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# Disulfiram as an anti-inflammatory agent: mechanisms, nano-delivery strategies, and applications in non-oncologic diseases

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Disulfiram (DSF), an FDA-approved drug for alcoholism, has recently emerged as a potent anti-inflammatory agent. It achieves this by targeting gasdermin D (GSDMD)-mediated pyroptosis, a key driver of inflammatory responses. This review explores the multifaceted anti-inflammatory mechanisms of DSF, including its inhibition of GSDMD pore formation, modulation of the STING pathway, suppression of RIPK1-dependent necroptosis, and disruption of FROUNT-mediated macrophage migration. Despite its promising *in vitro* efficacy, DSF's clinical application is hindered by its poor solubility, low bioavailability, and rapid metabolism. To overcome these limitations, advanced nano-delivery carriers—such as lipid-based nanoparticles, polymeric carriers, metal–organic frameworks, and peptide conjugates—have been developed to enhance targeted delivery, prolong circulation, and reduce off-target effects. These innovations hold significant promise for the treatment of diverse inflammatory diseases, including respiratory disorders (e.g., COVID-19 and acute lung injury), autoimmune conditions (e.g., lupus and graft-versus-host disease), and metabolic ailments (e.g., hepatitis and colitis). While challenges remain in clinical translation, integrating DSF with nanotechnology offers a transformative approach to harnessing its anti-inflammatory properties. This review highlights current advancements, unresolved questions, and future directions for optimizing DSF-based therapies in inflammation management.

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## 1. Introduction

Inflammation is a fundamental pathological response of the body, representing a defensive reaction of vascularized living tissues to various injurious stimuli. It is a common feature of the pathological processes of numerous diseases. While


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inflammation can be beneficial in resisting harmful external stimuli and limiting injury progression, excessive or dysregulated inflammatory responses, such as those seen in autoimmune disorders, can exacerbate tissue damage and contribute to disease severity.<sup>1–3</sup> The complexity and diversity of the cells involved in inflammatory responses, coupled with the intricate interplay of inflammatory mediators, make the rational use of anti-inflammatory drugs particularly challenging.<sup>4,5</sup> Furthermore, the lack of specificity in targeting distinct inflammatory pathways complicates the selection of appropriate therapeutic agents. Addressing these challenges requires a deeper understanding of the molecular mechanisms of inflammation and the development of targeted anti-inflammatory strategies.

Disulfiram (DSF), an FDA-approved medication for alcoholism, has recently emerged as a promising anti-inflammatory agent. It is a disulfide derivative of diethyldithiocarbamate (DEDTC), and it possesses the chemical structure  $C_{10}H_{20}N_2S_4$  or  $((C_2H_5)_2NCS)_2S_2$  (Fig. 2A). Compared to DEDTC, DSF exhibits enhanced lipophilicity, a critical pharmacological property that facilitates superior cellular membrane permeability.<sup>6</sup>

This characteristic renders DSF a more promising therapeutic candidate than DEDTC for clinical applications. Following oral administration, DSF undergoes conversion into a bis(diethyldithiocarbamate)–copper complex under gastric acidic conditions, facilitating absorption and distribution across the gastrointestinal mucosa. The copper complex subsequently degrades further in systemic circulation to form diethyldithiocarbamic acid (DDC). Due to its inherent chemical instability, DDC decomposes into carbon disulfide and diethylamine or forms a bis(diethyldithiocarbamate)copper(II) complex  $(Cu(DDC)_2)$ .<sup>7</sup> These metabolic derivatives ultimately mediate potent cytotoxic effects against malignant cells through multiple mechanisms, including proteasome inhibition, reactive oxygen species (ROS) generation, and cuproptosis.<sup>8–11</sup> Furthermore, DSF metabolism may generate reactive nitrogen species, contributing to its multifaceted pharmacological effects.<sup>7</sup> A groundbreaking discovery by Liu and colleagues at the Program in Cellular and Molecular Medicine, Boston Children's Hospital, revealed that DSF specifically inhibits gasdermin D (GSDMD), a key mediator of pyroptosis.<sup>12</sup> GSDMD was first identified as



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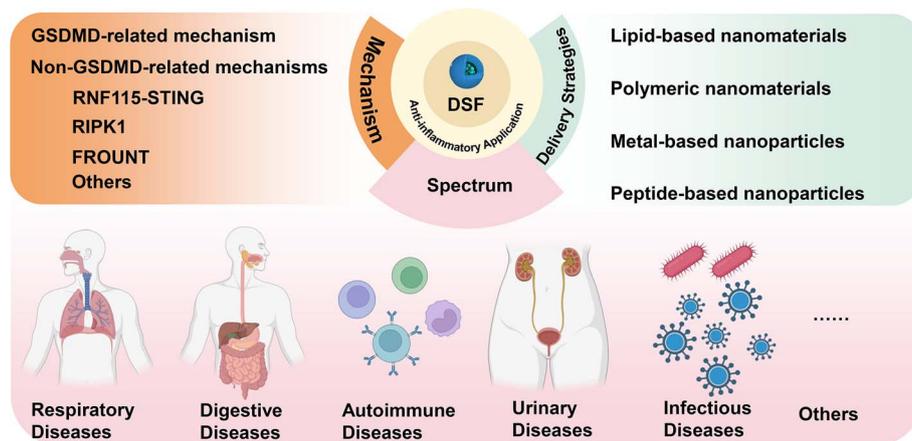


Fig. 1 Illustration of the anti-inflammatory mechanisms, delivery strategies, and disease spectrum of DSF. Image was created with BioRender (<https://www.biorender.com>).

a mediator of cellular focal death by Shao *et al.* in 2015, and pyroptosis was characterized as a form of programmed necrosis mediated by the Gasdermin (GSDM) family in 2018.<sup>13,14</sup> GSDMD is a protein that forms on cell membranes and can release a variety of inflammatory substances and immune response complexes.<sup>15–17</sup> As a newly discovered, potentially effective anti-inflammatory agent, DSF can alleviate the inflammatory responses by inhibiting the process of GSDMD pore formation, thereby suppressing both pore-formation-induced pyroptosis and its associated release of inflammatory substances.<sup>12,18–21</sup> Recent studies have explored the mechanisms underlying the anti-inflammatory effects of DSF. In addition to inhibiting GSDMD-mediated pyroptosis and inflammatory cytokine release as a specific GSDMD inhibitor, DSF could also alleviate inflammation by suppressing the signaling pathways associated with proteins, such as STING, RIPK1, and FROUNT.<sup>22–24</sup> Moreover, the application of DSF in inflammatory diseases has been validated through numerous mouse models of different non-cancerous diseases and has shown promise.<sup>23,25</sup>

Traditionally administered orally for alcoholism, DSF exhibits poor pharmacokinetic properties that limit its therapeutic efficacy.<sup>26–28</sup> Following oral ingestion, DSF must traverse the gastrointestinal mucosal barrier and undergo hepatic metabolism before reaching its target tissues. These processes are accompanied by low bioavailability and suboptimal targeting efficiency, primarily due to the drug's inherently poor aqueous solubility. Consequently, the anti-inflammatory potential of DSF is substantially compromised when delivered *via* conventional oral routes.<sup>29</sup> To address the challenges associated with targeted delivery and to achieve enhanced accumulation at lesion sites with minimized systemic side effects, various nano-delivery platforms have been extensively investigated.<sup>30,31</sup> These carriers explored for DSF delivery include lipid-based nanomaterials, polymeric nanomedicine, metal-based nanoparticles, and peptide-based nanoparticles.<sup>32–35</sup> They have successfully enhanced DSF's therapeutic efficacy and delivery efficiency while promoting gastrointestinal environment-responsive functionality of the delivery systems.

This review first explores the anti-inflammatory mechanisms of DSF, including both GSDMD-related and non-GSDMD-related pathways. Subsequently, it provides a comprehensive summary of recent advancements in DSF-based nano-delivery strategies designed for inflammatory diseases, to enhance the therapeutic efficacy and minimize adverse effects by optimizing drug-delivery systems. Finally, contemporary researches on the therapeutic applications of DSF in inflammatory diseases are summarized, highlighting emerging trends and innovative delivery approaches that expand its clinical potential (Fig. 1). By addressing delivery challenges, this work aims to bridge the gap between preclinical research and clinical translation, offering insights into the optimization of DSF's anti-inflammatory applications. Given the extensive coverage of DSF's applications in tumor therapy in existing literature, this review will focus on its therapeutic potential in non-oncologic diseases, with a particular emphasis on inflammatory conditions.<sup>8,36–38</sup>

## 2. Anti-inflammatory mechanisms of DSF

In recent years, extensive research has been conducted to elucidate the anti-inflammatory mechanisms of DSF, revealing multiple molecular pathways through which it exerts its therapeutic effects.<sup>39</sup> A pivotal mechanism involves the inhibition of GSDMD pore formation, which plays a critical role in mitigating inflammatory responses. Consequently, significant attention has been directed toward understanding GSDMD-related signaling pathways.<sup>40</sup> Beyond this, emerging studies have identified additional anti-inflammatory pathways associated with DSF, highlighting its potential as a multifaceted therapeutic agent for inflammatory diseases.<sup>22,41</sup> In this section, we systematically categorize and discuss these mechanisms into two primary groups: GSDMD-related and non-GSDMD-related pathways.

