

Review

Layered double hydroxide-induced modulation of oxidative stress in disease therapy

Jun Wang^{a,1}, Ouyang Su^{b,1}, Zhaoxu Meng^{c,1}, Lili Lu^b, Yake Qi^b, Zonghui Zhang^d, Zhou Li^{e,f}, Xiu Dong^{g,*}, He Lian^{c,*}, Yiping Mu^{h,*}

^a Graduate School, Liaoning University of Traditional Chinese Medicine, Shenyang, Liaoning 110847, China

^b Wuyi college of Innovation, Shenyang Pharmaceutical University, Shenyang 110016, China

^c School of Medical Devices, Shenyang Pharmaceutical University, Shenyang 110016, China

^d School of Pharmacy, Shenyang Pharmaceutical University, Shenyang 110016, China

^e Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing 100084, China

^f School of Biomedical Engineering, Tsinghua University, Beijing 100084, China

^g School of Basic Medical Sciences, Liaoning University of Traditional Chinese Medicine, Shenyang, Liaoning 110847, China

^h Central Hospital Affiliated to Shenyang Medical College, Shenyang 110024, China

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ABSTRACT

Oxidative stress plays a crucial role in the development of various diseases, including diabetes, cardiovascular diseases, cancer, and rheumatic disorders. It disrupts the redox balance and initiates a series of pathological changes. As two-dimensional inorganic solids with an open structure and anion-exchange properties, layered double hydroxides (LDHs) offer significant advantages in the biomedical field, such as drug carriers, antioxidant catalysts. This article outlines application of LDHs in the treatment of cancer, rheumatic diseases, bone disorders, diabetes, Alzheimer's disease, and other conditions. More importantly, this paper elaborates on the challenges faced by the application of LDHs, including the biological activity to be explored, the performance to be optimized, and their *in vivo* functions and molecular mechanisms to be clarified. The solution strategies have also been discussed, which pointed out the direction for promoting the clinical transformation and application of LDHs in the future.

Statement of Significance

1. This article systematically summarizes the preparation methods and properties of LDHs, with a focus on describing their mechanism in treating oxidative stress-related diseases.
2. The challenges faced by LDHs in clinical translation have been analyzed in detail, including issues such as synthesis standardization, biological activity and safety, as well as the precision of targeting and controlled release.
3. The solutions to the current problems have also been elaborated in detail, such as constructing matrix composites with inorganic compounds to optimize structure and performance, and using artificial intelligence to assist in material design, etc. All these will bring revolutionary changes to the realization of clinical transformation and the treatment of related diseases.

1. Introduction

In the intricate operating system of human body, redox balance maintains the stable function of various systems and organs, serving as a cornerstone of health [1]. However, a variety of factors, both endogenous and exogenous, constantly threaten this balance. Oxidative stress occurs when the body is exposed to harmful stimuli that disrupt the equilibrium between oxidative and antioxidant effects [2]. Oxidative stress, a critical factor in the development of numerous diseases, initiates a cascade of pathological changes akin to a domino effect, leading to a diverse array of serious consequences for the organism. It has become a major global health challenge.

For instance, in various major diseases such as diabetes [3],

* Corresponding authors.

E-mail addresses: dongyanxiu11@163.com (X. Dong), lianhe126@126.com (H. Lian), yiping.mu@symc.edu.cn (Y. Mu).

¹ These authors contributed equally to this work.

cardiovascular diseases [4], cancer, neurodegenerative disorders and rheumatic diseases [5,6], oxidative stress plays a central role. Although the existing treatment strategies (such as antioxidants, traditional drugs) have achieved certain results, they still generally encounter problems such as poor targeting, low bioavailability, easy development of drug resistance, and side effects [7]. Therefore, developing a new type of nanotherapy platform that can precisely regulate the oxidative stress microenvironment at the lesion site holds extremely significant clinical and social importance. This is also the urgency for writing this review.

