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REVIEW

Recent Research Advances in Multi-Functional Diallyl Trisulfide (DATS): A Comprehensive Review of Characteristics, Metabolism, Pharmacodynamics, Applications, and Drug Delivery Systems

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Abstract: Diallyl trisulfide (DATS) is an organic sulfur compound derived from garlic (Allium sativum L). DATS is characterized by its oily and volatile nature, exhibiting insolubility in water and ethanol, while being miscible with ether. This property enhances its extraction process and expands its applicability across various fields. Recent studies have elucidated the diverse effects of DATS, demonstrating significant progress in healthcare, the food industry, and nanoformulation research. Research on DATS is currently limited, hindering a comprehensive understanding and appreciation of its possibilities for future development. This review offers an in-depth examination of the characteristics of DATS, highlighting the significant advancements and benefits achieved in the fields of drug metabolism, pharmacological effects, clinical trials, food chemistry applications, and nanoformulation research over the past two decades. In addition, this review examines the future prospects of DATS, emphasizing its current development status and challenges, while serving as a crucial reference for advancing research, application, and innovation in the field.

Keywords: diallyl trisulfide, DATS, metabolism, pharmacological effects, food applications, clinical treatment, drug delivery systems

Introduction

Allium sativum L., a member of the Liliaceae family, is the botanical name for garlic, which was first recorded in the Shennong Bencao Jing.[1] It is commonly known as single garlic, single-headed garlic, or simple garlic and is found across China. Garlic is widely used as a flavor and ingredient in everyday meals and as part of traditional Chinese medicine formulations. It is acknowledged as a plant with dual uses for culinary and medicinal purposes.[2] Garlic has shown significant therapeutic potential as scientific research has progressed. Some researches indicate that the primary chemical constituents of garlic encompass sulfur-containing compounds (such as allyl methyl sulfide, S-allyl cysteine, and S-allyl mercaptocysteine), amino acids, glycosides, as well as a variety of trace elements.[3,4] Among them, diallyl trisulfide (DATS) is a volatile oily substance, which is the most active organic sulfide among the active ingredients in garlic. Additionally, DATS has demonstrated significant effectiveness across multiple domains, functioning as a therapeutic

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agent within the pharmaceutical sector, as well as an additive in both food and feed and as a chemical raw material in specific areas of the chemical industry.[5–7]

DATS exhibits a diverse array of pharmacological effects, encompassing antioxidant, anti-inflammatory, antibacterial, and anti-tumor properties, thereby garnering considerable interest from researchers worldwide.[8–11] Alongside basic research, comprehensive investigations on DATS have been systematically conducted in multiple fields, including pharmacokinetics, pharmacodynamics, pharmacology, and formulation development. Moreover, DATS has been included in multiple clinical trials and is widely used in food, feed, chemical, and pharmaceuticals.[12] This article evaluates the characteristics, applications, and research advancements of DATS, focusing on its drug metabolism, pharmacological effects, food applications, clinical trials, clinical applications, and developments in micro and nanoformulations. This review aims to improve comprehension and utilization of DATS in forthcoming advancements, establishing a theoretical basis for new drug research and innovation and facilitating the investigation of novel therapeutic targets. The objective is to furnish a comprehensive overview of advancements in DATS research spanning multiple disciplines and to provide valuable insights into its promising future potential.

Overview of DATS

Physicochemical Properties of DATS

The chemical formula of DATS is $C_6H_{10}S_3$, with a molecular weight of 154.28 g/mol. Its molecular structure consists of two allyl groups (-CH2=CH-CH2-) connected to three sulfur atoms, forming a trisulfide bond (-S-S-S-).[13,14] DATS is a liquid ranging from colorless to pale yellow (as shown in Figure 1), characterized by its intense garlic aroma. It exhibits insolubility in water but is easily soluble in organic solvents, including ethanol and ether. It is imperative to comply with specific guidelines for the appropriate use and storage of DATS, as it may change specific conditions, such as variations in temperature, light, and humidity.[15] Moreover, DATS has certain reactivity and can participate in various chemical reactions, such as sulfurization and addition reactions.[16] The acute toxicity of DATS is characterized by a relatively low LD50 value of 188.67 mg/kg. Research indicates that adults should limit their daily intake of DATS from garlic to a maximum of 359 milligrams, with garlic consumption not exceeding 84.5 grams.[17]

Metabolic Characteristics of DATS

DATS is a significant active component in garlic, and certain researchers have suggested the metabolic pathway of organic sulfur compounds in garlic, as illustrated in Figure 2. DATS is primarily offered in oral capsule or tablet form, attributed to its lipid solubility and user-friendliness for patients. A pharmacokinetic study of orally administered DATS (50 mg/kg) identified allyl methyl sulfone (AMSO2) as the predominant and most persistent metabolite of DATS. There

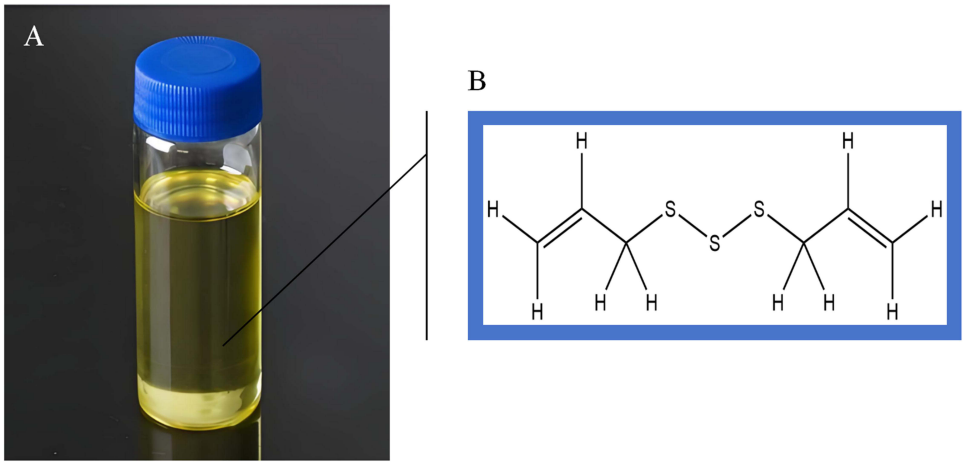

Figure 1 Appearance and structural formula of DATS.
Note: (**A**) The visual presentation of DATS; (**B**). The chemical structure formula of DATS.