### 2.1 GSDMD-related mechanisms

The Gasdermin (GSDM) family comprises a group of structurally related proteins implicated in immune-related pore



formation. Among them, GSDMD contains three distinct domains: an N-terminal cytotoxic domain, a C-terminal inhibitory domain, and a central flexible linker<sup>42,43</sup> (Fig. 2B). Under enzymatic cleavage by cysteine asparaginase (caspase), GSDMD releases the N-terminal structural domain (N-GSDMD). The N-GSDMD can insert into the cell membrane, and large oligomeric pores can thus be formed. These pores serve as a channel for the release of a variety of inflammatory factors and induce cellular pyroptosis. GSDMD can be activated by inflammasomes *via* both classical and non-classical pathways. In the classical pathway, GSDMD is spliced into N-GSDMD by the classical inflammasome after the activation of caspase-1 in

response to different stimuli. As for the non-classical pathway, GSDMD is induced to shear by the activation of caspase-4/5/11 after the entry of lipopolysaccharides (LPS) into the cytosol.<sup>44</sup>

GSDMD palmitoylation plays a pivotal role in the membrane translocation of N-GSDMD. Hu *et al.* demonstrated that DSF effectively suppresses apoptosis triggered by both classical and non-classical pathways. Intriguingly, this inhibition does not occur through interference with inflammatory caspase cleavage or other upstream events in GSDMD activation. Instead, DSF exerts its effect by covalently modifying Cys191, thereby impairing GSDMD pore formation.<sup>12</sup> Subsequent studies revealed that GSDMD and N-GSDMD undergo *S*-palmitoylation

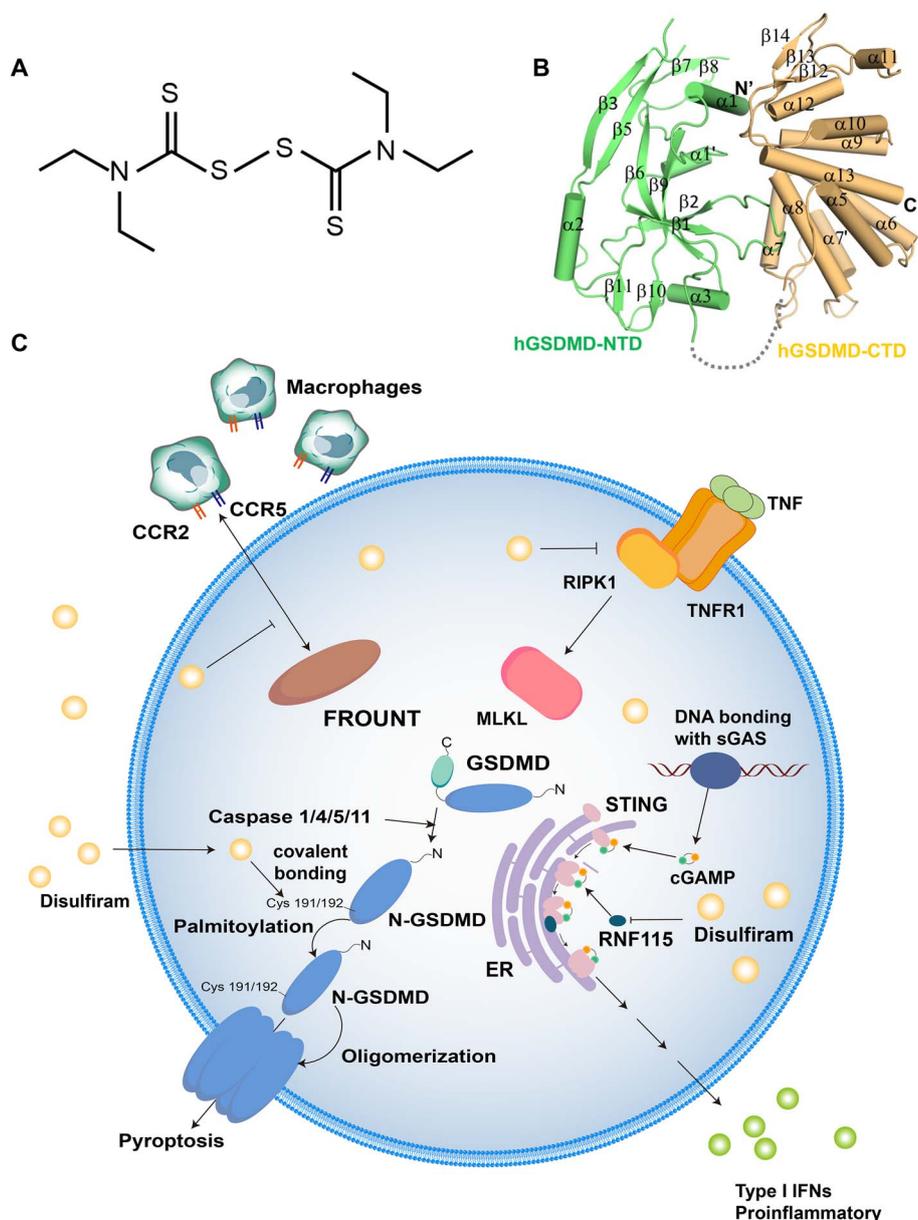


Fig. 2 (A) The molecular structure of DSF. (B) Overall structures of human GSDMDs.<sup>50</sup> This figure has been reproduced from ref. 50 with permission from Elsevier Publications copyright 2019. (C) The anti-inflammatory mechanisms of DSF mainly include the inhibition of GSDMD, STING pathway, FROUNT pathway, and RIPK1 pathway. CCR, chemokine receptors; TNF, tumor necrosis factor; TNFR1, tumor necrosis factor receptor 1; RIPK1, receptor-interacting protein kinase 1; MLKL, mixed lineage kinase domain-like; GSDMD, gasdermin D; sGAS, cyclic GMP-AMP synthase; cGAMP, cyclic GMP-AMP; STING, stimulator of interferon genes; ER, endoplasmic reticulum; IFN, interferon.



at cysteine residues Cys191 (human) or Cys192 (mice), a process catalyzed by multiple palmitoylating enzymes. Palmitoylated GSDMD/N-GSDMD exhibited enhanced interactions with caspases, amplifying the signaling cascade that drives pyroptotic cell death. This modification is critical for their proper localization to the cell membrane.<sup>44</sup> Investigations by Schiffelers *et al.* utilizing a variable domain of heavy chain-only antibody technology demonstrated that the stabilized GSDMD monomers could spontaneously penetrate the plasma membrane, indicating that membrane insertion served as a prerequisite for oligomerization.<sup>45</sup> This finding substantiated that the N-GSDMD, upon release, preferentially inserts into the cellular membrane prior to undergoing oligomeric assembly. Notably, DSF could effectively inhibit the formation of N-GSDMD, thereby preventing both its membrane insertion and the consequent oligomerization process that drives pyroptotic cell death. Similarly, necrosulfonamide and dimethyl fumarate inhibited inflammasome-mediated inflammation through the covalent modification of Cys191/Cys192 residues, thereby blocking GSDMD pore formation.<sup>12,46–48</sup> However, all these therapeutic agents face significant clinical limitations due to their mechanism of action, which involves non-selective cysteine modification, resulting in poor targeting specificity and substantial off-target effects. Among these compounds, DSF has attracted particular research interest owing to its established FDA approval status and extensive clinical history as an anti-alcoholism medication, providing a more favorable translational pathway compared to investigational compounds. Further elucidating the regulatory dynamics, Zhang *et al.* identified that APT2-mediated depalmitoylation of Cys191/Cys192, following GSDMD-membrane translocation, facilitates N-GSDMD oligomerization and promotes pyroptosis (Fig. 2C).<sup>22</sup> These findings underscore the dual significance of palmitoylation and depalmitoylation at the Cys191/Cys192 site in modulating pyroptotic pathways, identifying this residue as a promising therapeutic target. Supporting this, Zhuang *et al.* confirmed that DSF covalently binds to Cys192 in murine GSDMD, blocking palmitoylation and disrupting membrane localization. This mechanism effectively curtails the release of inflammatory mediators and subsequent pyroptotic cell death.<sup>49</sup>

The inflammatory factors and other mediators of immune responses released through GSDMD pores can be inhibited by DSF in inflammatory responses.<sup>20</sup> It has been reported that after the inhibition of GSDMD pore formation, the reduced release of IL-1 $\beta$  could significantly attenuate organ damage in sepsis and hepatitis.<sup>44,51,52</sup> As an extracellular meshwork consisting of a DNA backbone and a variety of granule proteins released by neutrophils in response to specific stimuli, neutrophil extracellular traps (NETs) can trap and kill pathogens and participate in the regulation of inflammatory responses.<sup>53,54</sup> Abnormalities in their release or action process can lead to a variety of autoimmune diseases and systemic inflammatory responses.<sup>55</sup> It was reported that DSF could reduce the release of NETs, thus alleviating the inflammatory response and NETosis triggered by NETs.<sup>56,57</sup> Therefore, it could be concluded that DSF may be a potential therapeutic agent for inflammatory responses in

terms of NET-related mechanisms. In addition to NETs, researchers have found that DSF can inhibit the release of macrophage extracellular traps, offering a potential therapeutic strategy for treating macrophage-associated inflammations.<sup>58</sup> However, the role of GSDMD pore channels in inflammatory responses and cellular pyroptosis remains to be further explored.

## 2.2 Non-GSDMD-related mechanisms

**2.2.1 RNF115-STING.** As a dimeric transmembrane protein on the endoplasmic reticulum, the stimulator of interferon genes (STING) is crucial for DNA-associated signaling communication. After the DNA in the cytoplasm binds to cyclic guanine nucleotide-adenine nucleotide synthetase, STING is activated by second messenger cGAMPs that bind to STING proteins and cause conformational changes.<sup>59–61</sup> Thus, aberrant activation of STING protein against its DNA can lead to severe autoimmune inflammatory responses.<sup>62,63</sup> RNF115 is an E3 ligase that can promote an inflammatory response mediated by the STING pathway through its interaction with STING proteins, and this response can be significantly ameliorated by DSF.<sup>64</sup> It was verified that the addition of DSF to peripheral blood mononuclear cells, which were isolated from systemic lupus erythematosus patients, resulted in a significant reduction in the expression of inflammatory factors and interferon *via* the STING pathway.<sup>22</sup> However, given that STING functions as a crucial cytosolic DNA sensor playing a pivotal role in anti-infection immunity, it is imperative to develop strategic methodologies, such as localized administration strategies, pulsatile agonist delivery systems or responsive nano-delivery strategies that ensure spatiotemporal precision in STING activation.<sup>22</sup>

**2.2.2 RIPK1.** Receptor-interacting protein kinase 1 (RIPK1) is a key serine/threonine kinase involved in cell death regulation, consisting of an N-terminal kinase structural domain, an intermediate RHIM structural domain, and a C-terminal death domain.<sup>65,66</sup> Huang *et al.* discovered that DSF could directly bind to RIPK1, inhibit the necroptosis signaling pathway mediated by the binding, and reduce the activation of the downstream mixed lineage kinase domain-like protein, thereby blocking acinar cell necrosis. Additionally, it was demonstrated that DSF could reduce inflammatory response by inhibiting the nuclear translocation of nuclear factor kappa-B and the expression of toll-like receptor 4 (TLR4). Meanwhile, DSF could also block the formation of NETs induced by damage-associated molecular patterns, further alleviating pancreatic tissue injury and systemic inflammation.<sup>23</sup>

**2.2.3 FROUNT.** FROUNT proteins can regulate monocyte/macrophage migration *via* chemokine receptors (CCRs), mainly CCR2 and CCR5.<sup>67</sup> Notably, CCR2 is reported to play a crucial role in the recruitment of monocytes, which contribute to the development of kidney inflammation and fibrosis.<sup>68</sup> FROUNT protein could promote pseudopod formation and monocyte/macrophage chemotaxis in the kidney, and DSF has been shown to target FROUNT to inhibit macrophage aggregation.<sup>24</sup>

Chen *et al.* employed an *in vivo* mouse model of crescentic glomerulonephritis induced by anti-glomerular basement



membrane antibody to investigate the therapeutic effects of DSF and its derivative DSF-41. Their findings revealed that both compounds effectively suppressed the migration and activation of monocytes/macrophages toward renal tissues by disrupting the FROUNT-CCR2/CCR5 interaction. This mechanism significantly attenuated renal macrophage infiltration and reduced the secretion of pro-inflammatory cytokines, including tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). Complementary *in vitro* studies further demonstrated that DSF impaired macrophage pseudopodia formation and chemotactic capacity, corroborating its anti-inflammatory role in glomerulonephritis pathogenesis.<sup>69</sup> In another study, Toda *et al.* established a nephritis model by the intravenous injection of anti-glomerular basement membrane antibody in Wistar-Kyoto rats, and DSF or its highly effective derivative DSF-41 was orally administered for intervention. The results showed that DSF specifically inhibited the interaction between FROUNT and chemokine receptors CCR2/CCR5, blocked the migration of monocytes/macrophages and the formation of their pseudopodia, and reduced the infiltration of renal macrophages (a decrease in CD68+ cells). Moreover, DSF downregulated the activation markers of macrophages, such as CD86 and major histocompatibility complex class II, as well as pro-inflammatory cytokines, including TNF- $\alpha$  and C-C motif chemokine ligand 2. Further, it alleviated podocyte injury and renal fibrosis.<sup>70</sup> These findings revealed that DSF inhibited the recruitment and activation of inflammatory cells *via* a FROUNT-dependent mechanism, thereby improving the pathological process of nephritis.

