemistry. The early findings on protein sulfur contents in skin diseases (summarized by Steiner, 1960) are strikingly well correlated with our present knowledge in relation to $H_2S$.

### 4.2 | Inflammation, pruritus, and cytoprotection

Several in vitro and in vivo studies have shown the anti-inflammatory effects of $H_2S$ as well as its participation in the resolution of inflammation and repair processes (Wallace, Ferraz, & Muscara, 2012). For example, Alshorafa et al. (2012) reported that treatment of HaCaT cells with the spontaneous $H_2S$ donor NaHS resulted in significant inhibition of the TNF-α-induced up-regulation of inducible NOS, **IL-6**, and IL-8 in a dose-dependent manner, via suppression of p38 MAPK, ERK, and NF-κB activation pathways. The study from Shimizu et al. (2013) showed that in mice with the cutaneous Arthus reaction, the exogenous application of NaHS resulted in attenuated inflammatory reaction, TNF-α and **IFN-γ** expression, and reduced number of neutrophils recruited to the skin lesions.

$H_2S$ also plays an important role on the pruritogenic response. We have previously shown that inhibition of endogenous $H_2S$ synthesis with **β-cyano-L-alanine** (a CSE/CBS inhibitor) results in significant potentiation of the scratching behavior induced by **compound**

48/80 in mice, along with increased neutrophil recruitment, as measured by myeloperoxidase activity (Rodrigues et al., 2017). Moreover, $H_2S$ donors can have important therapeutic applications for treatment of both histaminergic and non-histaminergic pruritus in mice (Coavoy-Sánchez et al., 2016; Rodrigues et al., 2017). Regarding the histaminergic pathway, the $H_2S$ donors sodium sulfide ($Na_2S$) and Lawesson's reagent (Figure 1) significantly reduced the pruritus induced in mice by the intradermal injection of either **histamine** or the mast cell degranulator compound 48/80, and these effects were, at least in part, mediated by stabilization of mast cells (Rodrigues et al., 2017). When histamine-independent pruritus was induced by the activation of **PAR2** with the peptide agonist **SLIGRL-$NH_2$**, the response was effectively reduced by NaHS, via **ATP-sensitive potassium channel** opening and involving the participation of NO (in a **cGMP**-independent manner). Furthermore, in this model, TRPA1 cation channels mediate the PAR2-induced pruritus, but $H_2S$ does not interfere with this pathway (Coavoy-Sánchez et al., 2016).

On the other hand, pro-pruriceptive effects of $H_2S$ have also been reported in the literature. The study by Wang et al. (2015) showed that the spontaneous $H_2S$ donors NaHS and $Na_2S$ (at doses within the $\mu mol \cdot kg^{-1}$ range; Figure 1) can induce intense scratching behaviour by the activation of **T-type calcium channels** in a dose-dependent manner. Again, these apparently contradictory data can be explained not only on the basis of the high doses of the $H_2S$ donors used, but also by taking into account the chemical characteristics of these donors. While $H_2S$ production in vivo follows a slow kinetic profile, the administration of spontaneous $H_2S$ donors will instantaneously yield very high amounts of this mediator, thus more closely resembling a toxic exposure to $H_2S$ than its physiological production.

The cytoprotective effects of $H_2S$ in the skin have been demonstrated in in vitro experiments with HaCaT cell cultures. In a chemical hypoxia-induced cell injury model, Yang et al. (2011) showed that the addition of NaHS significantly reduced cell injury and the inflammatory responses, as shown by the increased cell viability and GSH levels, and decreased ROS generation and reduced production of IL-1, IL-6, and IL-8. In addition, NaHS markedly reduced cobalt(II) chloride-induced COX-2 overexpression, $PGE_2$ production, and NF-κB activation. In another study, the same group (Yang et al., 2014) showed that NSHD-1 (an N-mercapto-based $H_2S$ donor; Figure 1) is able to protect HaCaT cells from methylglyoxal-induced injury and dysfunction. The anti-apoptotic effects of $H_2S$ were reported an in vitro model of cutaneous tissue transplantation (Henderson et al., 2010), where NaHS significantly decreased the apoptosis of 3T3 fibroblast cells in response to ischaemia–reperfusion injury.