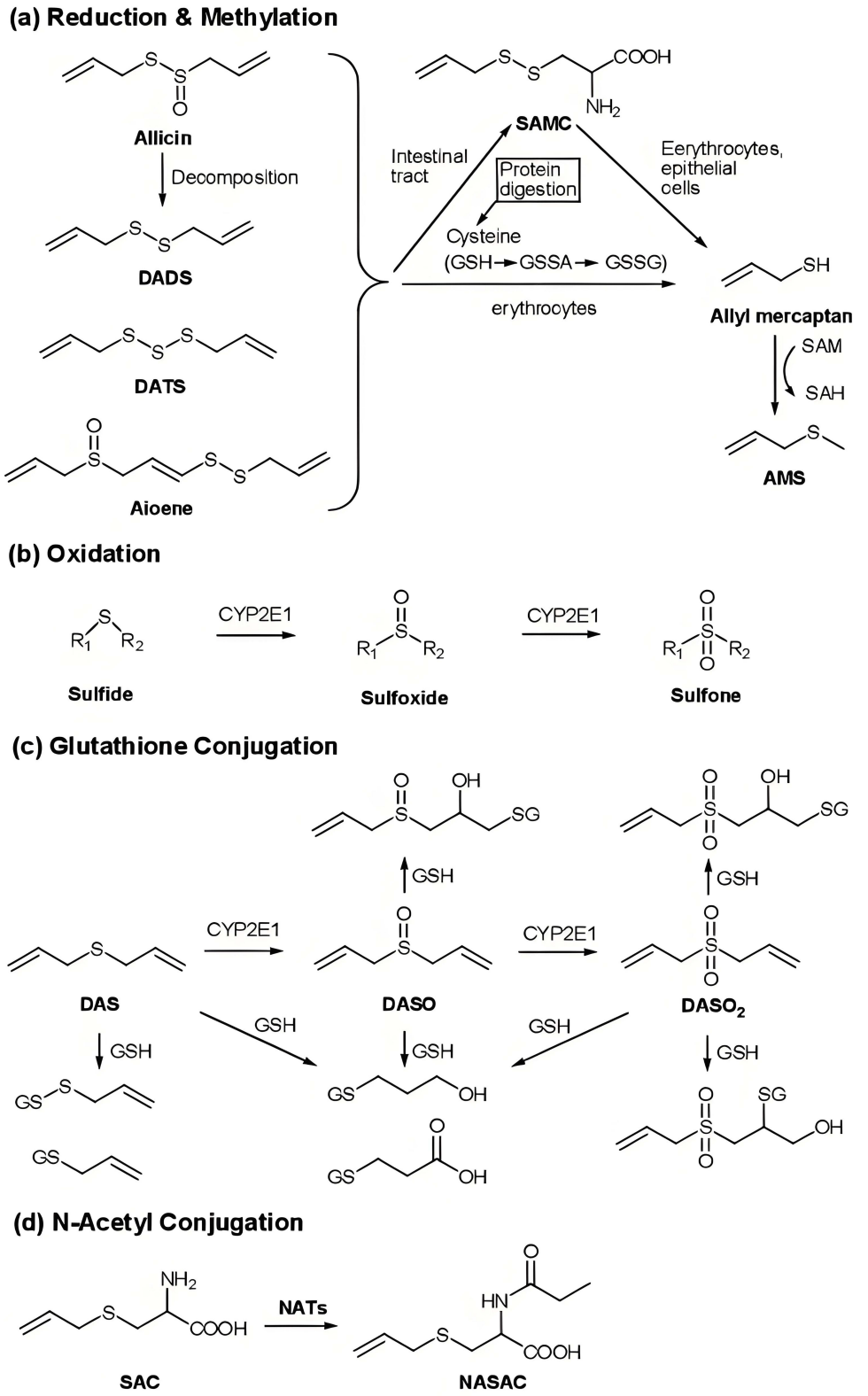

Figure 2 Proposed metabolic routes of organosulfur compounds derived from garlic.

Note: (**a**) The reduction and methylation pathways of organosulfur compounds; (**b**) The oxidative pathway of organosulfur compounds; (**c**) The glutathione conjugation pathways of organosulfur compounds; (**d**) The metabolic pathway of N-acetyl conjugation of organosulfur compounds. Used with permission from Gao CC, Jiang XY, Wang HN, Zhao ZX, Wang WH. Drug Metabolism and Pharmacokinetics of Organosulfur Compounds from Garlic. *J Drug Metab Toxicol*. 2013; 4: 159. © 2013 Gao C, et al. This is an open-access article distributed underthe terms of the Creative Commons Attribution License.[20]

Abbreviations: Proposed metabolic pathways of organosulfur compounds from garlic; GSH, glutathione (γ-Glu-Cys-Gly); GSSA, S-allyl mercaptoglutathione (γ-Glu-Cys-(S-allyl)-Gly); GSSG, oxidized glutathione; SAM, S-adenosyl methionine; SAH, S-adenosyl homocysteine; R1 or R2, saturated or unsaturated group; NATs, N-acetyl transferases.

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are several studies reporting the presence of methylallyl sulfoxide (AMSO) in addition to AMSO2.[18,19] Additionally, studies have also found that in metabolite excretion, AMSO and AMSO2 are mainly excreted through urine, followed by bile excretion. AMSO2, the metabolite, accumulates in minor quantities within major tissues, including the heart, liver, spleen, lungs, and kidneys.[20] Although two metabolites of DATS, AMSO and AMSO2, have been identified, no prototype drug was detected following DATS administration. Once DATS enters into the body, it is metabolized in the bloodstream. An in vitro study on blood cell systems revealed that DATS is metabolized into two metabolites: diallyl disulfide (DADS) and allyl mercaptan (AM).[20] After its deduction and verification, the complete metabolic process of DATS in vivo, namely DATS→DADS→Methyl Allyl Sulfide (AMS)→AM→AMSO→AMSO2, has been described. The rapid clearance of DATS prototype drugs from the bloodstream elucidates the misconception regarding DATS's inability to detect in vivo metabolic testing. DATS is a rapid metabolic process in the body; however, its metabolites AMSO and AMSO2, which exhibit longer retention times in animal plasma, may indicate that DATS and its metabolites could fulfill multiple roles within the physiological system.

In drug interaction studies, it was found that DATS can also affect the metabolism of some other drugs. A pharmacokinetic study involving DATS and nifedipine in rats demonstrated that chronic treatment with DATS elevated the oral bioavailability of nifedipine in rats, potentially through modifications in the intestinal metabolism of nifedipine.[21] Research has shown that caution may be required when using DATS or supplements containing DATS in combination with nifedipine, as elevated plasma concentrations may result in the toxicity associated with this adverse reaction. Therefore, DATS or DATS-rich garlic supplements should be used cautiously in conjunction with nifedipine in patients with cardiovascular disease. In another study exploring the interaction between DATS and dipyridamole, it was observed that DATS may have decreased the oral bioavailability of dipyridamole in rats by modifying its dissolution properties and intestinal absorption.[22] This suggests caution may be needed when using DATS or supplements containing DATS in combination with dipyridamole, as low plasma concentrations of dipyridamole may lead to sub-therapeutic effects on this drug. Therefore, combination therapy involving DATS should be used cautiously in clinical practice.

Pharmacological Effects of DATS

Antioxidant Properties of DATS

DATS acts as a natural antioxidant, efficiently neutralizing free radicals and diminishing oxidative stress in the body.[23] This antioxidant effect is significant in reducing cell damage, slowing down the aging process, and inhibiting cancer development. It mainly participates in antioxidant activity through the following ways: 1) Neutralizing free radicals: DATS has the ability to neutralize free radicals present in the body, including reactive oxygen species (ROS), thereby mitigating oxidative stress on cellular and tissue structures;[24] 2) Enhancing antioxidant enzyme activity: DATS can augment the activity of antioxidant enzymes like glutathione peroxidase (GSH-PX) and superoxide dismutase (SOD), fortifying the body's antioxidant defenses;[25] 3) Protecting cells from oxidative damage: Through its antioxidant properties, DATS can protect cells from damage caused by oxidative stress and maintain their normal structure and function.[26] In addition, DATS can also inhibit some signaling pathways related to oxidative stress, such as NF-κB, MAPK, etc., thereby reducing the inflammatory response and cell damage caused by oxidative stress.[24,27] The combined effects of DATS underscore its potent antioxidant properties, hinting at its extensive potential applications in addressing diseases linked to oxidative stress.