**2.2.4 Others.** In addition to these well-defined pathways, several emerging targets have been implicated in DSF's anti-inflammatory effects. Glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ )

plays a pivotal role in modulating the Nrf2/HO-1 pathway, which governs antioxidant responses, as well as the NLRP3 inflammasome pathway, which drives pyroptotic cell death. Consequently, GSK-3 $\beta$  is intricately linked to oxidative stress, pyroptosis, and inflammatory processes. Recent studies have demonstrated that DSF mitigates oxidative-damage-associated pyroptosis and inflammation by downregulating GSK-3 $\beta$  and NLRP3, thereby attenuating LPS-induced ulcerative colitis (UC) in both *in vivo* and *in vitro* models.<sup>71</sup> Intriguingly, Xiao *et al.* revealed that GSDMD-mediated pyroptosis also contributes to the pathogenesis of UC, indicating that DSF may exert its therapeutic effects through multiple concurrent mechanisms in the treatment of a single disease.<sup>72</sup> Furthermore, DSF has been identified as a specific inhibitor of TLR4. By covalently modifying Cys133 on myeloid differentiation protein-2, DSF disrupts TLR4 signaling, thereby suppressing the LPS-induced production of inflammatory cytokines, chemokines, and interferons in macrophages.<sup>41</sup> As research into the anti-inflammatory mechanisms of DSF continues to advance, novel therapeutic applications are steadily emerging. While current studies predominantly focus on GSDMD-related inflammatory pathways, non-GSDMD-dependent mechanisms, though less explored, hold significant promise for expanding the clinical utility of DSF.

### 3. Nano-delivery strategies of DSF

Despite the excellent *in vitro* anti-inflammatory activity of DSF, the clinical trials focusing on DSF oral administration show unsatisfactory results due to the first-pass elimination and low water solubility of DSF. Therefore, suitable nano-delivery

**Table 1** Typical examples of DSF-delivery strategies applied for inflammatory diseases<sup>a</sup>

Delivery strategies	Formulations	Mechanisms	Animal models	Advantages	Ref.
Lipid-based nanomaterials	Lipid nanoparticle with MCC950 and DSF	NLRP3 inflammasome inhibition	Mice, SP	High efficiency; low delivery dose	73
	DSF-loaded liposomes containing lung endothelial cell-targeting peptides	GSDMD inhibition	Mice, ARDS	Targeted delivery; ROS-responsive release; excellent cytocompatibility; minor systemic toxicity	32
Polymeric nanomedicine	Poly(lactic-co-glycolic acid)-based nanoparticles loaded with DSF	GSDMD inhibition	Mice, OA	Sustained release; intra-articular delivery	74
	DSF@PLGA NPs	Reduction in the release of TNF- $\alpha$ and IL-6	Mice, LI	Low cytotoxicity; selective uptake; specific aggregation in the liver	33
Metal-based nanoparticles	CuET nanocrystals	NLRP3 inflammasome inhibition	Mice, IBD	High bioavailability; high biodistribution in the intestine	75
	DSF-loaded CBFD NPs	Suppression of NLRP3 inflammasome-mediated pyroptosis	Mice, OLV-LIRI	High colloidal stability; effective accumulation and release of Cu <sup>2+</sup> and DSF	76
Peptide-based nanoparticles	C- $\beta$ -LG/DSF NPs	Inhibition of pyroptosis; reduction of neuroinflammation	Mice, TBI	Selective targeting; retention effect; enhanced accumulation; prolonged systemic circulation	77
	DSF-LF NP	GSDMD inhibition	Mice, sepsis and UC	Safety and effectiveness; combination therapy	35

<sup>a</sup> SP, septic peritonitis; ARDS, acute respiratory distress syndrome; OA, osteoarthritis; LI, liver injury; IBD, inflammatory bowel disease; OLV-LIRI, one-lung ventilation-induced lung injury and reperfusion injury; TBI, traumatic brain injury; UC, ulcerative colitis; ROS, reactive oxygen species.



strategies have been explored to improve the utilization rate of DSF in the treatment of inflammatory diseases (Table 1).

### 3.1 Lipid-based nanomaterials

Lipid-based nanomaterials represent a prominent class of drug-delivery systems characterized by their spherical structure, consisting of a lipid bilayer surrounding an aqueous core for drug encapsulation.<sup>78</sup> This design offers simplicity, excellent biocompatibility, and biodegradability, as lipids are naturally occurring components in biological systems. Among lipid-based nanomaterials, liposomes and lipid nanoparticles are the two primary types widely explored for therapeutic applications. Lipid nanoparticles have demonstrated significant potential in enhancing the efficacy of DSF while mitigating its systemic toxicity. For instance, Nandi *et al.* developed a dual-drug delivery system incorporating DSF and MCC950, an NLRP3 inhibitor, into LNPs.<sup>73</sup> This formulation exhibited superior *in vitro* performance compared to free drug combinations or single-drug nanoparticles. In a mouse model of LPS-induced septic peritonitis, the LNP-based therapy improved survival rates and reduced key inflammatory markers, including active caspase-1 and IL-1 $\beta$ , which are pivotal components of the NLRP3 pathway.<sup>73</sup> However, a notable limitation of LNPs is their reliance on endosomal escape mechanisms to release encapsulated drugs into the cytoplasm, which can restrict their broad application.<sup>79,80</sup> Furthermore, LNPs can elicit immune responses by activating the innate immune system, including the release of pro-inflammatory cytokines and the activation of the complement system.<sup>81–83</sup> This immunostimulatory effect may lead to systemic inflammatory reactions, which become more pronounced upon repeated administration of LNPs.<sup>84</sup> Certain cationic lipids employed in LNP formulations, such as dimethyldioctadecylammonium bromide, have been shown to exacerbate this immunostimulatory potential.<sup>85</sup>

Liposomes, another versatile lipid-based platform, are vesicular structures composed of single or multiple phospholipid bilayers, capable of encapsulating both hydrophilic and hydrophobic drugs.<sup>86,87</sup> To avoid damage to middle ear structures resulting from direct drug delivery, liposome-loaded DSFs have been developed to accomplish drug delivery from the middle ear to the cochlea's round window membrane, as well as to accomplish intracellular aggregation of DSF in the cochlea.<sup>88,89</sup> Furthermore, the incorporation of targeting peptides into liposomal formulations enhances the specificity of liposomal drug-delivery systems.<sup>90</sup> Recent investigations have revealed that DSF-loaded liposomes conjugated with lung endothelial cell-targeting peptides (DTP-LET@DSF NPs) demonstrated therapeutic potential in mitigating acute respiratory distress syndrome (ARDS) through the suppression of LPS-induced pyroptosis mediated by GSDMD (Fig. 3A). Structural characterization showed that DTP-LET@DSF NPs maintained a uniform spherical morphology with a distinct core-shell architecture, and the nanoparticles exhibited an average hydrodynamic diameter of  $277.44 \pm 3.54$  nm (Fig. 3B and C). The delivery strategy demonstrated the preferential accumulation of DTP-LET@DSF NPs in pulmonary vascular

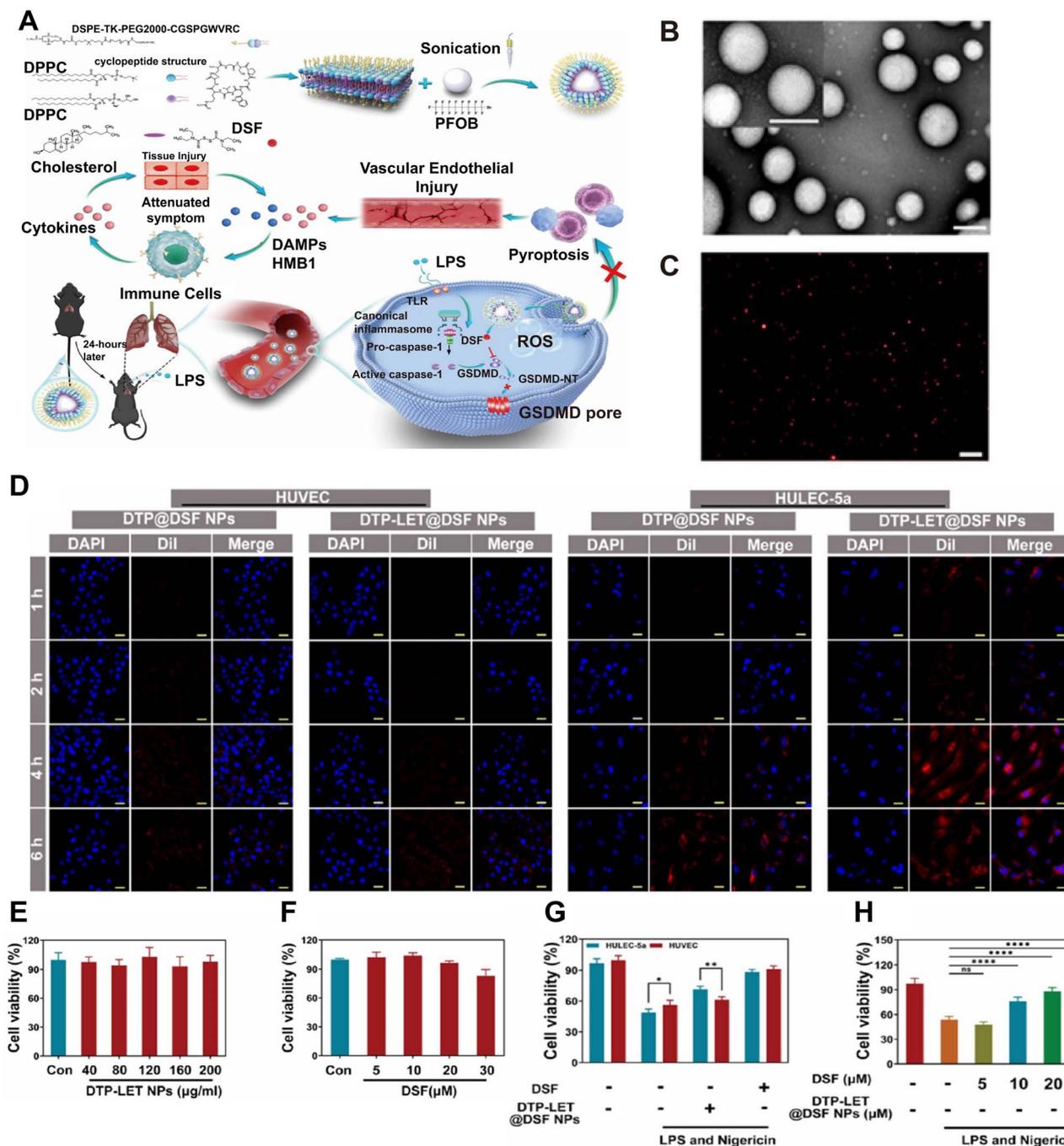
endothelial cells, with significantly reduced off-target distribution in other tissues (Fig. 3D). Comprehensive safety assessments revealed favorable biocompatibility profiles, as evidenced by the minimal systemic toxicity (Fig. 3E–G). However, comparative *in vitro* efficacy studies indicated that the nanoparticle formulation showed attenuated therapeutic outcomes relative to equivalent concentrations of free DSF (Fig. 3H).<sup>32</sup> Despite their success in oncology, the application of liposomal DSF in inflammatory diseases remains underexplored, with many problems to be solved, presenting a promising avenue for future research. Given that liposomes are characterized by their fundamental phospholipid bilayer structure, they exhibit superior biocompatibility and comparatively lower toxicity than LNPs.<sup>91,92</sup> This biomimetic membrane-like architecture results in minimally toxic by-products during *in vivo* degradation. The limited toxicity profile primarily stems from the residual organic solvents employed in conventional preparation methods.<sup>93,94</sup> Multiple liposomal formulations have received regulatory approval for clinical use, demonstrating a relatively mature pathway for clinical translation.<sup>95,96</sup> However, these systems face challenges related to long-term storage stability, particularly concerning drug leakage and liposomal aggregation.<sup>96</sup> Addressing these limitations requires the optimization of lyophilization protocols to enhance the formulation's stability and maintain its therapeutic efficacy during storage.

