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Unlocking the therapeutic potential of disulfiram in sepsis: Mechanisms and future directions

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Highlights

- Disulfiram modulates sepsis through multiple mechanisms, potentially reducing excessive inflammation and improving patient outcomes.
- The immunomodulatory effects of disulfiram are complex, influencing inflammatory mediators and immune cell function, thereby restoring immune homeostasis.
- Translating preclinical findings into clinical practice is challenging. Rigorous clinical trials and a more comprehensive understanding of the pharmacokinetics and adverse effects of disulfiram are essential.

Abstract

The leading cause of mortality within ICUs is sepsis; however, treatment options typically fail to appropriately regulate the severely dysregulated host response to this syndrome. Recently, there has been an unexpected observation that the common alcoholic aversion treatment disulfiram has exhibited additional immune-regulatory capabilities outside of its original purpose. Disulfiram has shown some effectiveness in preclinical settings at reducing pyroptosis as well as NLRP3 inflammasome activation. Currently there is no sound systematic evidence that supports the repositioning of disulfiram for use in sepsis; more importantly, significant deficiencies in the current research were also observed and deficiencies with respect to existing investigations indicated that future studies should adopt more precise clinical approaches in order to validate the therapeutic effect of disulfiram against sepsis. Integrating the existing evidence and bringing forward feasible directions for future research also constitutes another goal of this review, which helps us better highlight the value of disulfiram as a treatment in sepsis management and further streamline research and clinical translation efforts for the development of this topic in the near future.

Keywords: Sepsis, disulfiram, inflammation, cell death, signaling pathways

Introduction

The compound disulfiram was found at the end of the 19[th] century; it was originally created for industrial needs and mainly used as a vulcanization agent for rubbers. However, later on, it became known in the medical field due to its therapeutic effects [1]. The product's journey to being approved for medical treatment was rather accidental. It turned out to have some adverse reactions in the human body towards alcohol, therefore leading the FDA in the US to approve disulfiram as a solution to the problem. Alcohol dependence was moved under Disorders of Impulse Control in 1951. This transformation signified an important advancement—thanks to the unique mechanism of its action, disulfiram finally shook off the industrial chemical label that it had carried since the early days and became an actual therapeutic

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agent used in alcohol dependence treatment. Disulfiram increased bodily sensitivity to alcohol and thereby decreased drinking behaviors which proved helpful in treating individuals with alcohol dependence clinically [2].

Beyond addiction therapy, numerous diseases have been identified in which disulfiram exerts pharmacodynamic effects. These include oncological, cardiovascular, and inflammatory conditions, which have shown benefits [3, 4]. The ability of disulfiram to regulate different molecular pathways, particularly the anti-inflammatory pathway, provides a rationale for repurposing the drug for other applications [5].

There has been an increased interest among researchers regarding disulfiram as well as the fact that disulfiram might be a good candidate to participate in the drug repurposing efforts in pharmaceutical research and development. However, further studies will be conducted to further elucidate the role of disulfiram in terms of perioperative situation.

Sepsis presents an ongoing medical problem at the global level due to the underlying pathogenesis, complex mechanisms, and high mortality rate, despite significant advances in support strategies and antibiotic treatments [6]. Sepsis still represents one of the leading causes of mortality and long-term morbidity [7]. There is an immediate need to find an alternative, more effective means of treating sepsis to rescue patients from developing organ dysfunction, i. e., prolonged hypoperfusion and endotoxic shock states. Hence, repurposing some approved drugs or identifying totally new molecules has become a key part of sepsis pharmacotherapy efforts. Disulfiram can reduce inflammatory responses through multiple complex mechanisms, which has made it a promising candidate for sepsis treatment. Preclinical studies in animal models have shown that it not only lessens systemic inflammation but also alleviates organ damage and improves survival rates. Disulfiram can cut down on inflammatory reactions using many different methods, so there is some thought it might be a good choice for fighting sepsis. Results from studies using animals indicate that disulfiram can dampen down systemic inflammation, lessen organ damage, and increase survival rates compared to untreated subjects [8]. Still, most clinical trials with patients on disulfiram have focused on its safety, its effects on drug-resistant bacteria or its efficacy in treating cancer when it is given as part of another drug or intravenously [9]. These same investigators have reviewed whether disulfiram is able to modulate inflammatory cascades and other signaling pathways, as well as its current role is in managing sepsis. In addition, the review covers open questions about how this field is progressing and several points that warrant additional research.

Pathophysiology of sepsis

Sepsis is a critical medical condition caused by the body's hyperactive immune response to infection. Sepsis causes the whole-body inflammation and organ dysfunction, and at the very worst case it even turns into shock and leads to death [5, 10]. Clinically, due to the diversity of the organ's involvement in sepsis, its manifestations include both minor physiological changes and severe multiorgan failure [11]. The connections of the immune system, inflammatory mediators, coagulation pathways, and cell dysfunction to sepsis present many challenges in diagnosing and treating this condition, with a poorer prognosis resulting from this functional disturbance [12]. The resultant organ dysfunction or even failure is a critical clinical outcome that requires prompt and aggressive interventions to prevent further deterioration of complications and patient mortality.