Anti-Inflammatory Properties of DATS

DATS has exhibited notable anti-inflammatory properties across various inflammatory model systems. In a study on naphthalene-induced oxidative damage and inflammatory response, DATS treatment inhibited the production of naphthalene-induced ROS and SOD in A549 cells.[28] DATS can also reduce the production of naphthalene-induced inflammatory responses (TNF-α, IL-6, and IL-8) and inhibit the activity of NF-κB. In animal experiments, DATS inhibited the production of serum nitric oxide NO and myeloperoxidase (MPO) in the lungs of Kunming mice, and histological results showed that DATS inhibited naphthalene-induced lung injury, which is consistent with in vitro research results. The in vivo and in vitro results indicate that DATS may effectively attenuate naphthalene-induced lung injury. Another study revealed that pig epithelial cells exposed to LPS stimulate an elevation in TNF-α and IL-8 levels. However,

following treatment with DATS, it not only prevents the decrease in TNF-α and IL-8 secretion but also attenuates their mRNA expression.[29] These studies reveal the powerful ability of DATS to inhibit inflammatory responses.

Antibacterial Properties of DATS

DATS, a trisulfide compound derived from garlic extract, possesses potential antibacterial activity against foodborne pathogens. The study investigated the antibacterial activity of DATS against Campylobacter jejuni by evaluating the minimum inhibitory concentration (MIC) of Campylobacter jejuni 81–168 and 14 strains isolated from chicken carcasses.[30] Research indicates that scanning electron microscopy (SEM) analysis reveals the destruction and contraction of the bacterial cell membrane of Campylobacter jejuni following DATS treatment. The SEM results are shown in Figure 3. Time killing analysis further indicates that DATS has a dose-dependent in vitro antibacterial effect on Campylobacter jejuni during 24-hour treatment. Furthermore, DATS also demonstrated an antimicrobial effect in chickens through the decline of C. jejuni colony count of 1.5 log CFU/g (clonal sample) during the seven-day DATS treatment period. 14 ABC transporter-related genes responsible for bacterial cell homeostasis and oxidative stress were downregulated, indicating that DATS could decrease the bacterial ability against environmental stress. These findings collectively underscore the antibacterial activity of DATS against Campylobacter jejuni and propose its potential utilization as an antibacterial compound in the feed and food industries. Furthermore, a study contrasting the antibacterial efficacy of four diallyl sulfides present in garlic volatile oil against strains including Staphylococcus aureus and methicillin-resistant Staphylococcus aureus (comprising a total of 276 clinical isolates) revealed that DATS exhibited the superior antibacterial activity.[31]

Anti-Tumor of Properties DATS

DATS exhibits significant inhibitory effects on tumor cell proliferation and induces apoptosis in a wide range of cancer cell types. A mouse lung cancer model induced by 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) was utilized to investigate the chemo-preventive efficacy and underlying mechanism of DATS on lung tumor development.[32] The research findings indicated that DATS significantly decreased the incidence of NNK-induced lung tumors in mice. DATS has demonstrated the ability to modulate gut microbiota, specifically by augmenting the abundance of certain rodent species and suppressing tumor growth. Mechanistically, DATS activates the PPARγ pathway, thereby negatively regulating the NF-κB signaling pathway and inhibiting NF-κB-mediated inflammatory factors. These discoveries underscore DATS' potential as a novel chemopreventive agent for tobacco-induced lung cancer.

Overexpression of Np63 markedly boosts the self-renewal capacity of gastric spheroid-forming cells and elevates the expression levels of cancer stem cell (CSC) markers. Additional studies have revealed that ΔNp63 can directly interact with the promoter region of the crucial transcription factor Gli1 in the SHH pathway, thereby augmenting its expression and activating the Sonic Hedgehog (SHH) signaling pathway.[33] DATS effectively inhibits gastric CSC characteristics both in vitro and in vivo; however, the activation of the SHH pathway significantly diminishes this inhibitory effect. The upregulation of ΔNp63 via the SHH pathway diminished the inhibitory effect of DATS on gastric CSC characteristics. The findings demonstrate the ΔNp63/SHH pathway's significant role in suppressing gastric cancer stem cell characteristics by DATS. DATS demonstrates therapeutic efficacy against a diverse range of tumors, encompassing triple-negative breast cancer, ovarian cancer, and pancreatic cancer.[34–37]

Preclinical studies prove that DATS regulates multiple cancer hallmark pathways, including cell cycle, apoptosis, angiogenesis, invasion, and metastasis. DATS has been shown to arrest cancer cells at multiple cell cycle stages, with the G2/M arrest being the most widely reported.[12,38] Additionally, increased pro-apoptotic capacity due to regulating intrinsic and extrinsic apoptotic pathway components has been widely reported following DATS treatment. Invasion, migration, and angiogenesis represent emerging targets of DATS and support its anticancer properties.

The Protective Effect for Cardiovascular System of DATS

The endothelial dysfunction observed in diabetic patients following tissue ischemia is partly attributed to compromised angiogenesis. A study investigated the efficacy of DATS in promoting angiogenesis in a hind limb ischemia model using diabetic mice, with the aim of improving endothelial function and reducing cardiovascular disease risk.[39] The findings