In recent years, the rapid development of nanomaterials science has provided a new opportunity to address these challenges [8]. Among them, layered double hydroxides (LDHs) are a type of anionic clay material with unique two-dimensional layered structure and tunable chemical composition. Due to their simple preparation process, large specific surface area, good biocompatibility, and the ability to exchange ions between layers, they have shown great potential in various fields [9]. It is particularly noteworthy that the research on LDHs in the fields of energy and environmental catalysis has reached a profound and mature level. For instance, LDH-based materials are widely used to construct highly efficient p-n heterojunction photocatalysts (such as $\text{MoS}_2/\text{NiFe-LDH}$), which are employed for the photocatalytic degradation of organic pollutants and the decomposition of water for hydrogen production. The Z-type charge transfer mechanism of these materials significantly enhances the separation efficiency of photogenerated electron-hole pairs [10,11]. In the field of electrochemical energy storage and conversion, the composite structure of LDH and carbon-based materials (such as graphene, g- C_3N_4) (e.g., NiFe-LDH/graphene) effectively overcomes the drawback of poor conductivity of single LDH, and is widely applied in supercapacitors and efficient electrocatalysts, demonstrating excellent current density and stability [12–14]. Furthermore, through advanced synthesis strategies such as the

methanamide-assisted hydrothermal method, materials with three-dimensional open porous structures can be prepared, such as MgCr-LDH . Their remarkable photoelectrochemical (PEC) properties have further expanded their applications in the field of clean energy [15]. The above researches have fully demonstrated the powerful capabilities and high flexibility of LDHs as a functional nanoscale platform in material design, performance regulation, and composite enhancement.

However, compared to the abovementioned traditional fields, LDHs still represent a dynamic but under-explored frontier in biomedical field, particularly in the precise treatment of diseases related to oxidative stress. The uniqueness of LDHs lies in their inherent physical and chemical properties of LDHs, such as their catalysis, adsorption, and ion-exchange capabilities, which have been ingeniously applied in the complex internal environment of living organisms, thereby achieving various functions, such as targeted drug delivery, intelligent regulation (generation, removal, or conversion) of reactive oxygen species (ROS), and remodeling of the immune microenvironment [16–18]. For instance, the Fenton-like reaction catalytic activity of LDHs can be utilized for the chemical kinetic therapy of tumors [19]; the redox properties of the layer-bound metal ions (such as $\text{Ce}^{3+}/\text{Ce}^{4+}$, Mg^{2+}) can be employed to eliminate excessive ROS for anti-inflammatory purposes [20]; and the interlayer space can serve as an ideal carrier for various therapeutic molecules (such as small molecule drugs, genes, proteins) [21]. This functional shift and innovation from “industrial catalysis” to “biological regulation” is precisely the core focus of this review and also the unique value that distinguishes it from other reviews.

Based on this, this review aims to conduct a comprehensive and in-depth review and outlook on the application of oxidative stress regulation mediated by LDHs in disease treatment (Fig. 1). First, we systematically elaborate on the key mechanisms of oxidative stress in various