Sepsis is caused by a chain of inflammatory mediators and pathways that cause inflammation in the whole body and lead to dysfunction or failure of organs (**Figure 1**). Usually, sepsis occurs when the microbes are recognized based on their pathogen-associated molecular patterns (PAMPs) or endogenous damage-associated molecular patterns (DAMPs) [13, 14]. In addition, molecules of Toll-like receptors and C-type lectin are activated once PAMPs/DAMPs are recognized [15, 16]. Other pathways including nuclear factor kappa-B (NF-κB) pathway, complement system and inflammasome are subsequently activated, leading to an amplification of the damaging inflammatory cascade [16, 17].

The immune system is an important part of the development of sepsis, with its activation simultaneously acting as an aggressive and harmful mechanism. When there is an excess of inflammatory mediators, it causes hypercoagulation in the blood [18]. Mediators such as tumor necrosis factor-α, interleukin (IL)-1, and IL-6 are produced when a pathogen or toxin enters the body [19]. As the infection progresses, the immune system releases a variety of cytokines (inflammatory messengers), triggering what is known as a "cytokine storm," a phenomenon in which excessive cytokines flood the bloodstream [20]. As the disease develops, inflammation emerges as one of the immune system

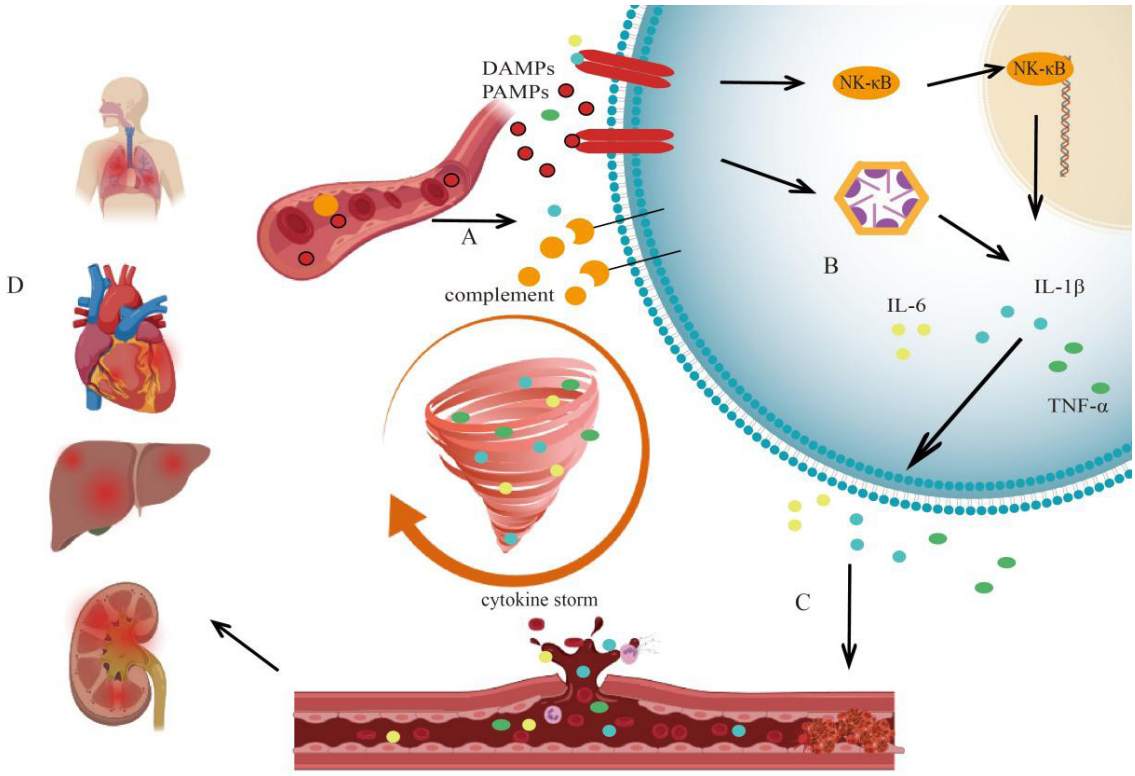

Figure 1. The pathophysiology of sepsis. Sepsis is triggered by a complex cascade of inflammatory mediators and associated pathways. (A) Sepsis is typically initiated by the recognition of microbial PAMPs or endogenous DAMPs, as well as complements, which activate downstream receptors, such as Toll-like receptors and C-type lectins, on the surface of cell membranes. The complement system is activated and recruits and activates immune cells; (B) The downstream inflammatory corpuscle pathway and NF-κB were activated, facilitating the release of inflammatory cytokines; (C) A substantial quantity of inflammatory cytokines is released into the bloodstream, resulting in a "cytokine storm". Tissue factor-mediated thrombin generation occurs concurrently with an imbalance or dysfunction of normal physiological anticoagulant mechanisms. Simultaneously, vascular endothelial cells are damaged, ultimately leading to systemic coagulation dysfunction, which can progress to disseminated intravascular coagulation in severe cases. Furthermore, sepsis can induce immunosuppression, diminish the immune system's resistance to infection, and increase susceptibility to secondary infection; (D) Organ oxygenation is impaired under the influence of multiple factors, such as hypotension and microthrombus formation. Endothelial cell injury further aggravates edema. Cell death intensifies, resulting in damage to multiple organ functions. PAMPs, pathogen-associated molecular patterns; DAMPs, damage-associated molecular patterns; NF-κB, nuclear factor kappa-B; TNF-α, tumor necrosis factor-α; IL, interleukin.