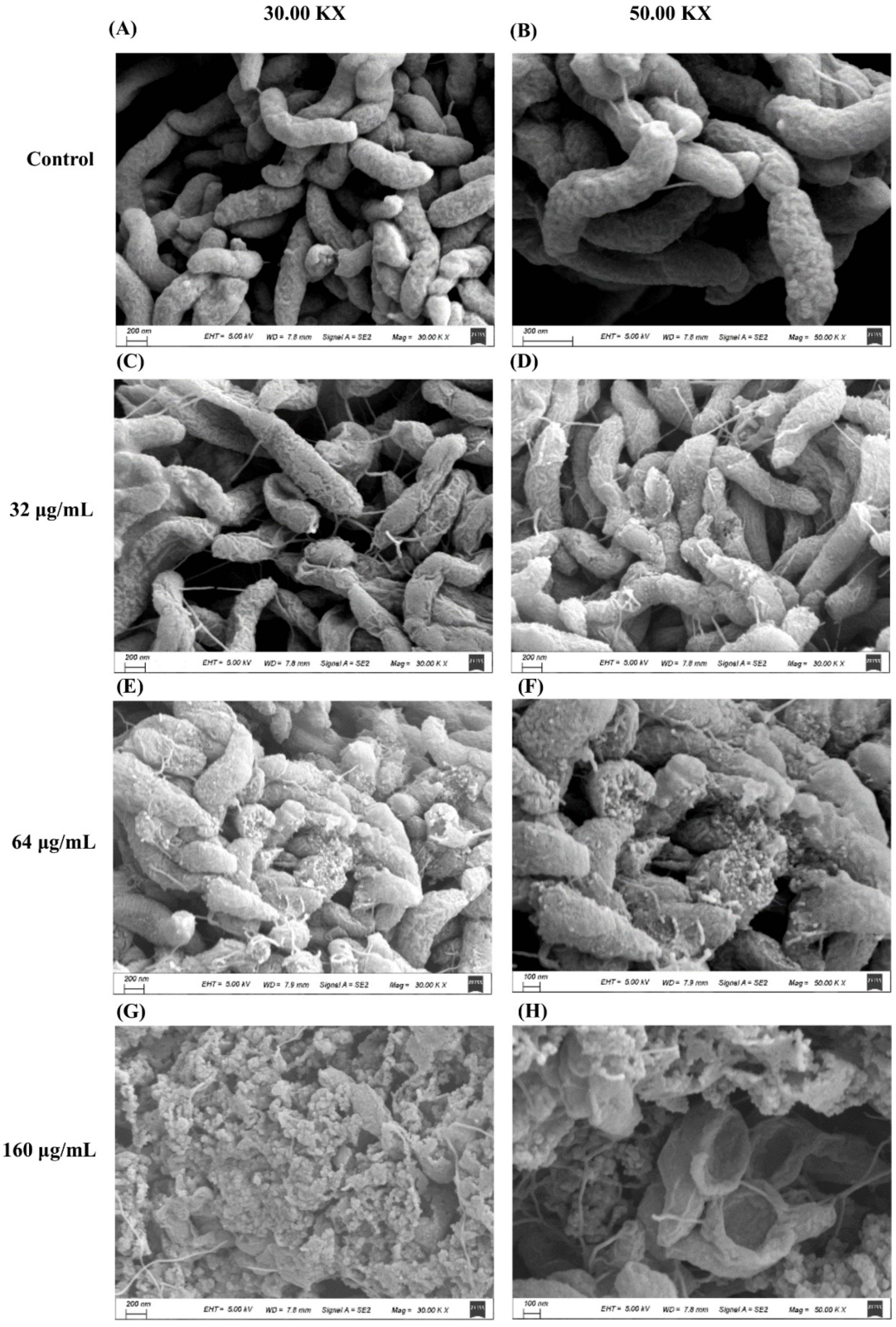

Figure 3 Scanning electron microscopy images of planktonic cells of C. jejuni strain 81–176, following 24 hours of treatment with DATS, were compared to those of the control group.The control was C. jejuni culture without DATStreatment (**A** and **B**). The treatment concentrations of DATS included 32 μg/mL (**C** and **D**), 64 μg/mL (**E** and **F**) and 160 μg/mL (**G** and **H**).

Note: Used with permission from Tang Y, Li F, Gu D, Wang W, Huang J, Jiao X. Antimicrobial Effect and the Mechanism of Diallyl Trisulfide against Campylobacter jejuni. *Antibiotics (Basel)*. 2021; 10(3): 246. © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.[30]

indicated that, following 14 days of ligation in streptozotocin-induced diabetic mice, there was a reduction in levels of eNOS, p-eNOS, and VEGF in ischemic skeletal muscle, accompanied by decreased blood perfusion, capillary density, and NO bioactivity in the hind limbs. Furthermore, there was an increase in oxidative stress and protein carbonyl levels. DATS treatment resulted in significant improvements in these parameters. Further research revealed that DATS exerts its influence on outcomes by activating the AMPK-mediated AKT/GSK-3β/HIF-1α pathway, thereby alleviating ischemia-reperfusion (MI/R) injury in diabetic contexts.[40] DATS enhanced cardiac function and decreased myocardial cell apoptosis, and at a concentration of 10 μM, it mitigated simulated ischemia-reperfusion injury in cultured H9c2 cells.

Concurrently, they discovered that AMPK and AKT/GSK-3β/HIF-1α signaling were downregulated in diabetic conditions. However, DATS notably enhanced the phosphorylation of AMPK, ACC, AKT, and GSK-3β, as well as the expression of HIF-1α, in the context of ischemia-reperfusion (MI/R). Furthermore, the PI3K inhibitor LY294002 abolished the stimulatory effect of DATS on AKT/GSK-3β/HIF-1α signaling without altering AMPK signaling. These findings suggest that DATS can protect against MI/R injury in diabetes by inhibiting cell apoptosis through AMPK-mediated AKT/GSK-3β/HIF-1α signal transduction, thereby promoting a cardio-protective effect. Besides, a study conducted on animal models of Ang II–induced vascular remodeling revealed that DATS significantly decreased mitochondrial fission, vascular smooth muscle cell (VSMC) differentiation, and vascular wall thickening in these models, which were regulated by ROCK1/Drp1 signaling.[41] The findings suggest that DATS alleviates Ang II–induced vascular remodeling by inhibiting Drp1-mediated mitochondrial fission in a ROCK1-dependent manner.

Immune Regulation of DATS

After administering DATS to mice with melanoma, there was a notable increase in the quantity of CD8+T cells and dendritic cells within their bodies, accompanied by a substantial decrease in the immunosuppressive activity of myeloid suppressor cells.[42] The restoration of T cell proliferation enhanced immune surveillance function. DATS enhances giant cell phagocytosis in WEHI-3 leukemia mouse models, boosts NK cell activity, and strengthens the immune response in these mice.[43] Treatment of fibroblast-like synovial cells (RA-FLS) derived from rheumatoid arthritis patients with DATS results in a significant decrease in the production of inflammatory cytokines, a reduction in cell viability, and the induction of apoptosis in these cells. Furthermore, Liang et al delved into the role of DATS in vivo by utilizing a mouse model of collagen-induced arthritis (CIA).[44] The research findings suggest that DATS has the capacity to reduce the production of inflammatory cytokines and regulate immune function by restoring the equilibrium between Th17 and Treg cells in the collagen-induced arthritis (CIA) mouse model.

Human Clinical Trials of DATS

As of November 2024, the human drug clinical trial research of DATS is still preliminary, although it has shown multiple potential pharmacological effects in vitro experiments and animal models. DATS has demonstrated a significant impact in antioxidant, anti-inflammatory, anticancer, and cardiovascular protection, but its application data in humans is still limited. A comprehensive meta-analysis of numerous clinical drug trials examining the anti-non-alcoholic fatty liver disease (NAFLD) effects of garlic, which encompasses various sulfur compounds such as DATS, revealed that the consumption of garlic supplements can decrease the incidence and severity of NAFLD. Furthermore, these supplements were found to inhibit liver steatosis, oxidative stress, and inflammation. The findings of this study suggest that garlic supplementation has a beneficial impact on the prevention and treatment of NAFLD.[45] However, most of these studies used mixed garlic extracts rather than purified DATS, so its specific NAFLD treatment mechanism still needs further exploration. In a clinical trial investigating the beneficial effects of aged garlic extract (AGE) on vascular elasticity, 122 patients with a Framingham risk score of 10 or higher were randomly and double-blindly assigned to receive either a placebo or 2400 mg of AGE daily for a period of one year, during which they were closely monitored.[46] It has been found that using AGE for 12 months' increases microcirculation in patients, thereby promoting wound healing. Additionally, there is a clinical study on the effects of using AGE garlic extract on weight loss and gut microbiota composition in obese women.[47] After 2 months of AGE use, significant reductions were observed in the subjects' BMI, fasting insulin levels, and insulin resistance homeostasis model assessment levels. However, these studies also used mixed garlic extracts and not purified DATS, so the specific effects still need further investigation. Therefore, future

research should focus on expanding sample sizes, conducting multi-center collaborations, and delving into the specific mechanisms of DATS to promote its clinical application. Long-term follow-up is essential for assessing the sustained efficacy and potential adverse effects of DATS, thereby ensuring its safety and effectiveness across various diseases. As more high-quality clinical trials are conducted, DATS is anticipated to emerge as a novel natural medicine for the prevention and treatment of a wide range of chronic illnesses, cancers, and cardiovascular diseases.