### 3.2 Polymeric nanomedicine

Homopolymers, copolymers, and natural polymers have been widely used in the design and preparation of various polymeric nanomedicine carriers. Polymeric nanomedicine can be more easily engineered into smart nanoparticles with a wide range of stimulus-responsive structures. Consequently, the application of polymeric nanomedicine improves the water solubility of conventional medicines and offers high responsiveness to local stimuli.<sup>97</sup>

Encapsulating DSF with quaternized palmitoyl glycol chitosan, characterized by a significant positive surface charge ( $+50.9 \pm 1.3$  mV), enhances the colloidal stability of nanoparticles and results in improved pharmacokinetics of DSF.<sup>98</sup> Combined with gelatin methacrylate microgels, polylactic acid–hydroxyacetic acid copolymer nanoparticles loaded with DSF can achieve burst release and sustain slow release of DSF, significantly ameliorating cartilage inflammation.<sup>74</sup> Some types of nanoparticles may cause hepatotoxicity since the metabolic pathways of nanoparticles are unclear, and most of them involve liver function.<sup>99</sup> However, DSF can be effectively delivered using poly(lactic-co-glycolic) acid nanoparticles (DSF@PLGA NPs), which show low cytotoxicity and selective uptake by THP-1 macrophage cells *via* micropinocytosis, inhibiting lipopolysaccharide-induced proinflammatory cytokine production *in vitro*. Furthermore, *in vivo* experiments have shown that DSF@PLGA NPs predominantly localize in the liver, particularly within CD68-positive Kupffer cells, and could significantly reduce thioacetamide-induced proinflammatory cytokine production and liver injury.<sup>33</sup>





**Fig. 3** (A) Liposomes incorporating a lung endothelial cell-targeted peptide to produce DSF-loaded nanoparticles (DTP-LET@DSF NPs). (B) TEM image of DTP-LET@DSF NPs; scale bars: 200 nm. (C) Fluorescence microscopy images of DTP-LET@DSF NPs; scale bar: 10 μm. (D) Cellular uptake of targeted nanoparticles visualized via Dil fluorescence; scale bars: 20 μm. (E and F) The cytotoxicity of different DTP-LET NPs or DSF concentrations to HULECs-5a,  $n = 5$ . (G) Comparison of the therapeutic efficacy of drugs in HULECs-5a and HUVECs,  $n = 5$ . (H) Cell viability of HULECs-5a under treatment with different drug concentrations,  $n = 5$ . This figure has been reproduced from ref. 32 with permission from American Chemical Society Publications copyright 2024.<sup>32</sup>

Some polymeric nanomaterials have limitations, such as poor pharmacokinetics, premature drug release into the bloodstream, accumulation in non-target tissues, and limited drug penetration in target tissues. Although the controllability of the physicochemical properties of nano-delivery systems can be increased by the addition of stabilizers, the addition may be

detrimental to the bioavailability and blood concentration maintenance time of DSF.<sup>100</sup> Stimuli-responsive nanomaterials are often used to construct polymeric nanoparticles to enhance the local responsiveness of the nano-delivery system.<sup>101</sup> Colon-targeted dexamethasone microcrystals (DXMCs) were developed using a layer-by-layer coating technique with chitosan



oligosaccharide, alginate, and Eudragit S100 ( $ES_1AG_4CH_5$ -DXMCs) (Fig. 4A). The microcrystals could release dexamethasone in a pH-dependent manner, preventing initial burst release in acidic environments and ensuring sustained release in the colon (Fig. 4B and C). Notably,  $ES_1AG_4CH_5$ -DXMCs

exhibited enhanced therapeutic efficacy in a mouse model of colitis compared to other DXMC formulations.<sup>102,103</sup> In another study, Yao *et al.* engineered a pH-responsive nanoplatform (CuS/DSF/EL/PVP) by functionalizing the surface of CuS/DSF composites with pH-sensitive copolymers, methacrylic acid-

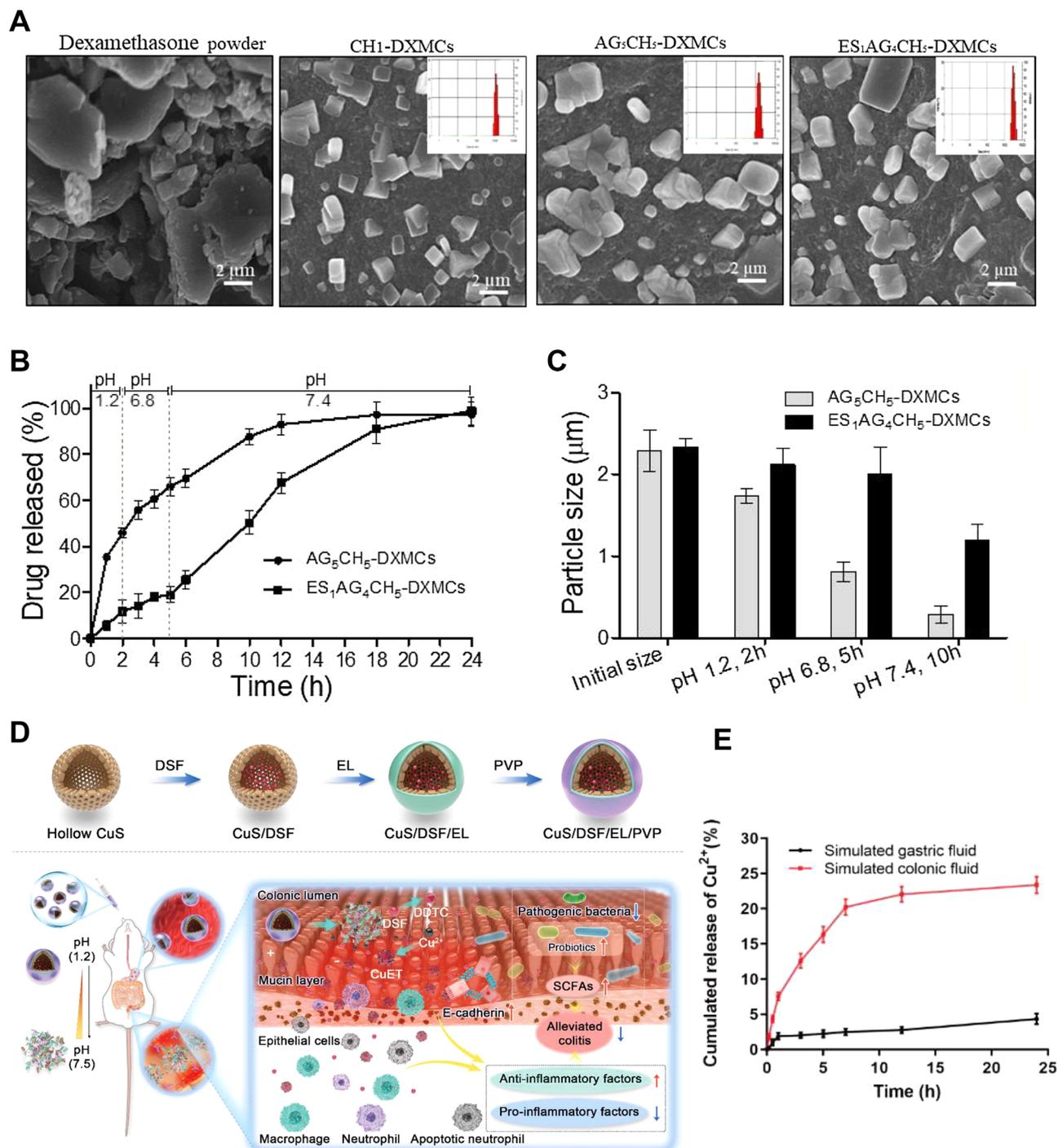


Fig. 4 (A) SEM images and particle-size distribution of dexamethasone powder, CH1-DXMCs,  $AG_5CH_5$ -DXMCs, and  $ES_1AG_4CH_5$ -DXMCs. (B) Drug release profile of  $AG_5CH_5$ -DXMCs and  $ES_1AG_4CH_5$ -DXMCs in a medium with gradually increasing pH. (C) Changes in the particle sizes of  $AG_5CH_5$ -DXMCs and  $ES_1AG_4CH_5$ -DXMCs at different pH values. This figure has been reproduced from ref. 102 with permission from Elsevier Publications copyright 2018.<sup>102</sup> (D) pH-Responsive CuS/DSF/EL/PVP nanoplatform. (E) Release of  $Cu^{2+}$  from the CuS/DSF/EL/PVP nanoplatform in gastric and colonic fluids. This figure has been reproduced from ref. 104 with permission from Elsevier Publications copyright 2024.<sup>104</sup>