responses and stimulates the production of the proteins involved in the production of clots in the body. Cytokine storms cause systemic inflammation while destroying important tissues, leading to sepsis (progression and development) [21-23]. Additionally, sepsis can lead to an immunodepression state, which suppresses the body's ability to fight infections. These opposite states of immunosuppression, resulting from hyperactivation of immune cells leading to exhaustion and apoptosis, along with an inadequate immune system, increase the risk of secondary infections and extend the disease period [24]. A compromised immune system increases susceptibility to secondary infections and can prolong the course of sepsis [25]. One of the distinctive signs of sepsis is deficient coagulation and injured vascular endothelial cells [18]. Sepsis-associated mediators increase the tissue factor expression, triggering the coagulation cascade. At the same time, the damage to the endothelial cell initiates the activation of platelets and coagulation, increasing the formation of micro-thrombus and resulting in disseminated intravascular coagulation, thus ameliorating coagulopathy is still an important challenge in sepsis research and treatment [26, 27].

Severe and complex changes take place in sepsis across multiple aspects including etiology, symptomatology, diagnosis, treatment, and prognosis, as well as through complicated and continuous dynamic mechanisms. In the initial period of sepsis, the immune system is activated instantly and powerfully with an intense inflammatory cascade and the corresponding initial immune response, involving the mobili-

zation of multiple types of immune cells such as neutrophils, macrophages and lymphocytes. Along with the release of large amounts of inflammatory mediators such as chemokines and prostaglandins, an acute inflammatory response occurs in sepsis, which is a defense reaction by which the body combats invading pathogens and eliminates them to maintain homeostasis. With the development of sepsis, however, the immune microenvironment gradually changes: the immune system rapidly switches from hyperactivation to suppression. Immune cells are now characterized by decreased immune function, diminished cytokine production, and increased regulatory T cell activity, among other alterations. Consequently, sepsis develops into a greater immunologic dysfunction, resulting in secondary infections and the increased severity and intricacy of the diseases [28, 29].

Therefore, a clear understanding of these dynamic, time-dependent changes in inflammatory and immune responses is critical for developing effective strategies to manage sepsis. With this knowledge, clinicians can deliver timely and targeted interventions. For example, immunomodulatory agents can be used strategically to boost immune function during the immunosuppressive phase or to reduce excessive inflammation in the early hyperinflammatory stage. By building on these insights to optimize treatment approaches, clinicians can improve patient outcomes and reduce the morbidity and mortality associated with sepsis [25].

Historical perspective of disulfiram

The chemical structure and properties of disulfiram

Disulfiram, chemically termed tetraethylthiuram disulfide and sold under the trade name Antabuse, is an organic compound with the molecular formula $C_{10}H_{20}N_2S_4$ [30]. Its core structure contains a disulfide bond that breaks down to form biologically active sulfhydryl groups [31]. At specific sites, disulfiram binds to the sulfhydryl groups of acetaldehyde dehydrogenase and oxidizes them, forming intramolecular S–S bonds. This interaction disrupts the normal function of acetaldehyde dehydrogenase, impairing its ability to convert acetaldehyde to acetic acid during ethanol metabolism in the human body [32]. As a result, acetaldehyde accumulates and leads to a variety of harmful bodily reactions, such as flushing of the face, headaches, and tachycardia. These adverse physical reactions act as impediments and discourage individuals from drinking alcohol. This antagonistic response toward alcohol can be utilized as a therapeutic strategy to encourage sobriety by fostering conditioned avoidance of alcohol among people dependent on alcohol [32, 33].

The metabolic process of disulfiram in the body

The metabolic processing of disulfiram is characterized by its chelating ability, which enables it to form stable complexes with metal cations, including iron, copper, and zinc [34]. The cleavage of its disulfide bond, the primary step in its biotransformation, is central to disulfiram metabolism [31]. Upon entering the body, disulfiram undergoes reductive cleavage of its disulfide linkages, yielding thiol derivatives capable of forming mixed disulfides with endogenous protein thiols (**Figure 2**) [35]. The main metabolite, diethyldithiocarbamic (DDC) acid, is further metabolized via multiple pathways. The first pathway involves glucuronidation, in which DDC is conjugated with glucuronic acid, enhancing its hydrophilicity and promoting renal excretion [36]. The second catabolic pathway includes non-enzymatic degradation, where DDC undergoes spontaneous decomposition in the absence of enzymatic catalysis [37]. Additionally, DDC may undergo methylation and oxidation, reactions mediated by specific enzymes, further modifying the metabolite to ensure its complete catabolism and eventual elimination from the body [38-40].