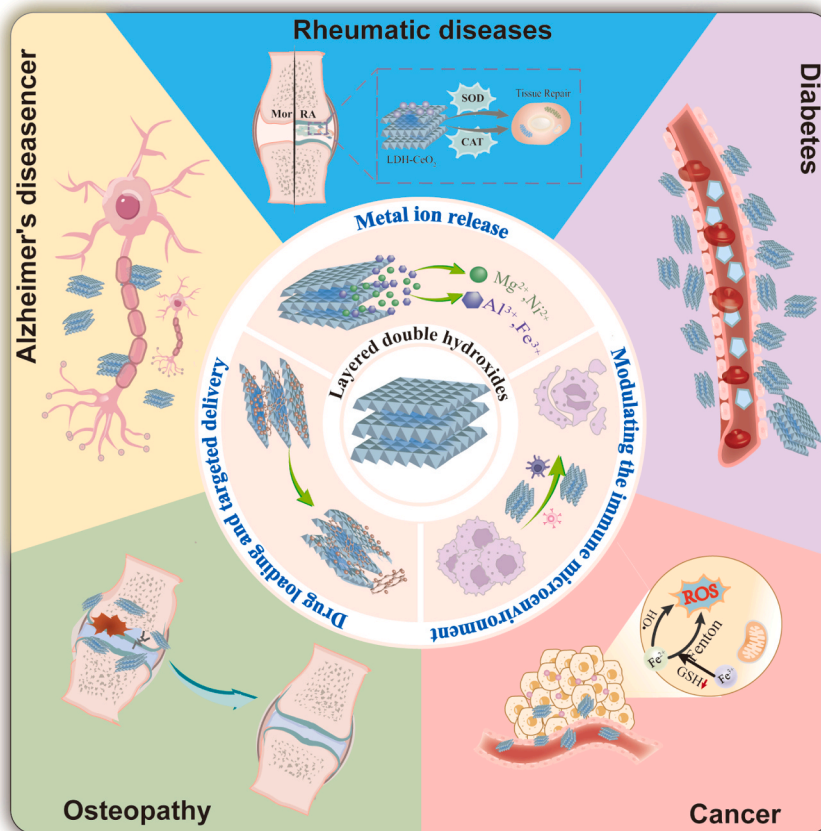


Fig. 1. Two-dimensional LDHs exhibit distinct advantages in the biomedical field and demonstrate exceptional potential for the treatment of diseases related to oxidative stress.

diseases. The we focus on introducing LDHs as an emerging biomaterial, highlighting the structure-function relationship in terms of antioxidant, catalytic, and drug-loading functions. Furthermore, we will elaborate in detail on the synthesis methods, modification strategies, as well as their latest application progress and mechanism of action in the treatment of major diseases such as cancer, rheumatic diseases, bone disorders, diabetes, and Alzheimer's disease. Finally, we will critically analyze the main challenges currently faced in the clinical translation of LDHs (such as synthesis standardization, biological safety, targeted precision, etc.), and provide an outlook on future research directions. Through the systematic summary and in-depth discussion in this review, we hope to provide researchers with solid theoretical basis and innovative ideas when designing advanced nanomedicines based on LDHs for the treatment of oxidative stress-related diseases.

2. Mechanisms of oxidative stress in disease

This section explores the potential effects of oxidative stress on various diseases, including diabetes, cardiovascular disease, cancer, inflammatory disorders, and neurodegenerative conditions. The specific mechanisms underlying these effects are detailed in Table 1 :

In diabetes, elevated blood glucose levels trigger a series of reactions, including increased glycolysis and sorbitol pathway activation, which leads to excessive production of free radicals and heightened oxidative stress [22]. This not only disrupts the normal function of insulin, leading to insulin resistance and affecting the uptake and utilization of glucose by various tissues in the body, but it also closely linked to multiple complications, such as cardiovascular lesions, neuropathy, and retinopathy, significantly reducing the quality of life of patients [23]. In cardiovascular diseases, obesity and associated metabolic disorders contribute to the formation of oxidized low-density lipoprotein, which triggers vascular endothelial dysfunction and thrombosis. Oxidative stress further impairs cardiac function, ultimately leading to atherosclerosis and heart failure, which pose significant threats to human life and health [24].

Oxidative stress also plays a crucial role in the development of cancer. Abnormal metabolism in cancer cells produces a significant amount of free radicals, which can alter gene expression, promote proliferation, invasion, and metastasis, and inhibit apoptosis, this complexity makes cancer treatment a considerable challenge [25]. Moreover, inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease, and kidney disease, are strongly associated with oxidative stress. Oxidative stress causes cartilage damage in rheumatoid arthritis. For inflammatory bowel disease, intestinal inflammation induces oxidative stress and compromises the integrity of the intestinal epithelial barrier [26]. For kidney disease, inflammation and immune activation lead to kidney damage, while oxidative stress further exacerbates the condition, potentially progressing to end-stage renal disease.