## 4.3 | Dermal wound healing and angiogenesis

Dermal wound healing is a physiological process that restores the anatomical structure and function of injured skin. It is a complex process that involves an early inflammatory reaction, angiogenesis, collagen deposition, formation of granulation tissue, re-epithelialization, and tissue remodelling. Several studies have recognized $H_2S$ as a molecule that accelerates the dermal wound healing process. For example, Cai et al. (2007) investigated the role of $H_2S$ in angiogenesis in a series of in vitro and in vivo experiments. Treatment of RF/6A endothelial cells with NaHS resulted in increased cell proliferation, migration, scratched wound healing, and tube-like structure formation, the last two processes being dependent on Akt phosphorylation. The effects of $H_2S$ on angiogenesis in vivo were assessed using a Matrigel plug assay in mice, as the intraperitoneal injection of 10 $\mu mol \cdot kg^{-1} \cdot day^{-1}$ NaHS (but not 200 $\mu mol \cdot kg^{-1} \cdot day^{-1}$) caused a significant increase in cellular infiltration, neovascularization, and Hb content, thus characterizing the pro-angiogenic effects of the $H_2S$ donor at low doses.

In another study, Papapetropoulos et al. (2009) conclude that endogenous $H_2S$ is a pro-healing factor, as this process was shown to be significantly delayed in $CSE^{-/-}$ mice. In this study, mice had 5% of their total body surface area burned by scalding, and throughout the observation period, wound areas in $CSE^{+/+}$ mice were consistently smaller than in $CSE^{-/-}$ mice. Moreover, the topical administration of NaHS accelerated the healing process (closure) of rat skin wounds caused by burning. Furthermore, Coletta et al. (2015) reported that the in vitro treatment of bEnd3 microvascular endothelial cells with 3-mercaptopyruvate (in order to increase 3MST-derived $H_2S$) promoted angiogenesis. In vivo, this substrate also caused a sustained increase in neovascularization and facilitated wound closure in a burn wound model in rats. In a previous study using the same model, Coletta et al. (2012) reported that the administration of NaHS contributed to microvessel growth and promotes wound healing and that this effect was dependent on **eNOS**-derived NO.

Using in vitro wound healing-related assays, Saha et al. (2016) observed that HUVEC in which CBS expression was knocked down demonstrated decreased migratory ability and wound closure rates. Liu et al. (2014) found that CSE expression was decreased in diabetic foot ulcers and that Type 2 diabetic db/db mice intraperitoneally treated with the $H_2S$ donors NaHS and 4-hydroxythiobenzamide (Figure 1) showed significantly improved wound healing via restoration of the endothelial progenitor cell functions and activation of **angiopoietin-1**. Moreover, the study from Zhao et al. (2017) shows that in diabetic ob/ob mice, CSE expression and $H_2S$ content are significantly reduced in granulation tissues of wounds in comparison with the control animals and that treatment of these animals with intraperitoneal NaHS results in significantly improved wound healing, which was associated with reduced neutrophil and macrophage infiltration and decreased production of TNF-α and IL-6. NaHS treatment also led to decreased **MMP-9** and increased collagen deposition and vascular-like structures in the granulation tissues of wounds in ob/ob mice.

A more recent study by Yang et al. (2019) shows that treatment with the $H_2S$ donor $Na_2S$ can also improve diabetic wound healing via inhibition of the release of neutrophil extracellular traps (NET; a process known as NETosis), both in vivo and in vitro. The delayed wound healing observed in diabetic db/db mice was accelerated by intraperitoneal treatment with $Na_2S$, in parallel with down-regulation of NET release and blockade of ROS-induced MAPK ERK1/2 and p38 activation. Wang et al. (2015) reported that in rats with streptozotocin-induced diabetes, topical treatment with a 2% NaHS-containing ointment resulted in accelerated wound healing, by promoting angiogenesis in the granulation tissues via augmented VEGF production. In addition,

reduced TNF-α expression and leukocyte adhesion, and enhanced antioxidant effects (due to increased SOD activity and decreased lipoperoxidation) were also characterized as mediators of the beneficial effects of $H_2S$ on wound healing in diabetes.