Application of DATS in the Food and Chemical Industry

Incorporating antioxidants into food helps prevent the oxidation and deterioration of fats and nutrients, thereby prolonging the shelf life and preserving the overall quality of the food.[48,49] Antioxidants can inhibit free radical reactions, reduce the generation of harmful oxidation products, and prevent food from developing odors, discoloration, and decreased nutritional value.[50,51] Moreover, antioxidants help improve food safety and prevent microbial growth and the formation of harmful substances, thereby ensuring that ingredients remain fresh and stable during storage and transportation. DATS, an organic sulfur compound derived from garlic, possesses a diverse array of potential applications in the food industry, attributed to its distinctive chemical structure and significant biological activity. DATS is a natural antioxidant with the ability to effectively combat and neutralize free radicals; Adding it to food can delay food's oxidation and deterioration process, thereby extending its shelf life.[52] Besides, due to its ability to inhibit peroxidation reactions, DATS may be suitable for use in fried foods, baked goods, and processed foods containing high-fat components to suppress peroxidation reactions during their storage process and reduce the generation of harmful oxidation products. DATS also demonstrates antibacterial and antifungal properties, effectively inhibiting the growth of various foodborne pathogens, including Escherichia coli, Staphylococcus aureus, and Salmonella.[53,54] DATS can serve as a natural preservative, and when added to meat, fish, and dairy products, it can prevent microbial contamination, ensuring food safety and quality.[55] This makes it of significant application value in food preservation and food safety.

The environmental pollution, evolution of resistance, and risks to human and aquatic animal health associated with pesticide application have attracted much attention globally. A study found that DATS from garlic essential oil control the destructive stored-product pest, Sitotroga cerealella.[14] The results revealed that the cuticular chitin content of pests decreased after DATS treatment. DATS treatment also reduced the thermal stability and crystallinity of chitin. These findings indicate that DATS is a potent biopesticide active against the moth. It establishes the basis for its use as an IPM and alternative to chitin synthesis inhibitors. Scholars have also discovered that certain phytochemicals, such as curcumin, quercetin, DATS, and thymoquinone, can mitigate the adverse effects of metal or metalloid exposure and may serve as viable alternatives to chelation therapy.[56] More significantly, these plant-based products exhibit a notable capacity to alleviate the toxic effects associated with arsenic poisoning. When used in combination with chemotherapy drugs, they can more effectively eliminate arsenic, reduce side effects, and are more practical than conventional treatments. Furthermore, antioxidants are often added to cosmetics to neutralize free radicals, reduce signs of skin aging such as wrinkles and pigmentation, and protect the skin from ultraviolet rays and other environmental factors.[57] DATS may also be included as a potential antioxidant, and its future application scope in the cosmetics field is expected to be further expanded.

Application of DATS in Traditional Chinese Medicine

DATS mainly exists in garlic (Allium sativum), a natural organic sulfur compound in garlic and related plants such as onions, chives, and other Allium plants. In traditional Chinese medicine, various medicinal herbs contain or associated with DATS: 1) Garlic: Contemporary research has demonstrated that sulfides, such as DATS found in garlic, possess diverse biological activities, including antioxidant, antibacterial, antiviral, and anticancer properties.[58] 2) Scallion: Scallion is also a plant of the Allium genus, and its entire plant can be used as medicine. Traditional Chinese medicine believes that scallion white has a warm, pungent taste and can dispel cold, promote yang, and detoxify.[59] Although scallions' main active ingredients differ from garlic's, they also contain some organic sulfur compounds, including small amounts of DATS or other similar sulfides.[60] 3) Chives: Chives are also members of the Allium genus, and their roots and leaves can be used as medicine. Traditional Chinese medicine believes chives are warm, pungent, sweet, and beneficial to the liver, kidney, and stomach meridians.[61] They enhance the warmth and strength of the liver and kidneys,

promote yang energy, and stabilize essence.[61] Leeks contain a certain amount of organic sulfur compounds, but the content of DATS is relatively low.[62] 4) Onion: Although onions are not commonly found in traditional Chinese medicine, they are also mentioned in some local medicinal plant lists. Onion belongs to the Allium genus, and its bulbs are rich in various organic sulfur compounds, including possible DATS.[63] However, there is relatively little research on its application in traditional Chinese medicine.[62]

It should be noted that although those mentioned above Chinese medicinal materials belong to the Allium genus and contain organic sulfur compounds, their specific composition ratios and contents may vary depending on factors such as variety, growth environment, and processing methods. Especially for particular compounds like DATS, their forms and concentrations may differ significantly in different plants. Therefore, if it is to obtain specific pharmacological effects, such as utilizing the antioxidant or antibacterial properties of DATS, garlic extract is usually used directly, or purer DATS is obtained through chemical synthesis.

Research on Drug Delivery System Based on DATS

DATS Nanoparticles

The transportation of both endogenous and exogenous hydrogen sulfide (H_2S) and the in situ generation of oxygen (O_2) within atherosclerotic plaques contribute to inhibiting inflammatory cell infiltration and mitigating disease progression. However, uncontrolled release of gas donors can impede the drug from achieving therapeutic concentrations and induce toxic effects. To address this, researchers have developed metal-organic cages (MOC)-68 doped with MnO_2 nanoparticles encapsulated with DATS, a micro environmentally responsive nanomedicine that locally delivers H_2S and O_2 to inflammatory cells within plaques.[64] This nanomedicine exhibits excellent monodispersity and stability, protecting DATS from circulation degradation. The research found that this kind of DATS containing MnO_2 nanodrug doped with MOC-68 has great prospects as a new treatment and diagnosis platform for atherosclerosis. The synthesis and delivery process of the nanomedicine in this study is shown in Figure 4.

Cardiac arrest (CA) is the leading cause of death worldwide. Even after successful cardiopulmonary resuscitation (CPR), most survivors suffer from permanent myocardial and brain damage. Researchers have employed mesoporous iron oxide nanoparticles (MIONs) as carriers for DATS, and further modified these MIONs with polyethylene glycol (PEG) and lactoferrin (LF) to prolong their circulation time and enhance their targeting to the brain. This approach has led to the development of a novel targeted H_2S release system, termed DATS@MION-PEG-LF.[65] DATS@MION-PEG-LF Both in vitro hypoxia/reoxygenation models and in vivo CA/CPR models have shown practical protective effects against cerebral and cardiac ischemic injury after cerebral infarction, with significant improvement in cardiovascular and cerebrovascular function and the possible increase in survival rate. This work provides a unique platform for H_2S targeted controlled release based on MIONs and offers a new approach for combined myocardial and brain protection.