In the field of neurodegenerative diseases, both Alzheimer's disease and Parkinson's disease are significantly influenced by oxidative stress [27]. The central nervous system is highly susceptible to oxidative damage because of its unique physiological structure and functions. In Alzheimer's disease, oxidative stress contributes to the abnormal aggregation of β -amyloid and tau proteins, which triggers neuronal death and cognitive decline [28]. Parkinson's disease leads to impaired motor control due to the loss of dopaminergic neurons and the aggregation of α -synuclein [29].

In conclusion, oxidative stress plays a crucial role in the occurrence and development of major diseases such as cancer and diabetes through disrupting the intracellular redox balance. These mechanisms cover a series of pathological processes ranging from excessive generation of free radicals, abnormal activation of signaling pathways to impaired cellular functions. A thorough understanding of these mechanisms serves as a crucial theoretical foundation for the subsequent design of targeted intervention strategies based on LDHs.

Table 1
The Influence Mechanism of Oxidative Stress on Diseases.

Disease type	Influence Mechanisms	Concrete performance	Literature examples
Diabetes	Islet function impairment	ROS can directly damage the DNA, proteins and lipids of pancreatic β cells, leading to cell apoptosis or functional impairment, resulting in reduced insulin secretion and aggravated hyperglycemia state.	[30]
	Metabolic disorders	Oxidative stress inhibits the activity of key enzymes involved in glucose metabolism (such as hexokinase and pyruvate kinase), causing disorders in glucose metabolism and leading to a decline in glucose clearance efficiency.	[31]
	Vascular complications	ROS can damage vascular endothelial cells, disrupt permeability, induce thickening of the basement membrane (such as the renal glomerular basement membrane), and promote vascular occlusion and tissue ischemia.	[32]
Cardiovascular diseases	Disruption of vascular homeostasis	Oxidative stress can promote the expression of adhesion molecules (such as VCAM-1 and ICAM-1) within endothelial cells, attract the adhesion and infiltration of inflammatory cells, intensify vascular wall inflammation, and disrupting the barrier function and anticoagulant performance of the vascular endothelium.	[33]
	Abnormal activation of smooth muscle cells	Oxidative stress promotes the transformation of vascular smooth muscle cells from a contractile to a synthetic phenotype by activating signaling pathways such as mitogen-activated protein kinase (MAPK), thereby enhancing their proliferation and migration capabilities.	[34]
	Promotion of thrombosis	Oxidative stress can damage the anticoagulant function of vascular endothelium,	[35]

(continued on next page)

Table 1 (continued)

Disease type	Influence Mechanisms	Concrete performance	Literature examples
Cancer	Induction of DNA damage and mutations	promote platelet activation and aggregation, stimulate the production of coagulation factors, and inhibit the activity of the fibrinolytic system.	[36]
		Excessive ROS attacks the DNA of cells, causing damage such as base oxidation and breakage, leading to the activation of oncogenes (such as Ras, Myc) or the inactivation of tumor suppressor genes (such as p53, PTEN), thereby promoting the transformation of normal cells into cancer cells.	
	Promotion of cancer cell proliferation	Oxidative stress can activate multiple cell proliferation signaling pathways such as PI3K/Akt and MAPK/ERK, stimulating the uncontrolled proliferation of cancer cells.	[37]
Inflammatory diseases	Influence on the tumor microenvironment	Oxidative stress can enhance the inflammatory response in the tumor microenvironment and attract the infiltration of inflammatory cells such as macrophages. The cytokines secreted by these cells will further promote oxidative stress and the development of tumors.	[38]
	Activation of inflammatory signaling pathway	ROS can directly activate key inflammatory signaling pathways such as NF-κB and MAPK, prompting inflammatory cells to release pro-inflammatory factors such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6).	[39]
	The disruption of immune cells balance	Oxidative stress promotes the polarization of pro-inflammatory macrophages (M1 type), enhances their pro-inflammatory activity, and simultaneously inhibits the functions of anti-inflammatory immune cells (such as regulatory T cells), weakening the inflammatory	[40]

Table 1 (continued)