Applications of disulfiram in medicine

Historically used in the treatment of alcohol addiction, disulfiram has garnered increasing attention from the scientific community for its potential applications in diverse medical conditions. This shift has led to extensive research exploring the pharmacological benefits of disulfiram in various nonalcoholic pathological states [41, 42]. A substantial body of literature highlights the role of disulfiram as an aldehyde dehydrogenase inhibitor in oncological therapeutics [43, 44]. Moreover, extensive research has elucidated the promising implications of disulfiram in a wide spectrum of pathological conditions, including its ability to reduce Clostridium-mediated 7α-dehydroxylation activity in the gut microbiota, inhibit the synthesis of secondary bile acids, and potentially improve nonalcoholic steatohepatitis [45]. Disulfiram has also been shown to enhance ADAM10 activity in peripheral blood cells, alleviate A-β plaque formation, and exhibit therapeutic potential in Alzheimer's disease mouse models [46]. Furthermore, disulfiram may be useful in

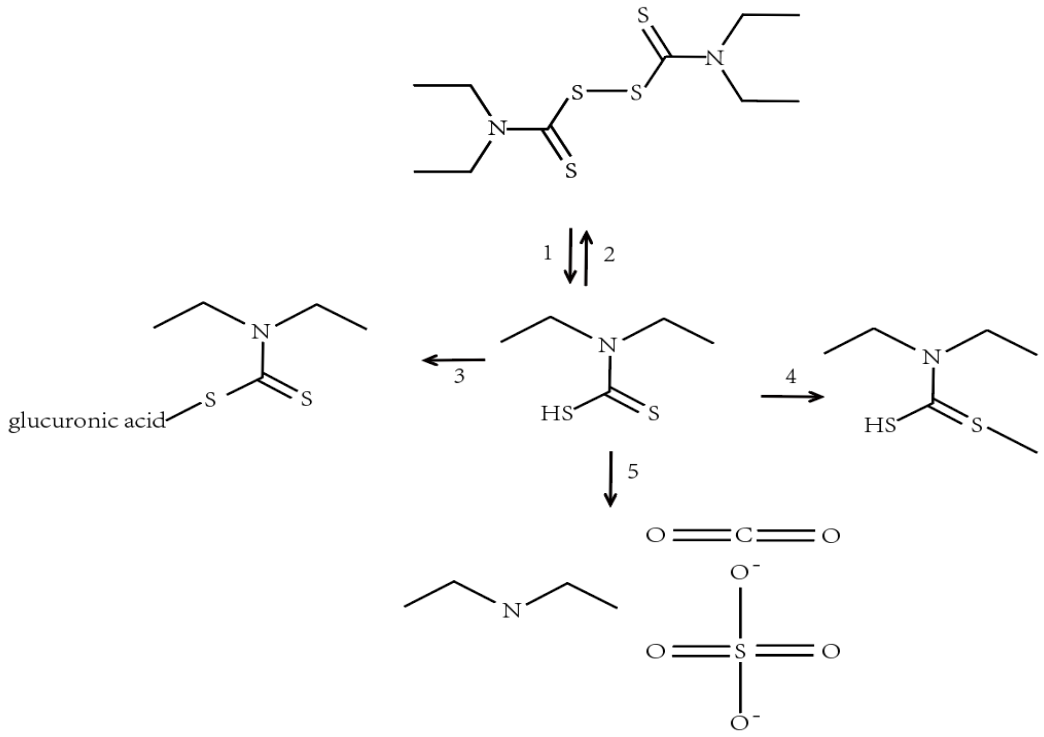

Figure 2. Metabolic processes of disulfiram. (1) Disulfiram undergoes cleavage to produce DDC; (2) DDC is re-oxidized to regenerate disulfiram through a reversible oxidative process; (3) DDC undergoes a conjugation reaction with glucuronic acid via the glucuronidation pathway, thereby enhancing its water solubility for subsequent excretion; (4) DDC undergoes methylation, resulting in the formation of a methyl ester derivative of DDC; (5) Disulfiram is degraded into diethylamine, carbon dioxide, and sulfate via a non-enzymatic pathway. DDC, diethyldithiocarbamate.

the treatment of obesity; however, the exact mechanism behind these beneficial effects remains obscure [47]. Regarding antibacterial activities, it is speculated that disulfiram can impede the growth of Pseudomonas aeruginosa via inhibiting PaBADH enzyme activity. Thus, it can suppress bacterial growth [48]. Some other studies also concluded that disulfiram might be efficacious for the treatment of Lyme disease, although the exact mechanism remains to be explored [49]. A recent report has shown that disulfiram exerts anti-sepsis effects by inhibiting macrophage pyroptosis [50]. Therefore, more and more research suggests that disulfiram is a potential therapeutic drug with pleiotropic benefits in a wide range of diseases [51]. It was suggested that its diverse impacts could result from via the modification of thiol (-SH)-containing enzymes and cofactors via different routes such as mixed disulfide formation, metal ion chelation, and non-enzymatic reactions [38]. Preclinical and early clinical results appear encouraging, but more studies are needed to validate the efficacy and safety. New uses of disulfiram present opportunities for treating a broader range of diseases. However, future studies need robust methods to achieve solid and dependable evidence; the potential adverse effects of disulfiram and the possible interaction between disulfiram and other drugs should also be thoroughly investigated. When a new clinical application of disulfiram is found, one has to evaluate whether it would benefit patients through the proper balancing of risks and benefits [51].