ethyl acrylate Eudragit L100-55 (EL) and polyvinylpyrrolidone (PVP) to achieve site-specific gastrointestinal drug delivery (Fig. 4D). *In vitro* release studies revealed the sustained drug release profile of the platform in simulated gastric fluid (pH 1.2) and significantly accelerated drug release in a simulated colonic fluid (pH 7.4), which confirmed EL's capacity to stabilize the nanopatform in acidic environments while enabling pH-triggered payload release and preferential drug accumulation in colonic tissues (Fig. 4E).<sup>104</sup> Despite the significant advancements in polymeric nanodrug delivery systems to date, with many polymeric nanomaterials (*e.g.*, poly(lactic-co-glycolic acid) (PLGA)) demonstrating favorable biodegradability and low acute toxicity, concerns remain regarding their safety profile.<sup>105</sup> Similar to liposomes, these systems face toxicity challenges as polymer-based nanocarriers are predominantly fabricated from organic solvents, such as tetrahydrofuran, chloroform, dimethylformamide, and methanol.<sup>106</sup> Crucially, complete solvent removal often proves technically challenging, and residual solvents have been well-documented as potential toxicological liabilities in pharmaceutical development. Polymeric nanomaterials offer diverse sourcing options and can achieve functional versatility through chemical modification. Although several polymer-based systems have obtained FDA approval (*e.g.*, PEG-PLA), establishing a foundation for clinical

translation, their widespread application remains constrained by significant challenges.<sup>107</sup> These include difficulties in maintaining batch-to-batch homogeneity during large-scale synthesis and substantial gaps in the understanding of their pharmacokinetic profiles.<sup>108</sup>

### 3.3 Metal-based nanoparticles

Metal-based nanoparticles have emerged as a widely used platform for delivering DSF, with copper-based systems being the most prominent. Copper ions ( $\text{Cu}^{2+}$ ) play essential roles in maintaining enzymatic and protein functions, participating in various physiological processes. Owing to their bioactive properties, including antioxidant, catalytic, anti-cancer, and anti-inflammatory effects,  $\text{Cu}^{2+}$ -based materials have been extensively incorporated into biomedical applications. DSF's primary metabolite, DDC, readily chelates  $\text{Cu}^{2+}$  to form a complex known as CuET, which exhibits significantly stronger anti-inflammatory activity than DSF alone.<sup>109</sup> However, CuET exhibits poor solubility in both aqueous and organic solutions (Fig. 5A), coupled with limited membrane permeability (apparent permeability coefficient  $<1 \times 10^{-6} \text{ cm s}^{-1}$ ) (Fig. 5B). To address these pharmacokinetic limitations, Xu *et al.* established a scalable coordination-driven self-

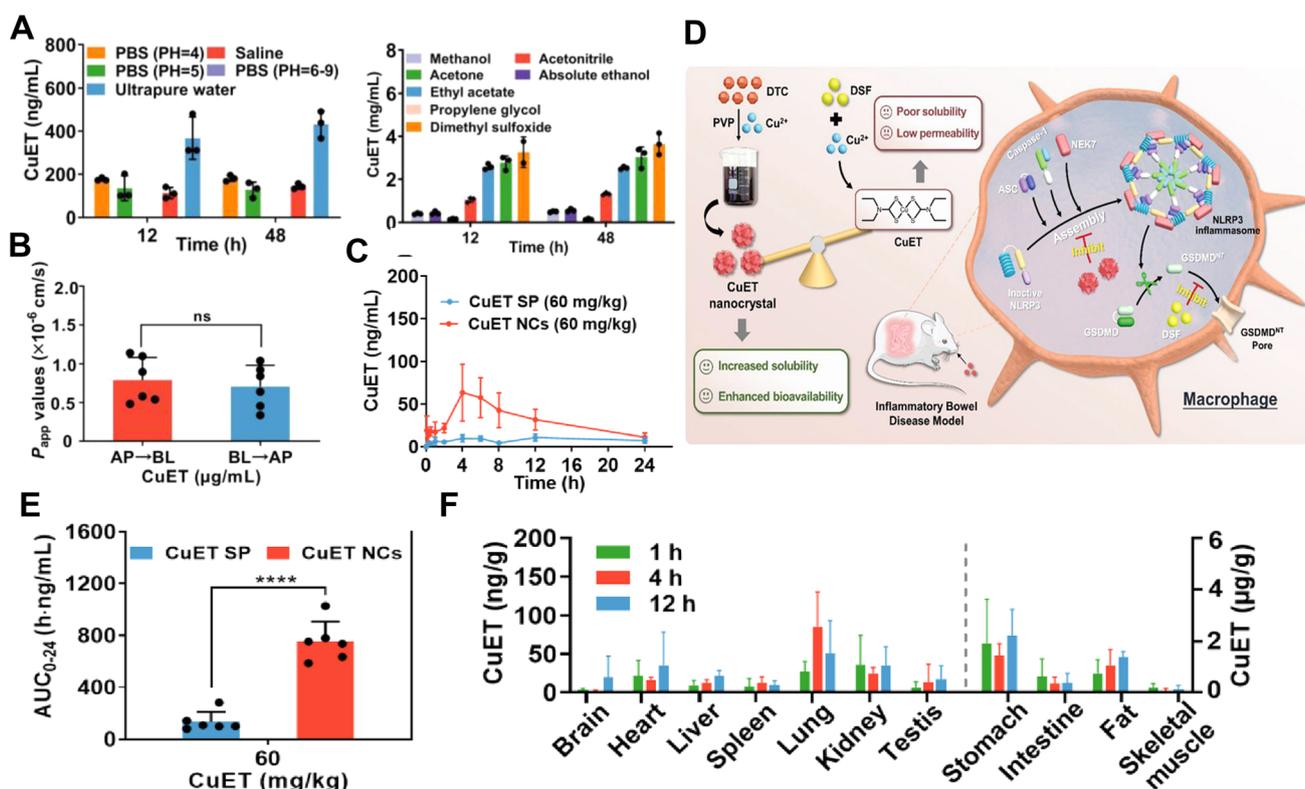


Fig. 5 (A) Equilibrium solubility of CuET in various common solvents. (B) Apparent permeability values of CuET transported across transwells. (C) Mean plasma concentration–time profiles of CuET SP and CuET NCs following oral administration at a dose of 60 mg kg<sup>-1</sup> in Sprague–Dawley rats. (D) Illustration of the mass production of CuET NCs to solve the key limitations of CuET druggability for inflammatory bowel disease (IBD) therapy. (E) Area under the concentration–time curves ( $\text{AUC}_{0-24}$ ) of CuET and CuET NCs. (F) Biodistribution of CuET NCs (60 mg kg<sup>-1</sup>) in major organs at various times after administration. This figure has been reproduced from ref. 75 with permission from Elsevier Publications copyright 2024.<sup>75</sup>



assembly strategy for synthesizing CuET nanocrystals (CuET NCs) (Fig. 5C).<sup>75</sup> Pharmacokinetic profiling revealed significantly elevated plasma concentrations of CuET NCs compared to those of conventional CuET suspensions at equivalent time points (Fig. 5D). Notably, the nanocrystalline formulation demonstrated a 6-fold increase in the area under the concentration–time curve ( $AUC_{0-24}$ ) relative to its free drug counterpart, indicating markedly improved bioavailability (Fig. 5E). Further biodistribution studies demonstrated that orally administered CuET exhibited sustained drug retention (>12 hours) in target tissues (Fig. 5F).<sup>75</sup> However, metal-based nanodelivery systems exhibit more pronounced toxicity compared to other types of nanomedicines. Metallic nanoparticles may release metal ions in biological environments, which can induce cytotoxicity through mechanisms such as oxidative stress and mitochondrial damage.<sup>110</sup> Notably, copper-based nanoparticles (Cu-NPs) demonstrate higher toxicity than their ionic counterparts, potentially attributable to their unique cellular internalization and processing mechanisms.<sup>111</sup> Furthermore, the progressive accumulation of metal ions may lead to long-term toxicity concerns, but there remains a paucity of comprehensive studies investigating the metabolic fate of and systematic detoxification strategies for metal-based nano-delivery systems, highlighting a critical gap in their translational development.<sup>112</sup>

In recent years, metal–organic frameworks have attracted increasing interest as nanocarriers. Due to their high specific surface area and porosity, they can be used for the high loading of therapeutic drugs, and with the assistance of organic materials, they can enhance certain properties of metal-based nano-delivery systems and reduce the side effects produced by metals.<sup>34</sup> A notable example involves a baicalin-coordinated  $Cu^{2+}$  nanoparticle co-loaded with DSF, which was applied to models of one-lung ventilation-induced injury and ischemia–reperfusion lung damage. This system effectively suppressed NLRP3 inflammasome-mediated pyroptosis, thereby attenuating inflammatory responses. The formulation demonstrated excellent colloidal stability under physiological conditions and enabled targeted co-release of  $Cu^{2+}$  and DSF within lung tissues. This strategy facilitated the *in situ* generation of CuET, minimizing off-target toxicity to other organs.<sup>76</sup> Similarly, metal–organic frameworks frequently exhibit toxicity, primarily attributed to the leaching of metal ions, resulting from the dissolution of nanoparticles in aqueous solutions and the subsequent formation of cytotoxic metal cations. This phenomenon has been well-documented, particularly for CuO NPs, where the released  $Cu^{2+}$  ions demonstrate significant biological toxicity.<sup>113</sup> Moreover, metal–organic frameworks demonstrate considerable potential for multi-drug loading by leveraging diverse host–guest interactions. However, the drug loading methodology, strength of these interactions, and subsequent drug-release behavior are intrinsically interrelated.<sup>114</sup> Achieving stable and controllable release profiles through the precise modulation of these parameters represents a critical challenge that requires comprehensive investigation and optimization in the context of large-scale production processes.

### 3.4 Peptide-based nanoparticles

Peptides are inherently water-soluble, and peptide–drug conjugates, formed *via* covalent bonding between peptides and therapeutic agents, significantly enhance the aqueous solubility and prolong the bioactivity of the payload drugs.<sup>115,116</sup> Cysteine–alanine–glutamine–lysine is a well-characterized peptide frequently employed for nanoparticle surface modification to improve the penetration efficiency of the blood–brain barrier.<sup>117–119</sup> Due to the limited ability of DSF to cross the blood–brain barrier, a recent study successfully achieved brain-targeted delivery of DSF by modifying  $\beta$ -lactoglobulin ( $\beta$ -LG) nanoparticles with cysteine–alanine–glutamine–lysine peptide. Morphological characterization confirmed that both CAQK-modified and unmodified  $\beta$ -LG/DSF nanoparticles maintained a spherical shape with a narrow size distribution. The hydrodynamic diameters of C- $\beta$ -LG/DSF and  $\beta$ -LG/DSF were  $156.54 \pm 4.52$  nm and  $144.91 \pm 2.21$  nm, respectively. *In vivo* studies using a murine traumatic brain injury model showed markedly enhanced DSF accumulation at the lesion site after the administration of C- $\beta$ -LG/DSF compared to the results observed with the unmodified  $\beta$ -LG/DSF at 6, 12, 24, and 48 hours post-injection.<sup>77</sup> These results demonstrate the efficient and lesion-specific delivery capacity of this peptide-functionalized nanoplatform.