Additionally, Zheng et al designed and constructed an active tumor therapy and diagnostic nanosystem using a one-pot biomineralization method coupled with surface functional modification, resulting in Bi_2S_3-Ag_2S-DATS@BSA-N_3 NYs. This nanosystem aims to enhance second near-infrared (NIR-II) fluorescence and photoacoustic (PA) imaging-guided photothermal therapy (PTT) and gas therapy (GT).[66] Utilizing the enhanced permeability and retention (EPR) effect to facilitate tumor accumulation, the overexpression of glutathione (GSH) within the tumor can expedite the production of H_2S through its reaction with encapsulated DATS nanoparticles. Simultaneously, the in situ release of H_2S not only serves as a therapeutic agent for gas therapy but also initiates the reduction of -N3(-) to -NH2(+), thereby enhancing the tumor-specific accumulation of the nanosystem. This activation process facilitates precise NIR-II/photoacoustic (PA) dual-mode imaging, guiding the synergistic anticancer efficacy of the nanosystem. DATS nanoparticles have also been used in heart transplantation, triple negative breast cancer, acute limb ischemia and cancer treatment. The detailed results are shown in Table 1.[67–70]

DATS Liposomes

The importance of studying liposome drug delivery systems stems from their capacity to achieve controlled and targeted drug release, thereby enhancing the precision and effectiveness of drug therapy. Additionally, they can mitigate the toxic

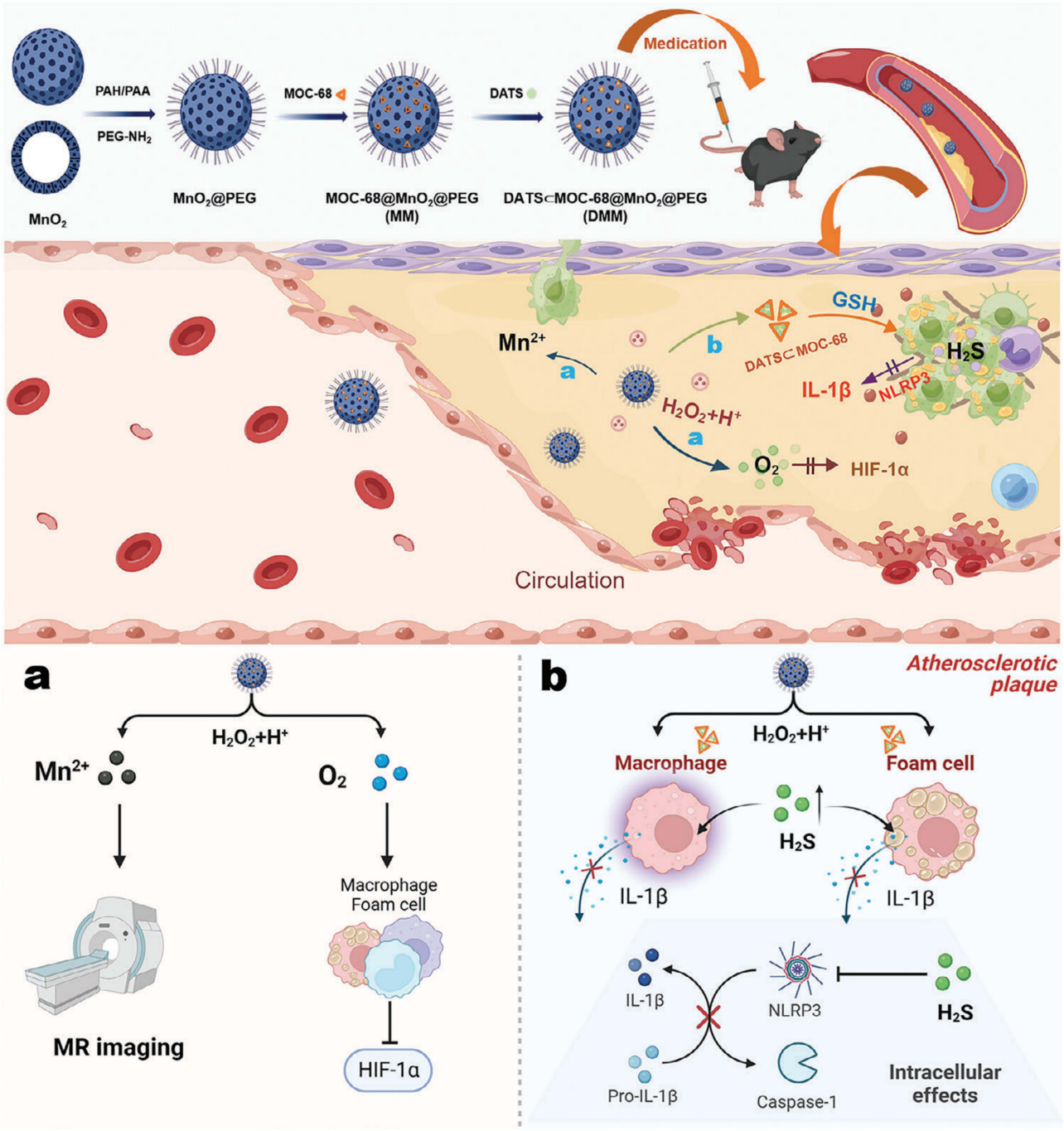

Figure 4 Schematic representation of the synthesis and delivery of a MOC-68-based MnO2@PEG nanoparticle loaded with DATS (DMM) nanomedicine, designed for MRI-visible dual gas therapy in the treatment of atherosclerosis.

Note: (**a**) DMM's dual role in hypoxia improvement and medical imaging; (**b**) DMM suppresses IL-1β secretion by modulating inflammatory pathways. Reproduced with permission from Li D, Chen J, Lu Y et al. Codelivery of Dual Gases with Metal-Organic Supramolecular Cage-Based Microenvironment-Responsive Nanomedicine for Atherosclerosis Therapy. *Small*. 2024; 20(40): e2402673. © 2024 Wiley-VCH GmbH.[64]

effects of drugs and enhance patient compliance and treatment safety. DATS has undergone extensive research in cancer models, yet its low solubility poses a barrier to clinical application. Researchers have prepared and characterized polyethylene glycol coated di stearoyl phosphatidylcholine/cholesterol (DSPC/Chol) containing DATSL loaded with DATS and DOXL liposomes encapsulated with doxorubicin (DOXO), for the purpose of improving the bioavailability of DATS and evaluating its chemoprevention and chemo-sensitization properties in AOM induced colon cancer models.[71]

DATSL and DOXL showed significant sensitivity in cell proliferation experiments, with IC_{50} doses reduced by more than 8 times and 14 times, respectively. Analysis of histopathology, cancer marker enzymes, and antioxidant enzymes showed that high-dose DATSL pretreatment and DOXL chemotherapy were highly effective in inhibiting AOM-induced colon cancer promotion. The combination of DATSL and DOXL indicates its potential as a treatment for colorectal cancer in this study. The results shown in Table 1.