The role of disulfiram in the pathophysiology of sepsis

The role of disulfiram in the immune response

The effects of disulfiram on the inflammatory response

New evidence in the latter half of the twentieth century suggested that disulfiram may regulate oxidative stress and set the stage for exploring the function of disulfiram in inflammatory reactions [52-54]. Other studies have also demonstrated that disulfiram can effectively inhibit inflammatory responses [52, 55]. Lian et al. reported that local administration of disulfiram reduced psoriasis-like dermatitis in murine models [56]. Similarly, in a mouse model of Parkinson's disease, disulfiram significantly inhibited neuroinflammation and associated dopaminergic neuron death, resulting in motor function restoration [57]. In the digestive sys-

tem, disulfiram inhibits colonic macrophage activation, thereby alleviating ulcerative colitis [58]. Disulfiram also exerts immunomodulatory effects in systemic lupus erythematosus by reducing proteinuria, serum anti-dsDNA levels, and renal immune complexes, and it has been found to ameliorate crescentic glomerulonephritis [59, 60]. In the respiratory system, disulfiram has been found to attenuate lung injury in a murine model of cytomegalovirus pneumonia, leading to improved survival rates [61]. Furthermore, disulfiram mitigates vascular smooth muscle inflammation induced by angiotensin II and suppresses inflammatory responses in chondrocytes [62, 63]. These findings indicate that disulfiram may play a role in managing various inflammatory conditions. Nevertheless, more work needs to be done to clarify the underlying mechanisms and to develop it as a targeted therapy for inflammatory diseases.

The effects of disulfiram on immune cell function

Several studies suggest that disulfiram's impact on the immune system is likely mediated by the regulation of multiple immune cell functions. For example, research has shown that it can inhibit monocyte-to-macrophage migration, block chemotaxis, and suppress macrophage activation, which may contribute to the remission of glomerulonephritis [60]. It might also be effective in suppressing the development of macrophage pseudopods, which might hinder cell migration and invasion [64]. In fungal keratitis, disulfiram reduces the host immune response by decreasing the recruitment of macrophages and neutrophils [65].

Moreover, it regulates neutrophil extracellular traps (NETs), which are critical for neutrophil function. Studies have demonstrated that disulfiram can reduce multiorgan dysfunction and lower sepsis mortality by inhibiting NET release [8, 66]. In addition, it activates Ca^{2+}-ATPase of the sarcoplasmic reticulum, thereby suppressing IgE-induced eosinophil activation [67]. Furthermore, disulfiram exerts antitumor effects by acting on immune cells [68, 69]. For example, the disulfiram-copper complex can promote dendritic cell maturation, induce T cell cytotoxicity and improve antitumor immune responses [68, 70]. These findings indicate that disulfiram might be beneficial for various immune conditions, including inflammatory disorders and cancer.

Inflammatory signaling pathways involving disulfiram

Sepsis is triggered when microbe-derived PAMPs or endogenous DAMPs are detected by pattern recognition receptors [71]. This identification is critical for triggering subsequent signaling pathways [72]. Disulfiram, by virtue of its biochemical mechanisms, interacts with several signaling pathways (**Figure 3**). Notably, it inhibits the inflammatory response mediated by the cGAS-STING axis via RNF115. Additionally, disulfiram downregulates the complement system, a series of plasma proteins whose aberrant activation during sepsis can exacerbate tissue damage [73, 74]. At a further downstream level, disulfiram inhibits reactive oxygen species and the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, potentially mitigating pyroptosis, necroptosis, and mitochondrial dysfunction associated with the pathogenesis of sepsis [75, 76]. Disulfiram's interaction with autophagy, a process responsible for cellular degradation and recycling, as well as its effects on metabolic reprogramming and the coagulation cascade, suggests its potential for alleviating the cellular and systemic damage characteristic of sepsis [72]. Given the intricate network of signaling pathways involved in sepsis and their contribution to cellular and organ dysfunction, the regulatory role of disulfiram presents a promising avenue for therapeutic intervention.

The effects of disulfiram on the NF-κB signaling pathway

The transcription factor NF-κB is a key regulator of the inflammatory signaling pathways, particularly in sepsis [72]. PAMPs and DAMPs activate Toll-like receptor 4 on cellular membranes, initiating a cascade that ultimately activates NF-κB, leading to the induction of an inflammatory response. Recent research has highlighted the potential of disulfiram and its DSF-Cu complex to reduce the activation of NF-κB and TGF-β signaling pathways [77]. Specifically, this involves inhibiting the nuclear translocation of NF-κB subunits and promoting apoptosis in affected cells [77, 78]. Previous studies have demonstrated that disulfiram can inhibit TGF-β-induced epithelial-mesenchymal transition and the acquisition of stem-like properties in breast cancer cells via the ERK-NF-κB-Snail signaling axis [79].