Notably, peptides and proteins often possess functional domains that can themselves exert therapeutic effects, potentially acting synergistically with DSF. Lactoferrin (LF), a multifunctional glycoprotein with potent antimicrobial and anti-inflammatory properties, has been incorporated into a DSF-LF nanoparticle system (DSF-LF NPs) that combines the immunosuppressive activities of both components. This formulation effectively inhibited macrophage pyroptosis and the release of inflammatory cytokines in both LPS-induced sepsis and UC models.<sup>35</sup> Compared with other nanocarrier systems, peptide-based nanoparticles for DSF delivery remain underexplored. Nevertheless, their unique biological functions and promising preliminary results warrant further investigation. The literature reports relatively few peptide materials exhibiting harmful or toxic properties, as peptides' toxicity is predominantly determined by their physicochemical characteristics. These critical parameters include the amino acid sequence, net charge, molecular length, amphipathicity, hydrophobicity, and adopted secondary structures.<sup>120</sup> The strategic modulation of these properties may offer a viable approach to mitigate the potential toxicity of therapeutic peptides. Additionally, the elimination of residual toxic solvents during the manufacturing process represents a critical challenge in peptide-based nano-delivery systems, with significant implications for scalable production and clinical translation.

## 4. The spectrum of inflammatory diseases treated by DSF

Beyond its well-characterized molecular mechanisms and advancements in nano-delivery systems, DSF has demonstrated therapeutic potential across a wide range of inflammatory disease models. Its ability to inhibit key inflammatory



pathways, particularly GSDMD-mediated pyroptosis, has positioned DSF as a versatile candidate for the treatment of inflammation-driven conditions. This section provides a detailed overview of DSF's application in various non-oncologic inflammatory diseases, including respiratory, digestive, autoimmune, urinary, infectious, and other systemic disorders.

#### 4.1 DSF for respiratory diseases

SARS-CoV-2, the virus responsible for COVID-19, primarily targets the respiratory system and is associated with various pulmonary complications. During the COVID-19 pandemic, efforts were made to identify effective therapeutic agents, and a retrospective cohort study reported that DSF use was associated with reduced morbidity and mortality in COVID-19 patients.<sup>121</sup> However, the exact underlying mechanisms remain incompletely understood. Owing to its anti-inflammatory, antioxidant, and antiviral properties, DSF and related sulfur-containing compounds have attracted attention for the treatment and prevention of SARS-CoV-2-induced complications.<sup>122</sup> A recent study revealed that SARS-CoV-2 activates GSDMD, leading to the release of NETs, which contribute to COVID-19-associated lung injury and arthritis.<sup>123,124</sup> In addition, DSF exhibited broad-spectrum inhibition of coronavirus major protein by targeting the Cys44 residue of the highly conserved major protein of coronavirus, validating the feasibility of DSF for treating COVID-2019-induced diseases resulting from other mechanisms.<sup>125</sup>

Beyond viral infections, various etiological factors can induce lung injury and provoke inflammatory responses, resulting in symptoms such as dyspnea, cough, hemoptysis, and chest pain. Zhao *et al.* found that DSF significantly alleviated LPS-induced lung inflammation in acute lung injury by targeting GSDMD and reducing the lung wet-to-dry weight ratio, total cell count, macrophages, and neutrophils in bronchoalveolar lavage fluid, as well as decreasing the serum levels of TNF- $\alpha$  and IL-6.<sup>126</sup> In a subsequent study, Zhao *et al.* demonstrated that DSF treatment significantly suppressed NET formation compared to hypoxia/reoxygenation-stimulated neutrophils (Fig. 6A). Simultaneously, it significantly reduced the number of fragmented mitochondria, decreased the mitochondrial membrane permeability, and reduced the production of mitochondrial ROS and adenosine triphosphate while increasing the mitochondrial length in hypoxia/reoxygenation neutrophils by inhibiting GSDMD (Fig. 6B).<sup>127</sup> These findings indicate the therapeutic potential of DSF in lung ischemia-reperfusion injury through the attenuation of NET formation and the preservation of mitochondrial homeostasis. Moreover, a recently developed baicalin-based copper-coordinated nanomedicine co-loaded with DSF was shown to attenuate one-lung ventilation-induced lung injury in preclinical models without inducing toxicity, which suggested that DSF treatment could be considered as a novel and promising therapy for lung injury.<sup>76</sup>

Additionally, a recent bioinformatic analysis of chronic obstructive pulmonary disease patient samples from the GEO database revealed elevated expression of GSDMD in airway epithelial cells. Subsequent *in vivo* investigations demonstrated

that DSF treatment in ozone-induced chronic obstructive pulmonary disease mouse models yielded significant therapeutic benefits, including the improvement of histopathological alterations and the reduction of oxidative stress markers. Mechanistically, DSF was shown to attenuate ozone-induced occludin suppression and partially restore the expression of tight junction proteins ZO-1 and E-cadherin.<sup>20</sup> These findings substantially expanded the potential clinical applications of DSF in inflammatory airway disorders, particularly for chronic obstructive pulmonary disease management.

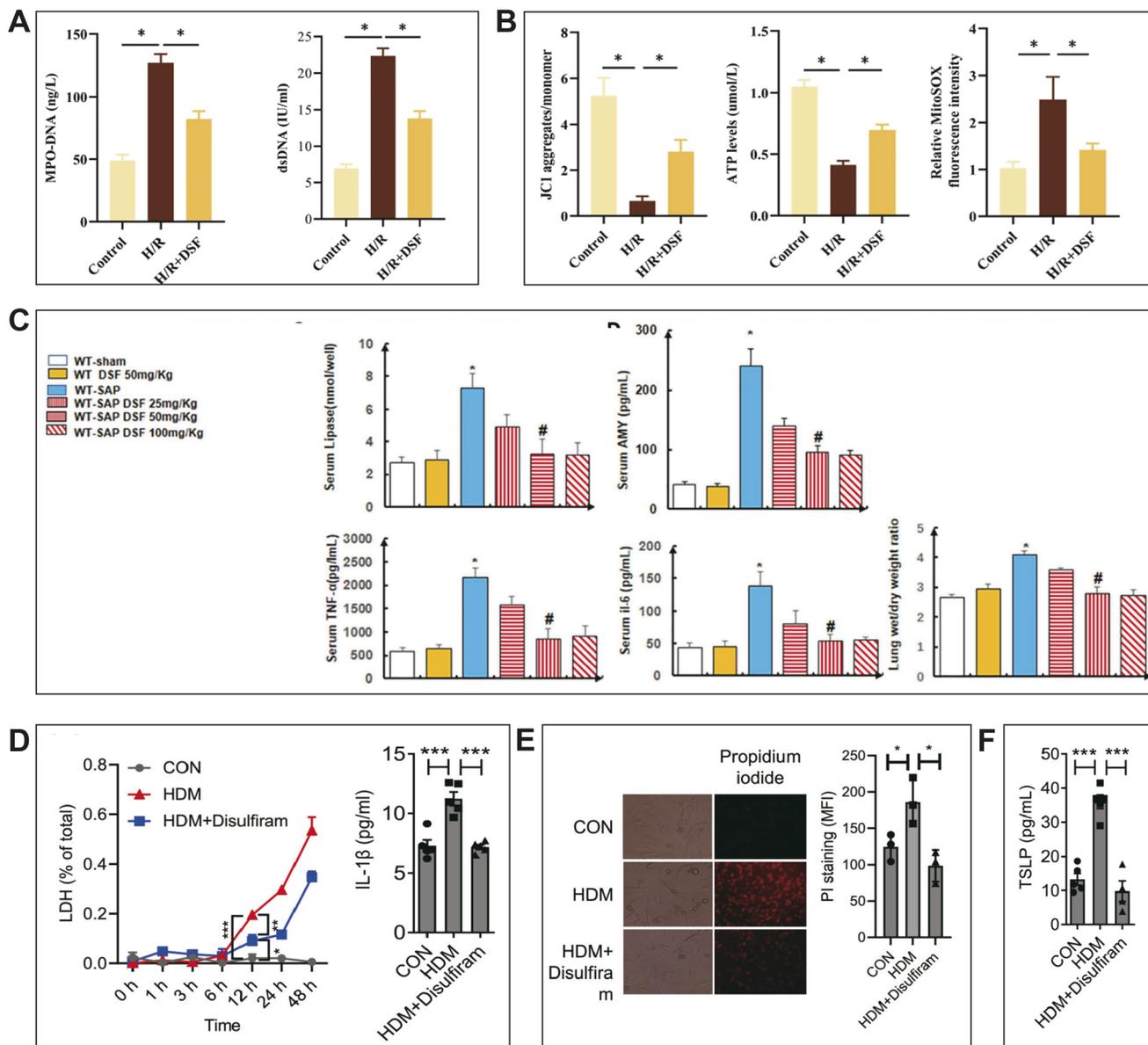
#### 4.2 DSF for digestive diseases

DSF has demonstrated substantial therapeutic potential for use in various digestive tract inflammatory diseases, functioning by targeting pyroptosis and modulating the associated inflammatory pathways. Hepatitis, characterized by hepatocellular degeneration, necrosis, and inflammation, may progress to cirrhosis if left untreated. DSF has been shown to mitigate hepatocyte pyroptosis and suppress hepatic inflammation by downregulating NLRP3, GSDMD, and caspase-1 expression both *in vitro* and *in vivo*, ultimately reducing IL-1 $\beta$  release and improving liver function.<sup>31</sup> Additionally, DSF has been implicated in the regulation of autophagy, bile acid metabolism, and gut microbiota composition, further contributing to its efficacy in ameliorating cirrhosis and non-alcoholic steatohepatitis.<sup>130,131</sup> Intriguingly, a recent investigation revealed that DSF conferred protective effects against acetaminophen-induced acute liver injury through the modulation of gut microbiota composition. Comparative analysis demonstrated that DSF-treated mice exhibited significantly higher Shannon index and Chao index relative to the control group.<sup>132</sup> Notably, DSF administration induced marked alterations in 20 distinct bacterial genera, among which *Akkermansia muciniphila* has been mechanistically demonstrated to exert hepatoprotective effects *via* the regulation of the PI3K/Akt signaling pathway in acetaminophen-induced liver injury.<sup>133</sup> However, the precise mechanisms underlying DSF-mediated modulation of gut microbial abundance remain to be fully elucidated and warrant further investigation.