Disease type	Influence Mechanisms	Concrete performance	Literature examples
Neurodegenerative diseases	Inhibition of antioxidation and repair	suppression mechanism. Long-term oxidative stress will deplete endogenous antioxidant substances such as glutathione (GSH) and superoxide dismutase (SOD), weakening the antioxidant defense system in the body; ROS inhibits the activity of tissue repair-related factors, hinders the regeneration and repair of damaged tissues, and prolongs the inflammatory process.	[41]
		Oxidative stress causes conformational changes in specific proteins in neurons through oxidative modification, leading to the loss of normal functions and an increase in aggregation tendency.	[42]
	Abnormal protein aggregation and deposition	Abnormal protein deposition forms amyloid plaques, Lewy bodies, etc., causing damage to neurons.	[43]
	Disruption of intracellular calcium homeostasis	ROS can damage the calcium channel functions of neuronal cell membranes and endoplasmic reticulum, resulting in abnormal elevation of intracellular Ca ²⁺ concentration.	
	Disruption of mitochondrial function	Excessive Ca ²⁺ ions activate calcium-dependent proteases (such as caspases), accelerating protein degradation and neuronal apoptosis.	[44]
		Oxidative stress can damage mitochondrial DNA (mtDNA) and respiratory chain complexes, leading to mitochondrial dysfunction. The released cytochrome c and other substances can trigger the neuronal apoptosis pathway and accelerate neuronal death.	

3. The advantages of LDHs

LDHs, a class of layered materials characterized by their two-dimensional nanostructures, are also referred to as hydrotalcites, hydrotalcite-like materials, or anionic clays. They primarily consist of positively charged lamellae and interlayer anions [45]. The chemical formula for LDHs is $[M_{1-x}^{2+}M_x^{3+}(\text{OH})_2]^x A_{x/n}^{n-} \cdot z\text{H}_2\text{O}$, where M^{2+} and M^{3+} denote the divalent and trivalent metal ions, respectively, and A^{n-} represents the interlayer equilibrium anion. The open structure and unique anion-exchange properties contributed to their distinctive advantage in biomedical applications (Fig. 2).

3.1. Structure-activity relationship

The regulatory activities of LDHs on ROS including generation, clearance, transformation, and targeted regulation are clearly related to their core physicochemical properties, such as metal cation composition, interlayer anion type, morphological size, and modification method. This association serves as the core foundation for achieving “material function customization - precise disease treatment” and is also a key gap in this research field:

3.1.1. The role of cation ions

The types, oxidation states, and molar ratios of metal cations in LDHs directly determine the “direction” (production of ROS / removal of ROS) and “intensity” of ROS regulation, and are the core driving factors of the structure-activity relationship [46]. By relying on the catalytic ability of some cations, Fe^{3+} , Ni^{2+} , Co^{2+} , etc. in LDHs act as typical catalysts for Fenton/Fenton-like reactions that produce ROS, and they can further amplify ROS damage by consuming GSH [47]. The redox cycling capabilities relying on other cations, such as Ce^{3+} , Mn^{2+} , and Mg^{2+} are the main ions for eliminating ROS [48]. Biocompatible ions (Mg^{2+} , Zn^{2+}) can be co-doped with catalytic ions to achieve functional complementarity,

and the molar ratio regulates the activity intensity.

3.1.2. The role of anion ions

The inter-layer anions optimize the targeting and persistence of ROS regulation through different mechanisms [49]. Inorganic anions, such as Cl^- and CO_3^{2-} , regulate the release of cations through by controlling the rate of ion exchange rate and through pH buffering effects [50]. Organic or biological active anions (phenols, ascorbic acid) directly participate in ROS reactions, forming an “adsorption - catalysis - regeneration” cycle, thereby enhancing the sustainability of regulation [51].

3.1.3. Morphology and modification methods

The 50–120 nm nanosheets can enhance the exposure of active sites due to their high specific surface area, and are easily internalized by tumor cells and macrophages, enabling precise regulation of intracellular ROS [52]. The micron-sized LDHs (1–5 μm) is suitable for local sustained-release, such as joint cavity administration, as it can slowly release the active ingredient, thereby continuously regulating local oxidative stress [53]. Furthermore, surface modifications (such as BSA and chitosan) can prolong the circulation time in the body, while the composites formed with metal nanoparticles (Au NPs) will enhance the catalytic or photothermal - ROS synergistic effects [54].