Wu et al. (2016) developed nanofibres able to release $H_2S$ in a pH-dependent manner by electrospinning polycaprolactone (PCL) containing JK-1 (a pH-controlled $H_2S$ donor; Figure 1). These $H_2S$-releasing nanofibres (called "PCL-JK1") were employed as a wound dressing in a murine model of cutaneous wound healing and found that such dressings enhanced wound repair and regeneration, including enhanced neovessel formation and increased collagen deposition. More recently, Lin et al. (2017) have produced an $H_2S$-releasing depot formulation (termed "NaHS@MPs") for treatment of diabetic wounds. The formulation involves a microparticle system that comprises hydrophobic phase-change materials (1-tetradecanol and paraffin wax) that provide an in situ depot for the sustained release of $H_2S$. The topical treatment of wounds in diabetic db/db mice with NaHS@MPs promoted increased proliferation and migration of epidermal keratinocytes (re-epithelialization), as well as increased angiogenesis, by inducing a sustained phosphorylation of ERK1/2 and p38 and thus accelerating the healing of full-thickness wounds. Taken together, all these studies clearly show that $H_2S$ contributes to wound healing by attenuating inflammation and increasing angiogenesis.

### 4.4 | Psoriasis

Alshorafa et al. (2012) showed that patients with psoriasis present with serum $H_2S$ levels significantly lower than those found in healthy subjects. In addition, in both primary psoriatic lesions and NCTC 2544 human keratinocytes, the $H_2S$ donor NaHS not only reduced basal expression and secretion of IL-8 but also interfered with that induced by **IL-17** and **IL-22** by reducing ERK phosphorylation levels (Mirandola et al., 2011). In line with these findings, we have observed that in a murine model of psoriasis (induced by the topical application of the immunomodulator **imiquimod**), the topical administration of a microemulsion system containing the slow-release $H_2S$ donor **GYY-4137** (Figure 1) had beneficial effects by controlling pruritus, reducing neutrophil recruitment to the sites of lesion, and improving the clinical severity index of the disease (Schmidt et al., 2015).

### 4.5 | Melanoma

Endogenous $H_2S$ has been involved in the regulation of cancer. Working with human melanoma samples, Panza et al. (2015) have shown that CSE expression is very high in primary tumours, low in metastatic lesions and almost silent in non-lymph node metastases. In fact, the primary role played by CSE was confirmed when it was observed that the overexpression of CSE in human melanoma cells led to spontaneous apoptosis. In this report, it is also shown that diallyl trisulfide (DATS, 100 μM, one of the active components present in garlic oil; Figure 1) inhibits cellular proliferation of the human melanoma A375 cells (the most lethal type of skin cancer cells) via suppression of NF-κB activity and inhibition of Akt and ERK pathways. These results are supported by a proof of concept performed in vivo by using an animal melanoma model in which the administration of the CSE substrate L-cysteine (600 $mg \cdot kg^{-1}$) or the $H_2S$ donor DATS (50 $mg \cdot kg^{-1}$) significantly inhibited tumour growth in mice.

In an earlier study, Wang, Yang, Hsieh, and Sheen (2010), also making use of the human melanoma A375 cells as well as basal cell carcinoma cells (the most prevalent form). DATS (25 μM) inhibited growth of both cell types by increasing intracellular ROS generation and cytosolic $Ca^{2+}$ mobilization and by decreasing mitochondrial membrane potential without having significant effects on normal keratinocyte HaCaT cell growth. In a more recent study from the same group (Wang, Chu, Hsieh, & Sheen, 2017), DATS (at 10 and 25 μM) inhibited the invasion ability of A375 cells, lowered protein expression and activation of the metalloproteinases **MMP-2** and MMP-9, and inhibited metastasis via regulation of F-actin aggregation. Moreover, DATS exerts inhibitory effects on A375 cell adhesion parallel to a decrease in protein expression of integrins α4, **α5**, **αv**, **β1**, **β3**, and **β4** and activation of **focal adhesion kinase**, thus resulting in a non-migratory phenotype that could explain the antimetastatic potential of the $H_2S$ donor DATS.