Acute pancreatitis (AP), which is often accompanied by severe abdominal pain, vomiting, and fever, requires urgent therapeutic intervention due to its potential progression to systemic inflammatory response syndrome. Recent findings have demonstrated that DSF exerts significant protective effects in AP by targeting GSDMD and modulating multiple inflammatory pathways. DSF administration led to reduced serum levels of lipase, amylase, TNF- $\alpha$ , and IL-6, thereby alleviating pancreatic inflammation (Fig. 6C).<sup>128</sup> Furthermore, DSF was shown to downregulate RIPK1 expression in pancreatic acinar cells, interfere with the TXNIP/HIF-1 $\alpha$  axis, and inhibit GSDMD-dependent NET formation, collectively contributing to the attenuation of AP severity in murine models.<sup>23,134,135</sup>

In the context of IBD, such as radiation-induced enteritis and UC, DSF has demonstrated efficacy through the inhibition of GSDMD-mediated pyroptosis. Notably, it has been reported that dual deficiency of GSDMD and GSDME is essential for achieving





**Fig. 6** The therapeutic potential of DSF in respiratory system diseases, digestive system diseases, and autoimmune diseases. (A and B) DSF inhibited GSDMD to suppress NET formation and mitochondrial dysfunction. This figure has been reproduced from ref. 127 with permission from Springer Nature Publications copyright 2024.<sup>127</sup> (C) Inhibition of pyroptosis with DSF alleviated the inflammation of the pancreas and lungs. This figure has been reproduced from ref. 128 with permission from Frontiers Publications copyright 2021.<sup>128</sup> (D) DSF reduced the release of cytokines, such as IL-1 $\beta$  and thymic stromal lymphopoietin (TSLP), by airway epithelial cells under the stimulation of house dust mite. (E) PI staining showed that DSF could reduce cell apoptosis. (F) DSF reduced the release of TSLP. This figure has been reproduced from ref. 129 with permission from John Wiley and Sons Publications copyright 2024.<sup>129</sup>

optimal therapeutic benefit in colitis.<sup>72</sup> Accordingly, DSF has been extensively applied as a GSDMD-specific inhibitor in experimental IBD models.<sup>71,75,136,137</sup> Moreover, the delivery of pH-responsive nanomaterials enables the precise release and concentration control of DSF.<sup>138</sup> In the context of chronic inflammatory diseases, such as IBD and chronic pancreatitis, the implementation of nano-delivery systems featuring sustained-release kinetics or environmental responsiveness may effectively mitigate the potential off-target effects and toxicity associated with DSF therapy. Such advanced delivery

platforms could potentially enhance therapeutic efficacy through the spatiotemporal control of drug release while simultaneously reducing systemic exposure in non-target tissues.

#### 4.3 DSF for autoimmune diseases

The prevalence of autoimmune diseases has steadily increased, driving demand for effective immunomodulatory therapies. DSF has shown promising efficacy in mitigating various autoimmune conditions and transplant-associated immune



rejection. *In vitro* studies demonstrated that DSF suppressed LDH and IL-1 $\beta$  release in airway epithelial cells stimulated by house dust mite extract (Fig. 6D), reduced apoptosis (Fig. 6E), and inhibited the secretion of TSLP (Fig. 6F).<sup>129</sup> In systemic lupus erythematosus mouse models, DSF inhibited GSDMD pore formation, leading to decreased immune complex accumulation, reduced organ damage, and improved clinical scores.<sup>139,140</sup> Besides, DSF could also be used for the treatment of autoimmune prostatitis and systemic sclerosis due to its inhibitory effect on GSDMD, reducing the scorched death of its tissue cells.<sup>17,141</sup> The therapeutic effect of DSF in autoimmune diseases may also involve the inhibition of the STING/MITA signaling cascade, further suppressing inflammation and autoimmunity.<sup>22</sup> DSF has also proven effective in treating macrophage activation syndrome, a severe and potentially fatal complication of autoimmune diseases, by targeting GSDMD in macrophages and reducing IL-18 secretion.<sup>142</sup>

As critical mediators of inflammatory injury, macrophages contribute to both acute cellular allograft rejection and chronic injury, with their infiltration linked to poorer graft function and prognosis.<sup>143</sup> In 2021, Sun *et al.* found that DSF could target macrophage pyroptosis and thus inhibit acute graft-versus-host disease.<sup>144</sup> Furthermore, it was shown that DSF could induce M2 macrophage polarization by inhibiting NLRP3 inflammasome-mediated cellular pyroptosis, which could improve fat graft retention.<sup>145</sup> Besides, DSF could reduce macrophage aggregation and inhibit the expression of pro-inflammatory factors in lung transplantation, attenuating acute rejection after lung transplantation in rats.<sup>146</sup>

#### 4.4 DSF for urinary diseases

Kidneys can suffer from various inflammatory diseases, and irreversible renal failure can easily occur if the diseases are not treated properly. DSF has demonstrated robust therapeutic efficacy in various renal inflammatory disorders. Specifically, DSF inhibits monocyte and macrophage recruitment by targeting the FROUNT signaling pathway, thereby reducing inflammatory infiltration and tissue injury in models of glomerulonephritis.<sup>24,70</sup>

Studies have shown that DSF exhibits good therapeutic efficacy in the treatment of glomerulonephritis.<sup>70,147,148</sup> *In vitro* lactate dehydrogenase release and immunofluorescence assays and *in vivo* studies on the passive Heymann nephritis rat model have confirmed that DSF could inhibit the activation and membrane translocation of the pyroptosis executive protein, GSDMD, and inhibit the activation of the NLRP3-ASC-Caspase-1/IL-18/GSDMD signaling pathway. Furthermore, it has been verified that DSF significantly reduces the abnormal expression of podocyte injury markers (*e.g.*, Desmin and WT-1) and improves proteinuria and glomerular podocyte fusion.<sup>149</sup> DSF also shows therapeutic efficacy in focal segmental glomerulosclerosis. Through the doxorubicin-induced podocyte injury mouse model pretreated with DSF, the decreased expression levels of Tmem30a, nephrin, and WT1 in ADR-induced mouse podocytes were reversed by DSF (Fig. 7A). Meanwhile, the expression levels of NLRP3, N-GSDMD/GSDMD, cleaved

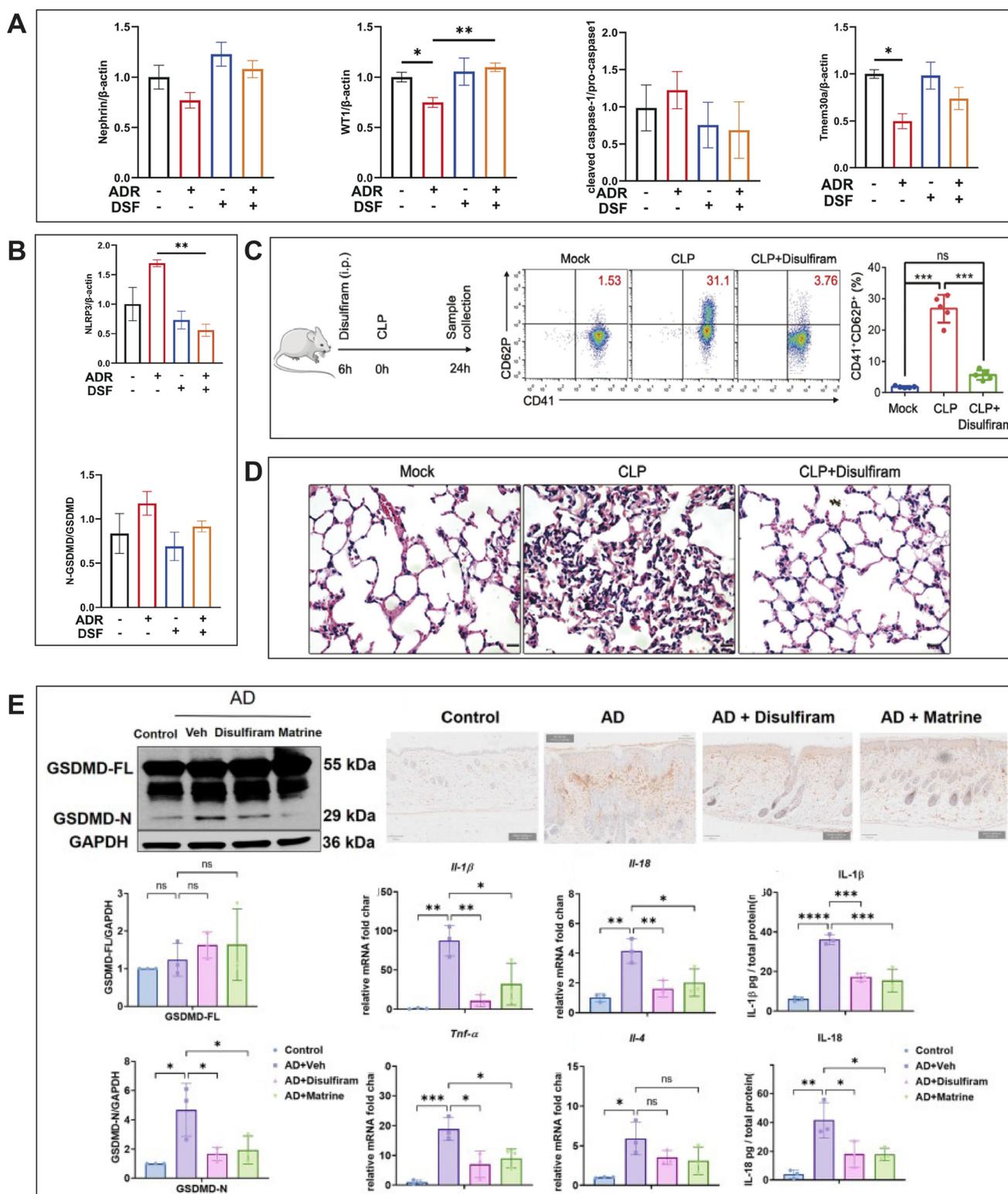
caspase-1/pro-caspase-1, and IL-1 $\beta$ /pro-IL-1 $\beta$  were significantly decreased (Fig. 7B).<sup>147</sup> These results indicated that DSF alleviated ADR-induced podocyte pyroptosis. In another study, Huang *et al.* discovered that DSF had a protective effect on mice with membranous nephropathy induced by LPS-induced acute kidney injury. After DSF administration, the LPS-induced pathological damage of the renal tissue and renal dysfunction were significantly alleviated. In particular, ROS and malondialdehyde were significantly reduced, while the activity of superoxide dismutase markedly increased. Besides, the expression levels of NLRP3, caspase-1 p20, and IL-1 $\beta$  were reduced.<sup>148</sup>