While much of the current research on disulfiram's interaction with the NF-κB pathway focuses on cancer, these findings could offer valuable insights into sepsis management. Notably, disulfiram has been shown to promote apoptosis and inhibit tumor proliferation by modulating the NF-κB signaling pathway [80, 81]. The

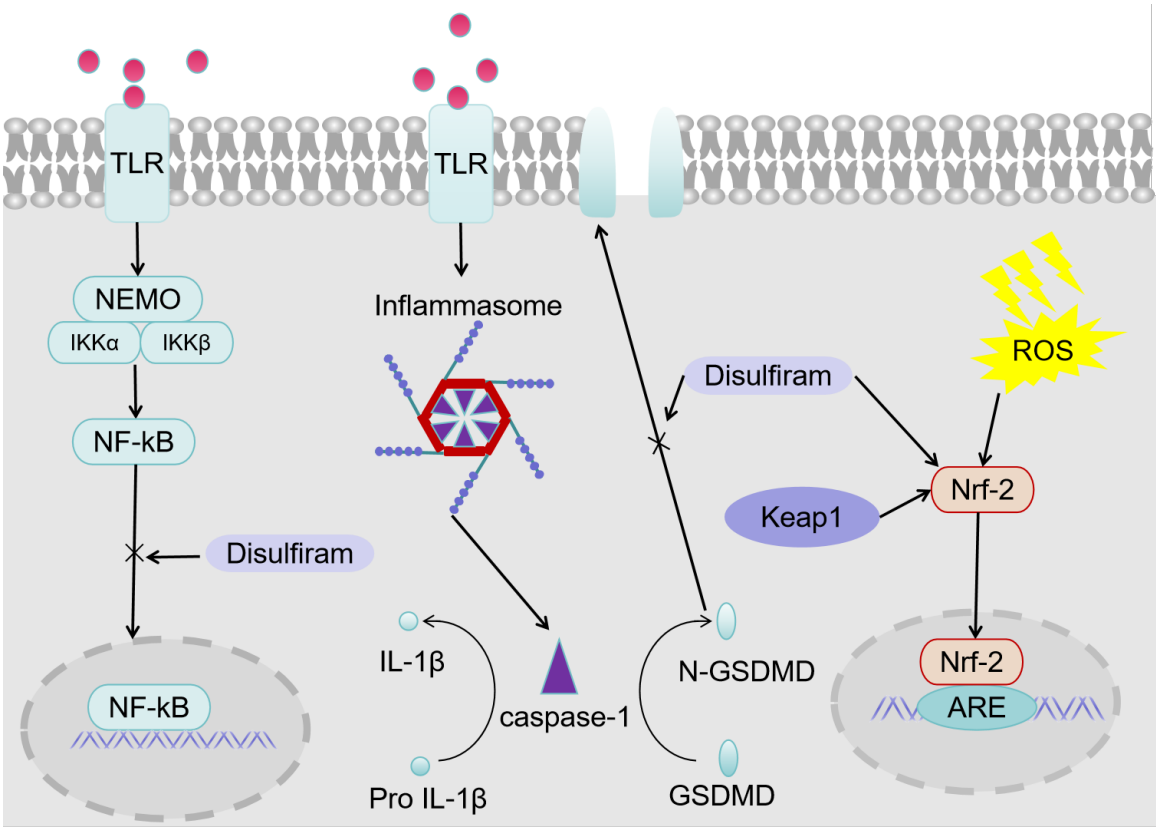

Figure 3. The molecular pathways through which disulfiram modulates immune responses. Disulfiram and its copper complex significantly influence cellular immune signaling by interfering with key pathways such as the NF-κB and TGF-β pathways. These compounds inhibit the nuclear translocation of NF-κB subunits and attenuate the transcriptional activity of essential inflammatory pathways. Furthermore, they induce apoptosis, contributing to their therapeutic effects in vivo. Disulfiram also inhibits the formation of gasdermin D pores in cellular membranes, which is a critical step in pyroptosis, a form of programmed cell death associated with inflammation. Moreover, the copper complex enhances the phosphorylation of p62 protein, which promotes competitive interactions with Keap1, a regulatory protein that typically mediates the degradation of Nrf2. This interaction stabilizes and prolongs the half-life of Nrf2, a master regulator of the antioxidant response, facilitating cellular defense against oxidative stress. NF-κB, nuclear factor kappa-B; IL, interleukin; TLR, toll-like-receptor; NEMO, NF-kappaB essential modulator; GSDMD, gasdermin-D; ARE, antioxidant response elements; ROS, reactive oxygen species.

extrapolation of these effects to the regulation of the inflammatory response in sepsis is a potentially significant area for future investigation. However, the precise mechanism by which disulfiram suppresses the NF-κB pathway in sepsis remains unclear. As most research has focused on oncology, experimental validation of the inhibitory effects of disulfiram on the NF-κB pathway in sepsis is crucial. This would not only expand the potential therapeutic strategies for sepsis but also enhance our understanding of its pathophysiology.