Table 1 Summary of DATS Drug Delivery Research

Author	Delivery System	Carrier Material	Size	Application	Major Findings
Li[64]	Nanoparticles	MnO_2 & DATS	300 nm	Atherosclerosis	Macrophage polarization↓, formation of foam cells↓, NLRP3 and interleukin-1 β↓, the plaque burden, inflammatory infiltration, and hypoxic conditions within the plaques↓
Sun[65]	Nanoparticles	DATS	229 ± 32 nm	Cardiac arrest	Excellent biocompatibility, the controllable release of H_2S mode, heart and brain targeting features. Good anti-apoptosis, anti-inflammatory, and antioxidant properties.
Zheng[66]	Nanoparticles	DATS	~325 nm	Cancer	EPR effect↑, H_2S release↑, realize accurate NIR-II/PA dual-mode imaging
Xia[67]	Nanoparticles	DATS	236 ± 34 nm	Heart transplantation	Protect cardiomyocytes from ischemic and reperfusion injury, BCL-2 expression↑, BAX expression↓, TNF-α and IL-1β↓
De[68]	Nanoparticles	DATS	168.2 ± 3.78 nm	Triple-negative breast cancer	Demonstrates a superior therapeutic effect on MDA-MB-231 cells in comparison to MCF-7 cells, BCL-2 expression↓, anticancer effect↑
Zhang[69]	Nanoparticles	Melatonin & DATS	220 nm	Acute limb ischemia	ROS↓, H_2S release↑, enhance angiogenesis and microcirculation reconstruction in ischemic limbs
Liu[70]	Nanoparticles	Cinnamaldehyde & DATS	123.5 ± 26.6 nm	Cancer	ROS in cancer cells↑, glutathione↓, therapeutic effect of cancer↑
Alrumaihi[71]	Liposomes	DATS	135.5 nm	Colorectal cancer	Sensitivity in cell proliferation experiments↑, IC_{50} decreased by 8 times, therapeutic effect of colon cancer↑.
Chen[72]	Nanoemulsion	Diallyl sulfide, Diallyl disulfide, and DATS	10.8 nm	Hypertension and cognitive impairment	TNF-α, IL-6, IL-1 β↓, blood pressure↓, cognitive impairment↓
Mao[73]	Nanoemulsion	DATS	172.8~191.2 nm	Bacterial and fungal infection	Biocompatibility↑, particle size↓, intravenous stimulation↓, controllable concentration of free DATS
Mao[74]	Nanoemulsion	DATS	180.8~325.1 nm	Bacterial and fungal infection	Biocompatibility↑, particle size↑, intravenous stimulation↓
Hu[75]	Microneedle	Glucose oxidase and DATS	426 nm	Cancer	Photodynamic/sonodynamic effects↑, achieve tumor starvation and gas therapy, controlled release of GOx and H_2S, therapeutic effect↑
Ju[76]	Micelle	DATS	-	-	Stimulation and degradation of DATS↓
Jiang[77]	Microspheres	β-cyclodextrin and DATS	1~5 μm	Lung cancer	CD86 expression and TNF-α in tumor-associated macrophages↑, A549 cell apoptosis↑, H_2S↑, proliferation and dissemination of lung cancer cells↓
Lin[9]	Capsule	Glutathione & DATS	-	Inflammatory bowel disease	Solubility of DATS↑, H_2S↑, inflammatory cytokines↓
Su[78]	-	DATS	-	Bacterial infection	Eliminate biofilms, H_2S↑, and cytokines related to regeneration↑, stimulate the polarization of macrophages toward M2 phenotype for reshaping the immune microenvironment

Notes: ↑ represents an increase in the level of the indicator, ↓ represents a decrease in the level of the indicator, - represents that the item has no content.

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DATS Nanoemulsion

The nanoemulsion drug delivery system is an advanced drug delivery technology that significantly enhances drugs' solubility, stability, and bioavailability by encapsulating them in nanoscale droplets.[79,80] This advanced drug delivery system enhances treatment effectiveness, minimizes adverse effects, and offers innovative approaches for managing complex medications, thereby fostering the development of personalized medicine. A recent study demonstrates that a high-dose nanoemulsion prepared using Tween-80, glycerol, grape seed oil, and water, containing black garlic extract (which includes DATS), can significantly lower systolic blood pressure in rats by elevating bradykinin and nitric oxide levels while decreasing aldosterone and angiotensin II levels.[72] In the Morris water maze experiment, they exhibited a significant reduction in escape latency and swimming distance, coupled with an increase in the time spent in the target quadrant. Additionally, these improvements were accompanied by decreased acetylcholinesterase activity and malondialdehyde levels in the hippocampus, as well as elevated glutathione levels and enhanced activities of superoxide dismutase, catalase, and glutathione peroxidase. Furthermore, there was a notable decrease in inflammatory factors. Besides, the nanoemulsion formulation also significantly lowered blood pressure and improved learning and memory abilities in rats. Researchers are developing a nanoemulsion to deliver DATS for the systemic treatment of bacterial and fungal infections. Lecithin has been chosen as the primary emulsifier, with the incorporation of two distinct co-emulsifiers to create a stable nanoemulsion with small particle sizes, designated as DATS@nanoemulsion.[73] Utilizing cellular ATP and GTP concentrations as indicators, researchers employed an in vitro compatibility model involving human umbilical cord endothelial cells to assess the reduction in intracellular ATP and GTP levels induced by venous stimulation in the DATS@nanoemulsion. This reduction varied in a concentration-dependent manner with the addition of different co-emulsifiers, relative to free DATS. Nanoemulsion is a delivery system suitable for lipophilic and intravenous stimulating drugs. Optimizing the composition of emulsifiers is an effective way to reduce DATS@nanoemulsion intravenous stimulation. Furthermore, the researchers conducted an in-depth analysis of the oil phase components involved in the formulation of nanoemulsion, optimising the preparation process for DATS@nanoemulsion and a subsequent reduction in its effects on venous stimulation.[74] The results shown in Table 1.

DATS Microneedle

Microneedle technology enables effective transdermal drug delivery through the use of small needle arrays that penetrate the skin's stratum corneum, greatly enhancing treatment effectiveness and patient adherence.[81,82] Furthermore, microneedles offer the advantages of being minimally invasive, painless, and user-friendly, presenting a safe and convenient alternative for vaccination, cosmetic applications, and localized treatment of diverse medical conditions. Phototherapy and sonodynamic therapy (SDT) are commonly employed in the synergistic treatment of tumors and have garnered significant attention. However, an unfavorable tumor microenvironment, characterized by altered levels of pH, H_2O_2, oxygen, and glutathione, can diminish the therapeutic efficacy of combined phototherapy and SDT. Herein, a novel Bi-based soluble microneedle (MN) is introduced, specifically designed for CT imaging of breast tumors and the enhancement of phototherapy/sonodynamic therapy (SDT) through starvation therapy and gas therapy.[75] The MN is loaded with glucose oxidase (GOx) and diallyl trisulfide to induce tumor starvation and gas therapy, respectively. Controlled release of GOx and H2S can be achieved under ultrasound or near-infrared laser irradiation. Both in vitro and in vivo results demonstrate the high therapeutic efficacy of this multifunctional MN through the synergistic effect of starvation therapy, gas therapy, and enhanced phototherapy/SDT. This designed multifunctional MN offers a promising approach for synergistic phototherapy and SDT, with the results summarized in Table 1.

DATS Micelle

As an advanced drug carrier, micelles exhibit significant advantages in enhancing drug solubility and achieving precise drug delivery due to their excellent stability and biocompatibility, and are widely used to improve the efficacy of anticancer drugs.[83,84] DATS, a thioether compound, possesses high water insolubility, irritates blood vessels, and undergoes rapid degradation in normal conditions. Therefore, developing an appropriate delivery system for DATS and conducting related stability studies are crucial for its clinical application. Researchers have successfully formulated

a DATS micelle injection through the self-assembly of propylene glycol, ethanol, Tween 80, and water. This formulation effectively mitigates the irritation and degradation of DATS.[76] The high-pressure liquid chromatography-UV assay method was established and validated for the quantitative determination of DATS micellar injection. Gas chromatography-mass spectrometry identified the major degraded compounds as diallyl disulfide and diallyl tetrasulfide. 3-ethenyl-3,6-dihydro-1,2-dithiin and 3-ethenyl-3,4-dihydro-1,2-dithiin might be the thermal decomposed products of DATS in the process of gas chromatography-flame ionization detector analysis. The results are shown in Table 1.