#### 4.5 DSF for infectious diseases

Severe infections may progress to sepsis, characterized by a dysregulated host immune response and potentially life-threatening organ dysfunction. Recent studies have highlighted the role of GSDMD-mediated pyroptosis, alongside the activation of inflammasomes and STING1, in exacerbating coagulation and systemic inflammation during sepsis progression.<sup>152</sup> Comprising molecules such as high-mobility group box 1, extracellular cold-inducible RNA-binding protein (eCIRP), heat shock proteins, S100 proteins, histones, and mitochondrial DNA, damage-associated molecular patterns have been ascertained as danger signals (also known as alarmins) that instigate inflammatory responses in sepsis.<sup>153–155</sup> Tan *et al.* developed both LPS-induced endotoxemia and cecal ligation and puncture (CLP)-induced sepsis mouse models, and demonstrated that DSF treatment, either as pretreatment or co-administration, significantly reduced the serum levels of eCIRP, IL-6, and TNF- $\alpha$ , effectively attenuating the systemic inflammatory response. Moreover, the use of GSDMD-knockout mice confirmed that these protective effects of DSF were mediated by the inhibition of GSDMD-driven pyroptosis.<sup>156</sup> *In vitro* experiments further validated that LPS activates the caspase-11/GSDMD pathway, resulting in the formation of N-GSDMD pores on the cell membrane and promoting the release of inflammatory cytokines, including eCIRP. DSF inhibited N-GSDMD oligomerization and thus reduced the release of pro-inflammatory cytokines from macrophages and neutrophils, highlighting its potential as a therapeutic agent for sepsis.

In DSF-treated CLP mice, platelet activation, measured by the percentage of CD41<sup>+</sup>CD62P<sup>+</sup> platelets, was significantly reduced compared to the case in the CLP-only group (Fig. 7C). Histopathological analysis showed that DSF administration alleviated lung tissue edema and vascular congestion in septic mice (Fig. 7D).<sup>150,157,158</sup> Notably, mitochondria carrying N-GSDMD can be transferred *via* microvesicles, activating the mitochondrial ROS/GSDMD axis in neutrophils, which contributes to NET formation, tissue damage, and coagulation disorders.<sup>159–161</sup> DSF has been shown to suppress N-GSDMD oligomerization, thereby inhibiting NET formation and reducing the release of mitochondrial DNA and ROS. The restoration of the mitochondrial membrane potential in DSF-treated groups indicated reduced levels of apoptosis and necroptosis. *In vivo* studies confirmed that DSF pretreatment





**Fig. 7** The therapeutic potential of DSF in urinary system diseases, infectious diseases, and other inflammatory diseases. (A) DSF alleviated podocyte injury by inhibiting ADR-induced pyroptosis. (B) The expression levels of NLRP3, N-GSDMD/GSDMD, caspase-1/pro-caspase-1, and IL-1 $\beta$ /pro-IL-1 $\beta$  were significantly decreased. This figure has been reproduced from ref. 147 with permission from Elsevier Publications copyright 2024.<sup>147</sup> (C) The percentage of blood CD41<sup>+</sup>CD62P<sup>+</sup> platelets was detected using flow cytometry. (D) DSF-treated mice had reduced lung tissue edema and vascular congestion. This figure has been reproduced from ref. 150 with permission from *International Journal of Biological Sciences* Publications copyright 2024.<sup>150</sup> (E) DSF or matrine inhibits the formation of N-GSDMD and the release of IL-18 and IL-1 $\beta$  in the skin tissue of AD mice. This figure has been reproduced from ref. 151 with permission from Elsevier Publications copyright 2023.<sup>151</sup>



reduced platelet activation, NET formation, and organ damage in both CLP- and LPS-induced acute lung injury models. These protective effects were also observed in microvesicles isolated from bronchoalveolar lavage fluid, further validating DSF's therapeutic potential in infectious inflammation.<sup>150</sup>

#### 4.6 DSF for other inflammatory diseases

In addition to respiratory, digestive, autoimmune, urinary, and infectious conditions, DSF has shown therapeutic efficacy in other inflammation-associated diseases through the inhibition of GSDMD activation and NET formation. Notably, DSF impairs the activation of peptidylarginine deiminase 4, which plays a key role in the formation of NETs by mediating histone citrullination. Since NETosis is closely linked to the activation of the NLRP3 inflammasome and GSDMD, DSF effectively suppresses this cascade. In patients with diabetic foot ulcers, DSF treatment significantly decreased the expression of NET markers, such as citrullinated histone H3 and cell-free DNA, as well as key proteins in the NLRP3 signaling pathway, indicating strong anti-inflammatory activity.<sup>162</sup> A high-throughput screening study involving 41 184 small-molecule compounds identified DSF as a potent inhibitor of NLRP3 inflammasome activation. DSF dose-dependently reduced ASC speck formation and IL-1 $\beta$  secretion. In a human forearm patch test model using sodium dodecyl sulfate to induce irritant contact dermatitis, pretreatment with 5% DSF cream significantly alleviated erythema and blood perfusion, as assessed by laser speckle imaging. Furthermore, the IL-18 levels in the stratum corneum were markedly reduced in the DSF group, and the therapeutic effects of DSF is comparable to those of topical corticosteroids and superior to those of cream-based vehicles ( $p < 0.001$ ).<sup>163</sup> Furthermore, a study focusing on the Gene Expression Omnibus database analysis showed that the expression of GSDMD was upregulated in the skin of patients with atopic dermatitis. *In vivo* experiments demonstrated that DSF significantly reduced epidermal hyperplasia, dermal thickening, and mast cell infiltration in a murine AD model. Mechanistically, DSF inhibited GSDMD cleavage and downregulated pyroptosis-associated cytokines, such as IL-1 $\beta$ , IL-18, and TNF- $\alpha$ , thereby mitigating cutaneous inflammation (Fig. 7E).<sup>151</sup> Additionally, DSF exhibits dual antimicrobial and anti-inflammatory properties. It has been reported that DSF can suppress IL-1 $\beta$  release both *in vitro* and *in vivo*, suggesting that DSF could serve as a valuable antifungal and antibacterial agent or as an adjunct to existing antimicrobial therapies.<sup>164</sup> Evidence indicates that DSF can be used to combat a broad range of pathogens, including bacteria and fungi, providing an expanded therapeutic profile for inflammation associated with infectious etiologies.<sup>165,166</sup>

## 5. Summary and prospect

This review highlights recent advances in the research on the anti-inflammatory effects of DSF and elucidates its underlying mechanisms. Its central mode of action involves the covalent modification of cysteine residues crucial for palmitoylation and depalmitoylation on GSDMD, thereby disrupting its proper

membrane localization and oligomerization. Given the pivotal role of GSDMD in pyroptosis and inflammatory responses, the inhibition of this pathway by DSF significantly attenuates inflammation.<sup>48</sup> In parallel, DSF modulates several key signaling pathways, including FROUNT, STING, and RIPK1, progressively constructing a broader mechanistic framework for its anti-inflammatory activity.

DSF has emerged as a broad-spectrum therapeutic agent with demonstrated efficacy across systemic inflammatory diseases, cancer, metabolic disorders, and infectious diseases.<sup>167</sup> Given the broad spectrum of inflammatory diseases implicated, current evidence demonstrates that conditions, such as IBD, sepsis and lung injury, are mechanistically linked to inflammasome activation and subsequent pyroptosis.<sup>72,126,156</sup> This pathophysiological understanding has incentivized considerable research efforts on exploring DSF as a therapeutic intervention for these disorders.<sup>72,126,156</sup> Furthermore, multiple nano-delivery platforms engineered for DSF administration have demonstrated promising therapeutic efficacy across these disease models. These collective findings highlight the substantial clinical potential of DSF-based therapies in the management of inflammasome-mediated inflammatory conditions, particularly IBD and sepsis. However, its poor aqueous solubility and low oral bioavailability, due to extensive first-pass metabolism and physiological barriers, significantly hinder its clinical translation. Consequently, optimizing DSF delivery remains a critical priority. The lessons learned from DSF-based nano-delivery systems developed for oncologic applications may serve as valuable references for inflammatory disease contexts.<sup>36,168</sup>

Nano-delivery systems offer a promising solution to overcome DSF's pharmacokinetic limitations. The four major nanotechnologies discussed—lipid-based, polymer-based, metal-based, and peptide-based systems—each possess unique advantages and limitations. Collectively, they enhance DSF's solubility, targeting efficiency, and therapeutic index while minimizing systemic toxicity. Although the research on nano-delivery systems in inflammation is less extensive than in oncology, the accumulating evidence underscores the potential of nanotechnology to extend DSF's clinical utility for inflammatory diseases.

However, nanomedicines still face some problems in applications. Currently, the most common route of nanomedicine delivery is the parenteral route, which cause adverse reactions in long-term administration of nanomedicines. Also, patient compliance and the convenience of drug administration may make this route inferior to the oral route. Furthermore, nanomedicine application is limited in clinical drug trials and industrial production links. Although the preclinical research related to nano-delivery systems is booming, the clinical translation rate is low. Most of the preclinical-clinical translations involve basic nanomedicines, while nanomedicines with specific functions, good targeting characteristics, and environmental sensitivity have not yet been successfully applied.<sup>169</sup> To the best of our knowledge, clinical trials of nano-formulated DSF therapies for inflammatory diseases remain to be initiated. Additionally, most efficacy evaluations are based on



animal models, such as murine systems, which may not fully reflect human pathophysiology. The applicability and safety of nanomaterials with comparable physicochemical properties in humans remain uncertain. The intrinsic features of nanomaterials, such as small size, surface charge, and specialized surface chemistry, pose the risk of inducing oxidative stress or cytotoxicity, especially when manufacturing processes are suboptimal. Thus, rigorous quality control and standardization of synthesis methods are essential to ensure clinical safety.

In conclusion, DSF exhibits potent anti-inflammatory properties and, when integrated with nano-delivery strategies, holds significant promise for the treatment of inflammatory diseases. However, to bridge the gap between laboratory research and clinical practice, further efforts are required to optimize nano-carrier design, enhance formulation scalability, and establish robust regulatory frameworks. Advancing these aspects will be key to unlocking the full therapeutic potential of DSF in future anti-inflammatory applications.

## Author contributions

Qiwen Jiang: conceptualization, investigation, formal analysis, writing – original draft preparation and editing. Mengni Jiang: conceptualization, formal analysis, writing – original draft preparation and editing. Yanwei Lv: conceptualization, investigation, writing – reviewing, and editing. Xinyuan Zhang: investigation, writing – reviewing. Shige Wang: conceptualization, resources, supervision, writing – reviewing and editing. Jiulong Zhao: conceptualization, funding acquisition, writing – reviewing and editing.

## Conflicts of interest

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

## Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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