3.2. Effective catalyst

Since the surface of LDHs is uniformly covered by tri-coordinated hydroxyl groups, it can participate in the catalytic redox process and serve as reaction sites [55], fundamentally addressing the issue of oxygen vacancy deactivation commonly encountered in metal oxide catalyst systems. Meanwhile, the robust H-transfer redox mechanism in LDHs system is the key reason for the exceptional activity and reaction selectivity of LDHs catalysts.

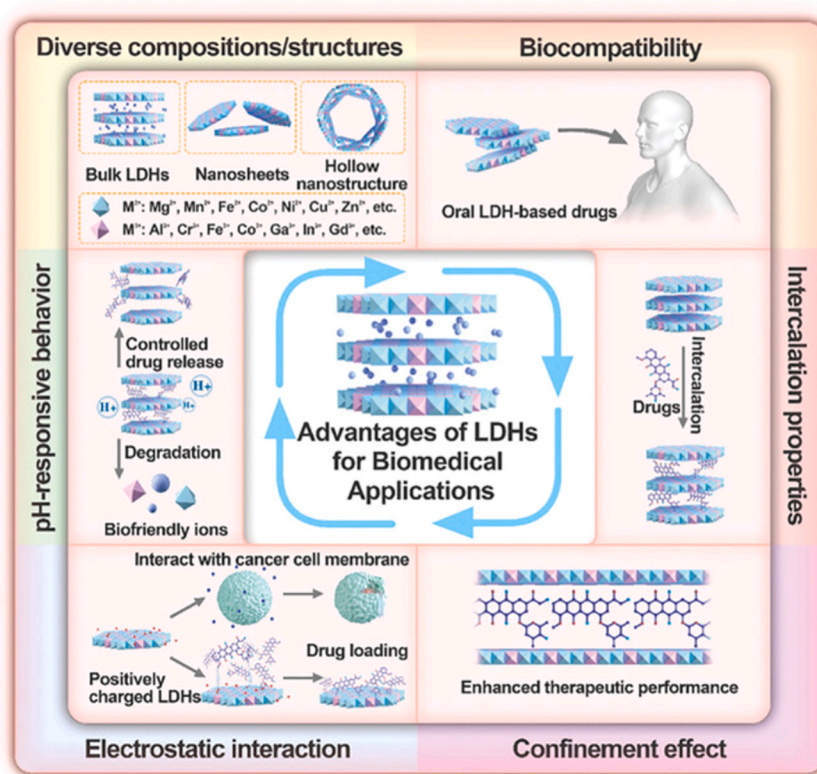


Fig. 2. Diagrammatic presentation of the characteristics and advantages of LDH-based nanomaterials for biomedical applications. Reproduced and adapted with permission from ref [64]. Copyright (2022) Chem Soc Rev.

3.3. Effective drug carrier

Their structure of LDHs is similar to that of hydro magnesite, in which $\text{Mg}(\text{OH})_2$ is incorporated within a layer of hydro magnesite, each Mg^{2+} ion is surrounded by six OH^- ions arranged in octahedral geometry, with the octahedra sharing edges to form an infinite two-dimensional layer. LDHs nanosheets stratify LDHs into individual highly anisotropic layers. The layered LDHs nanosheets can function as both carriers and active substances [56], providing innovative applications as building blocks for the development of various functional nanocomposites and nanostructures. The laminar structure and ion-exchange properties of LDHs can also be utilized for bioimaging. By immobilizing imaging reagents in the interlayer space or on the surface, and loading various imaging agents, such as fluorescent dyes and paramagnetic metal ions [57], the imaging signals could be enhanced and modulated. Moreover, as the drug carrier, LDHs can significantly enhance the stability and bioavailability of medications while minimizing their side effects. For example, chemotherapeutic agents such as methotrexate and doxorubicin are encapsulated in LDHs to facilitate controlled release and targeted delivery [58].