De Cicco et al. (2017) showed that acetyl deacylasadisulfide (100 μM; Figure 1), a natural $H_2S$ donor isolated from the latex of the plant *Ferula assa-foetida*, can induce apoptosis of the human melanoma cell lines PES 43 and A375 via reduction of NF-κB activity, decreased expression of the anti-apoptotic proteins c-FLIP, X-linked inhibitor of apoptosis protein, and **Bcl-2**, and inhibition of the phosphorylation and activation of both Akt and ERK proteins. In a previous investigation, this group observed that the hybrid compound **ATB-346** (100 μM; Figure 1), an $H_2S$-releasing naproxen derivative, inhibits human melanoma cell proliferation by inhibiting pro-survival pathways associated with NF-κB and Akt activation. Furthermore, oral administration of ATB-346 (43 $\mu mol \cdot kg^{-1}$) to mice resulted in significant growth delay of the melanoma tumours (up to 70%), without affecting body weight (De Cicco et al., 2016). In a recently published study from the same group, Ercolano et al. (2019) show that another $H_2S$-releasing naproxen derivative, naproxen-4-hydroxybenzodithioate (naproxen-HBTA; at 10 and 30 μM; Figure 1), induced caspase 3-mediated apoptosis and inhibited human melanoma cell proliferation, migration, invasion, and colony formation in vitro. In addition, the authors also show the beneficial effects, in vivo, of this $H_2S$-releasing naproxen derivative, as the daily oral treatment of mice with 14.5 $mg \cdot kg^{-1}$ of naproxen-HBTA resulted in significant suppression of melanoma growth and progression.

Although the antiproliferative effects of increased production of CSE-derived $H_2S$ were reported, the study from Leikam et al. (2014) showed that CSE overexpression in tumour cells had pro-tumorigenic functions and that the blockade of CSE enzymic activity in human melanoma cells not only reduced proliferation rates and enhanced cell sensitivity to $H_2O_2$ but also induced senescence. Therefore, the role of CSE-derived $H_2S$ on tumour regulation cannot be absolutely defined as this may be related to the actual amounts of $H_2S$ produced by this enzyme in the different cell systems studied, bearing in mind the