The effects of disulfiram on the gasdermin D (GSDMD)-dependent pyroptotic pathway

Pyroptosis, a highly inflammatory form of programmed cell death, plays a significant role in sepsis pathogenesis [82]. This process is initiated by the interaction of PAMPs and DAMPs with TLRs, resulting in inflammasome assembly and activation [19, 83]. The activation cascade proceeds with the proteolytic maturation of pro-caspase-1 into caspase-1, which subsequently cleaves the precursors of the proinflammatory cytokines IL-1β and IL-18, facilitating their secretion [84]. Concurrently, caspase-1 cleaves GSDMD, promoting the translocation of its N-terminal fragment to the plasma membrane. This results in the formation of pores, disruption of cellular integrity, and induction of pyroptosis [85]. In this context, disulfiram has emerged as a potential therapeutic agent capable of inhibiting GSDMD activity [86]. It binds to the Cys191 residue of human GSDMD, preventing pore formation and thereby inhibiting the cellular lysis associated with pyroptotic cell death [87]. This positions disulfiram as a promising candidate for modulating pyroptotic pathways in sepsis.

Recently, researchers found disulfiram being able to protect organs by inhibiting GSDMD especially through blocking detrimental NETs

released during sepsis [8]. Studies show that disulfiram may suppress NETs and make use of caspase-11/GSDMD pathway to alleviate ischemia reperfusion acute kidney injury [88]. Moreover, evidence suggests that disulfiram may also promote the healing of diabetic foot ulcers, indicating that its inhibition of NET formation via the NLRP3-Caspase-1-GSDMD pathway could be one of its potential therapeutic mechanisms [89]. Furthermore, these studies present multiple beneficial mechanisms of action for disulfiram in diseases involving immune abnormalities. Considering the role of disulfiram in GSDMD-mediated pyroptosis, it is worth studying and revealing the underlying mechanisms, which may provide novel targets for sepsis treatment.

The effects of disulfiram on the nuclear factor erythroid-2 related factor 2-antioxidant response element (Nrf2-ARE) signaling pathway

The Nrf2-ARE signaling pathway is the main defense mechanism against oxidative stress. Nrf2 is a major transcription factor in the pathway [90, 91]. When Nrf2 is exposed to oxidants, it dissociates from Keap1 that exists in the cytosol and translocates into the nucleus, and interacts with ARE. Enhancing Nrf2 activation can regulate the transcription of numerous cytoprotective genes that encode antioxidant enzymes and detoxifying proteins [92]. In sepsis, an exacerbated systemic inflammatory response results in elevated levels of reactive oxygen species and inflammatory mediators, leading to widespread tissue injury [72]. Enhancing the Nrf2-ARE pathway is crucial for cellular and tissue resilience, as it helps mitigate oxidative stress and attenuates proinflammatory cascades [93]. Recent evidence indicates that disulfiram enhances the stability and transcriptional activity of Nrf2, likely through the augmentation of p62 phosphorylation by the DSF-Cu complex. This interaction disrupts the Keap1-Nrf2 complex, stabilizing and prolonging Nrf2 activity [94]. As a result, disulfiram upregulates downstream antioxidant defense genes, creating an environment conducive to cellular protection against oxidative damage, attenuating inflammation and tissue damage induced by reactive oxygen species [94]. It's speculated that disulfiram modulates the glycogen synthase kinase-3 beta -Nrf2- NLRP3 axis, thereby inhibiting oxidative stress-induced pyroptotic cell death; by downregulating the expression of glycogen synthase kinase-3 beta and NLRP3 and upregulating the expression of Nrf2, the activity of Nrf2 is increased, oxidative stress is reduced, and immune defense is activated [95]. This indicates that disulfiram could be a potential candidate to modulate the Nrf2-ARE pathway besides treating alcohol addiction, meanwhile it is supposed that disulfiram's wide-range immunomodulatory activities surpass the boundary of the addiction therapy, and it serves as an antioxidative and anti-inflammatory agent and has been shown beneficial to intervene in oxidative stress and inflammation.

Impact of disulfiram on sepsis progression

Sepsis is primarily treated with antibiotics to kill off infection and also by controlling any adverse inflammation response secondary to the infection. Empirical data has found that disulfiram changes immune pathways, suggesting that disulfiram may affect the pathogenesis of sepsis [74]. The primary mechanism of disulfiram involves modulation of the cellular redox state, where oxidative stress is closely linked to cellular injury and inflammation. By enhancing the Nrf2-ARE pathway, disulfiram bolsters the body's antioxidative defense, offering protection against oxidative damage [94, 95]. Furthermore, the ability of disulfiram to inhibit the NF-κB signaling cascade represents another therapeutic opportunity [96]. As NF-κB is central to the synthesis and release of pro-inflammatory mediators, its inhibition by disulfiram could significantly reduce inflammatory tissue damage [77, 78].

In addition to its immunoregulatory functions, disulfiram exhibits antimicrobial properties, although this is not its primary mechanism of action. This characteristic could complement traditional antibiotic therapy for sepsis by inhibiting the proliferation of specific pathogens, thereby aiding in the management of the infectious source [97-100]. Furthermore, experimental data highlight the efficacy of disulfiram in ameliorating cardiac dysfunction in animal models of LPS-induced cardiac injury. Disulfiram administration preserves left ventricular function and attenuates cardiomyocyte apoptosis, likely by suppressing oxidative stress and inhibiting the NLRP3 inflammasome [4, 75]. Furthermore, disulfiram can also inhibit pyroptosis by blocking the transfer of cathepsin B from lysosomes into the cytosol; it can prevent activation of the NLRP3 inflammasome as described previously. Partially due to this effect, disulfiram treatment protects against lethal sepsis through its immunomodulatory effects [101].