DATS Microspheres

An innovative strategy has been proposed to augment the immunotherapy effect of chitosan in reducing tumor-associated macrophages (TAMs) by continuously generating H_2S to inhibit the growth and metastasis of lung cancer.[77] Chitosan has been proven to effectively reprogram TAMs to hinder cancer metastasis, yet its efficacy hinges on the re-exposure of chitosan from the chemical corona. To achieve this, researchers designed an inhalable microsphere (termed F/Fm) capable of degrading under the influence of lung cancer matrix metalloproteinases, thereby releasing two distinct types of nanoparticles. Under an external magnetic field, these nanoparticles can aggregate and, through enzymatic hydrolysis reactions, re-expose chitosan and release DATS, resulting in the production of H_2S. In vitro experiments have demonstrated that F/Fm successfully reprograms TAMs, promotes the apoptosis of A549 lung cancer cells, and inhibits their migration and invasion capabilities. In a mouse model, F/Fm not only effectively reprogrammed TAMs but also sustained H_2S production in the lung cancer area, significantly inhibiting the growth and metastasis of lung cancer cells. This provides a novel and effective strategy for combining chitosan and H_2S adjuvant chemotherapy in the treatment of lung cancer. The results are summarized in Table 1.

Other Nano-Formulations of DATS

Inflammatory bowel disease (IBD) is an intestinal inflammatory disorder. H_2S donors such as DATS have been used as anti-inflammatory mediators. However, due to its poor water solubility, an ideal method of administering DATS has yet to be established. A self-spraying coating system has been introduced, which is derived from a capsule loaded with DATS and possesses foaming capabilities, specifically designed for the treatment of colitis. This system is referred to as CAP-w-FC.[9] Following the rectal administration of CAP-w-FC into rats bearing colitis and its subsequent dissolution in the intestinal fluid, a spray coating system is self-assembled in situ. This system greatly promotes the dissolution of the poorly water-soluble DATS by producing nano-scaled micellar particles sprayed onto the colorectal tract's large luminal surface. Following colon epithelial cells' internalization of the micellar particles, their loaded DATS reacts with intracellular glutathione to yield H_2S. This exogenous H_2S then diffuses through plasma membranes to carry out its biological functions, including suppressing the overproduction of pro-inflammatory cytokines, inhibiting the adhesion of macrophages on the vascular endothelium, and repairing colonic inflamed tissues. This self-spray coating system may be used as a unique drug delivery technique for covering the large colorectal surface to treat IBD. The demand for non-antibiotic strategies to overcome bacterial biofilm infection resistance is increasing. Someone has proposed a novel "gas-sensitive hyperthermia" strategy that significantly kills bacteria through the intelligent design of Prussian blue-based nanocarriers (MSDG) sealed with metal-organic frameworks (MOFs).[78] Upon reaching the biofilm microenvironment (BME), acidity-triggered degradation of MOF facilitates the release of DATS, which subsequently reacts with glutathione to produce H_2S. This BME-responsive nano antibacterial agent targets biofilms, increasing their sensitivity to thermal radiation and facilitating tissue remodeling via immunomodulation, thus enhancing precision treatment for persistent implant-related infections. The outcomes are presented in Table 1.

Prospects

In recent years, DATS has also shown great potential for medical, food, and chemical engineering applications. It not only exhibits multiple pharmacological effects but also generates synergistic effects when combined with other bioactive substances or therapies. Studies have shown that the combination of DATS and cisplatin enhances antitumor activity while reducing side effects and improving the quality of life in gastric cancer xenograft mice.[85,86] Additionally, the combination of DATS and EGCG demonstrates significant synergistic anticancer effects on skin cancer cell lines,

achieved by inducing apoptosis and regulating related protein expression.[87] In addition to its antitumor effects, DATS can also be used in combination with the antioxidant vitamin C, demonstrating potential protective effects against oxidative stress induced by the semimetal arsenic.[88] In the fields of cardiovascular health, antimicrobial activity, and diabetes management, DATS shows synergistic potential when combined with relevant drugs, such as enhancing cardiovascular protection, improving antimicrobial efficacy, and aiding blood sugar control. However, research on these synergistic effects remains insufficient and requires further validation.

However, despite significant progress in its research, the application of DATS still faces several challenges. Despite DATS exhibiting a range of pharmacological effects, including antioxidant, antibacterial, anti-inflammatory, anticancer, and cardiovascular protective properties, there is a notable absence of corresponding human clinical trial studies. Consequently, it is not feasible to assess the therapeutic efficacy and safety of DATS in the context of various diseases. Furthermore, the bioavailability of DATS is low, especially when administered orally. It is easily degraded by enzymes in the gastrointestinal tract, resulting in a low absorption rate in the body.[89] Therefore, to improve its bioavailability, DATS is more suitable for exploring new drug delivery systems, such as nanocarriers, microcapsules, and other technologies. These technologies can protect DATS from external environmental influences, ensuring its effective release at the target site, especially in anti-tumor therapy.[90] DATS is prone to oxidation and volatilization in air and has poor water solubility, which limits its stability and application efficacy. To address these issues, its stability can be improved through chemical modification, encapsulation techniques (such as microcapsules and nanocapsules), the addition of antioxidants (eg, vitamin E, ascorbic acid), the use of light-protective packaging, or low-temperature storage. Additionally, the use of surfactants (eg, polysorbate 80), cyclodextrin inclusion complexes, or the formation of solid dispersions with carrier materials (eg, polyvinylpyrrolidone) can enhance solubility and reduce volatilization. Furthermore, high doses of DATS may exhibit toxicity to normal cells. This can be mitigated by determining safe dosage levels through pharmacokinetic and toxicological studies, developing targeted delivery systems (eg, antibody-conjugated nanoparticles, ligand-modified liposomes) to reduce toxicity, and employing combination therapies to both lower toxicity and enhance efficacy. Although DATS is considered a safe natural compound, its long-term safety requires further evaluation, and future research should focus on this aspect.[17] Moreover, due to significant variations in the source and quality of DATS in the market, there is an urgent need to establish a unified quality control system to standardize production and application, ensuring its safety and efficacy in medical, food, and other fields, while enhancing market competitiveness.

DATS is still believed to hold vast application potential in the future of pharmaceuticals, chemicals, and food. With the deepening of research into its biological mechanisms and the ongoing advancements in technology, DATS is anticipated to play a pivotal role in the treatment of anticancer, cardiovascular, and antibacterial diseases. However, further solutions are needed to address issues such as low bioavailability and poor stability. Through interdisciplinary collaboration or artificial intelligence analysis, the optimization of DATS in drug design, delivery systems, and production processes will accelerate its applications in anti-cancer, anti-oxidation, and anti-inflammatory fields, enhance market competitiveness, ensure product stability, and reduce costs.[91] In the future, DATS will occupy a prominent position within the pharmaceutical, chemical, and food industries, contributing even more significantly to human health and societal progress.

Conclusion

The potential and value of diallyl trisulfide (DATS) are immense, surpassing current limitations and challenges. Its unique bioactivity and multifaceted functions have had a significant impact on many industries. As research continues to advance, our understanding of DATS's mechanisms and application areas is becoming increasingly refined. Notably, the integration of DATS with nano-drug delivery systems has opened new directions for its application. Nanotechnology can enhance the bioavailability, targeting, and stability of DATS, thereby improving its efficiency in drug delivery and reducing potential side effects. DATS is poised to become a cornerstone in drug development and health management. Its widespread applications in the pharmaceutical, food, and chemical industries offer broader prospects for scientific research, human health, and societal progress. By further exploring the synergistic effects of DATS and nanotechnology, more precise and efficient therapeutic strategies can be achieved in the future, driving innovative applications across multiple fields.

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Disclosure

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