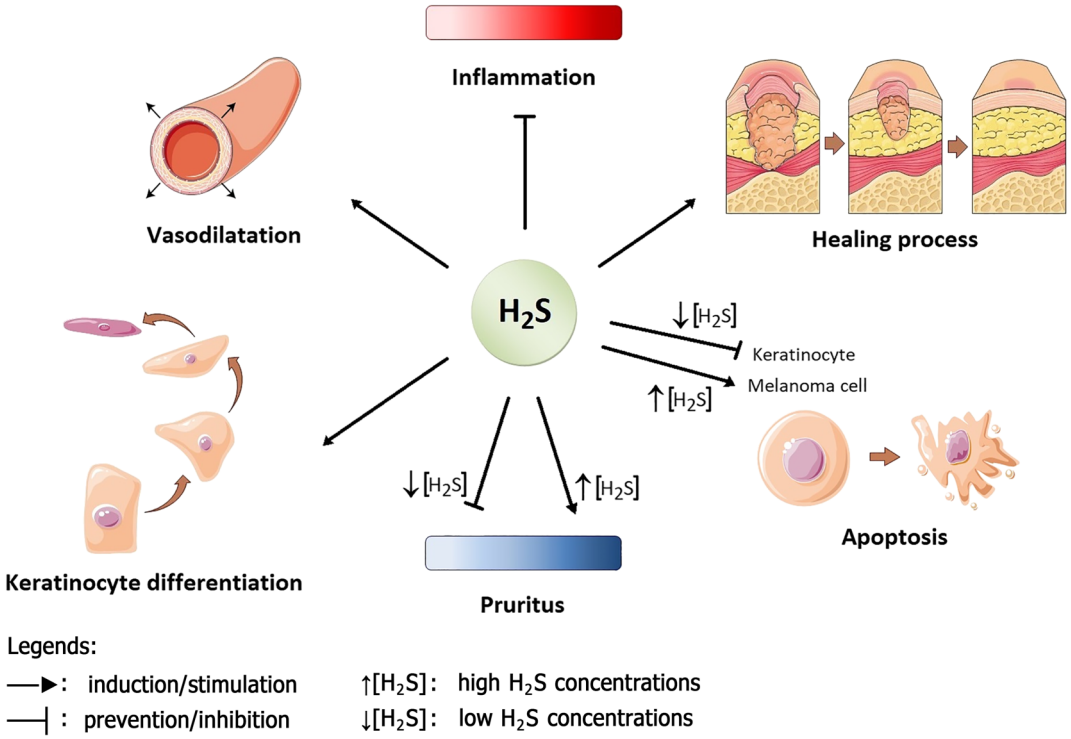


**FIGURE 2** Some of the effects of $H_2S$ in the skin include regulation of vasodilatation, induction of keratinocyte differentiation, and wound healing, in addition to regulation of apoptosis and modulation of pruritus and resolution of inflammation. ⟶: induction or stimulation; ⟊: prevention or inhibition; ↑[$H_2S$]: high $H_2S$ concentrations; ↓[$H_2S$]: low $H_2S$ concentrations

U-shaped pattern of the dose-concentration–response curves that $H_2S$ usually shows in many experimental models and systems.

## 5 | CONCLUSIONS

After the recognition of $H_2S$ as the most recent member of the gasotransmitter family, along with NO and carbon monoxide, many roles of $H_2S$ have been uncovered in different physiological regulatory systems. Specifically regarding $H_2S$ signalling in the skin, the information available to date supports the involvement of this molecule in physiological and pathological processes (Figure 2). In general, and similarly to NO, most of the effects of $H_2S$ are strongly dose or concentration dependent (as shown by U-shaped curves), which demonstrates many molecular targets with different affinities that will finally lead to stimulatory versus inhibitory responses, as it is the case with some skin processes, such as itching and apoptosis.

Because of the significant role of $H_2S$ in skin physiology, it is not surprising that altered $H_2S$ production contributes to the pathogenesis of many cutaneous diseases. Several $H_2S$-releasing compounds (such as $Na_2S$, NaHS, GYY-4137, ATB-346, DATS, naproxen-HBTA, and JK1; Figure 1) have been tested in experimental studies, and diverse results have been obtained. However, their intrinsic characteristics as $H_2S$ donors are so different (in terms of $H_2S$-releasing kinetics, pH dependence, capacity to enter the cell, or organelle specificity) that they should not be considered as generic "$H_2S$ donors" without taking their specific characteristics into account or conclusions drawn from consistent results when using different compounds for a given disease condition. Undoubtedly, these chemical entities comprise a new family of potential therapeutic tools for treatment of a variety of skin diseases by targeting their differential aetiological aspects (as anti-inflammatory, anti-pruriginous, cytoprotector, pro-angiogenic, and immunomodulator, by accelerating the healing process or controlling melanoma cell biology). It is thus clear that the development of new, better, and safer $H_2S$-based medicines will crucially depend on expanding our knowledge of the precise role of $H_2S$ and its targets in the different aspects of skin biology, as well as a more detailed understanding of the molecular actions of the different $H_2S$ donors.

### 5.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 (Alexander, Christopoulos et al. 2017; Alexander, Fabbro et al., 2017a,b; Alexander, Striessnig et al., 2017).

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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