Research gaps and future directions

Recent investigation shows promise for the application of disulfiram as an inducer of immu-

nomodulatory actions especially during sepsis [96]. Studies reveal that, in addition to lowering oxidative stress and suppressing inflammation, the compound also acts on some antimicrobial effects that might be considered as possible agents to reduce septic consequences.

However, despite these encouraging preclinical findings, a significant research gap remains in translating this knowledge into clinical practice. Although in vitro experiments and animal models offer valuable insights, they cannot fully replicate the complexities of human physiology. The discrepancy between controlled experimental conditions and the multifaceted nature of clinical sepsis, characterized by diverse etiologies and individual patient factors, poses challenges for the widespread application of disulfiram. Future research is needed to determine the feasibility of incorporating disulfiram into therapeutic regimens, particularly to clarify the precise mechanisms by which it modulates immune responses in sepsis. This immunomodulation depends on the delicate balance between proinflammatory and anti-inflammatory cytokine levels, suppression of inflammatory cascades, and preservation of immune homeostasis. Despite encouraging preclinical results, there is still a large research gap regarding the ability to translate the current knowledge of sepsis into the clinic. Although in vitro studies as well as animal models provide valuable insights, they do not adequately model all aspects of human physiology. The disparities between the controlled conditions of experimental research and the heterogeneous characteristics of clinical sepsis-stemming from its diverse etiologies and individual patient-specific factors-pose significant challenges to the broader application of disulfiram in clinical settings. More research needs to be done to see whether disulfiram could be used in the treatment protocols and to clarify the mechanisms by which disulfiram regulates the immune response, as these effects mainly result from modulating both pro- and anti-inflammatory cytokines, inhibiting pro-inflammatory cascade, and protecting immune homeostasis.

Moreover, differences between species and methodological limitations may lead to reactions that are different from human beings. In the laboratory, disulfiram concentration is much higher than the amount of human safety [102]. There are undoubtedly questions about the clinical significance of these studies. The disulfiram-ethanol reaction also poses a serious risk. Most clinical applications suffer from the severe limitation that people must totally prohibit alcohol intake and maintain a lasting state of abstinence from any kind of alcoholic beverage or product. Although disulfiram treatment can avoid the serious side effects like hepatotoxicity and peripheral neurotoxicity, rare occasions of some side effects do exist. However, to date, the detailed molecular, cellular and systemic mechanisms behind the interaction of human immune system and disulfiram remain unclear. As such, overcoming this challenge requires extremely rigorous methods, including conducting thorough PK studies and stringent controlled trials, disulfiram has been found to interact with many other medications such that it can decrease or increase their potency or cause other adverse reactions. One lesser-studied area is the complex interaction between disulfiram and medications used to treat sepsis, including various antibiotics (β-lactams, fluoroquinolones, glycopeptides, etc.) and vasoactive agents (norepinephrine, vasopressin). Disulfiram irreversibly inhibits aldehyde dehydrogenase and cytochrome P450 (CYP) enzymes, notably CYP2E1 and CYP3A4, which are key for the metabolism of many antibiotics and vasoactive agents [103]. The antioxidant effects of disulfiram may counteract the pro-oxidant mechanisms of certain antibiotics, thereby reducing their bactericidal efficacy. Sepsis-induced hepatic and renal impairments alter the pharmacokinetics of disulfiram; however, no study has characterized dose adjustments in this context.

Future studies should focus on the complexities and potential of disulfiram as a therapeutic agent for sepsis. These investigations should elucidate the dose-response relationship, therapeutic potential, and safety profile of disulfiram. Understanding the pharmacokinetic profile, possible adverse effects, and interactions with existing therapeutic regimens is thus crucial. As a result, encouraging findings from initial studies can lead to improved phases of clinical trials that may radically change the way sepsis is treated.

With further advances in research, efforts are underway to integrate biomarker analysis for predicting therapeutic effects and to develop personalized treatment regimens, which can not only boost our recognition of the role played by disulfiram in sepsis but also enable translational application of the agent so as to attain best possible treatment strategy based on individual needs.

Conclusion

In summary, further investigation of disulfiram's immunomodulatory effects, as well as its po-

tential application to sepsis therapy could open up new doors in biomedicine given that some initial pre-clinical evidence appears to indicate a possible benefit in this area. Additional work must focus on the immunological effects of this molecule and establish whether it offers therapeutic value against sepsis; more fundamental work is need to clarify the precise mechanisms through which disulfiram acts upon the immune system and inflammatory pathways in order to utilise it effectively as an immunomodulator for targeted therapeutic interventions; and ideally, thorough clinical trials would confirm whether disulfiram has therapeutic value in the setting of sepsis and demonstrate an acceptable safety profile.

The potential value of applying disulfiram as a novel therapeutic agent for the treatment of sepsis cannot be understated; however, caution is warranted in the pursuit of this goal, with a full appreciation of the scientific rationale guiding the potential immunomodulatory mechanisms to which it may contribute. It is only via robust research studies followed by meticulous clinical trials that the full therapeutic scope of using disulfiram in sepsis and other severe infection states will be defined.

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