3.4. Comprehensive therapeutic strategies for LDHs

LDHs can be treated with gene therapy, immunotherapy [59], and chemo-dynamic therapy [60]. In gene therapy, LDHs can protect genes from degradation and enhance the transfection efficiency [61]. In immunotherapy, it can serve as a carrier for nano-vaccines, activating antigen-presenting cells and enhancing the immune response of the body. In chemo-dynamic therapy, the catalytic activity of metal ions in LDHs is utilized to generate active substances such as hydroxyl radicals, inducing apoptosis of tumor cells [62]. LDHs can also be combined with other biomaterials to construct tissue engineering scaffolds with exceptional properties, such as those used for bone and nerve repair, offering innovative material options for the advancement of tissue engineering and regenerative medicine. By modulating the composition and structure of the scaffolds, it is possible to promote cell proliferation, differentiation, and tissue regeneration, thereby facilitating the repair of damaged tissues and organs. In addition, LDHs also possess antimicrobial properties, as it can release active metal ions, such as zinc ions and manganese ions [63]. It can inhibit the growth and reproduction of bacteria by damaging the cell membrane structure, or it can load antimicrobial drugs to achieve controlled release and enhance its antimicrobial effect.

This section systematically analyzes the core advantages of LDHs as biomedical materials, which are rooted in their unique layered structure and tunable physical and chemical properties. We focused on discussing the relationship between structure and function, that is how the types/valence states of metal cations, interlayer anions, morphological size, and modification methods directly determine their regulation function on ROS (i.e., production or elimination). Furthermore, LDHs can serve as efficient catalysts, drug/gene carriers, and can integrate multiple therapeutic strategies (such as chemodynamic therapy and immunotherapy), providing a multifunctional platform for achieving the integration of precise diagnosis and diseases treatment.

4. Preparation and modification of LDHs

4.1. The preparation of LDHs

Due to their unique structure and properties, the preparation process of LDHs is influenced by factors such as raw materials and methods. Variations in preparation conditions can cause differences in the structure and properties of the final products. At present, the laboratory preparation methods for LDHs include co-precipitation, hydrothermal synthesis, and ion exchange methods, etc.

Among them, co-precipitation is a widely used method. Muráth, S.,

et al. used metal salts and bases as raw materials to produce precipitates, which was subsequently processed to obtain LDHs. For example, when preparing MgAl-LDH , magnesium salts and aluminum salts were mixed in a certain proportion to form mixed salt solution. Under stirring, sodium hydroxide solution is gradually added. It is crucial to control the conditions, such as temperature, pH, and other conditions. After the reaction, the precipitate is subjected to centrifugation, washing and drying, and MgAl-LDH can be obtained [65]. The method is relatively simple to operate and can ideally control the composition and structure of the product. However, it requires stringent reaction conditions, and variations in these conditions can significantly impact the properties of the final product.

Gutiérrez Galán, D. K., et al. also prepared LDHs complexed with lycopene, they first dissolved metal salts (e.g., MgCl_2 , ZnCl_2 , AlCl_3 , etc.) in water (sodium carbonate was added if necessary), then added the alcohol solution of lycopene, mixed evenly, and adjust the pH to 9.5. After continuous stirring for 24 h, the composite LDHs was obtained through subsequent centrifugation, washing, and drying [7].

This process also employs the principle of co-precipitation, further demonstrating the flexibility of this method in practical applications. By altering the raw materials and reaction conditions, allowing for the creation of various functional LDHs composites with different functions can be prepared.

The hydrothermal method is often utilized in combination with co-precipitation method. Based on the co-precipitation method, the reaction solution is transferred to an autoclave, where the LDHs are generated in a high-pressure hot alkaline solution through heating. Somosi, Z., et al. re-dispersed the LDHs precursor in water, transferred it to a stainless steel high-pressure reactor (with PTFE), sealed, and placed in an oven for 24 h at 120°C [66]. Compared to the conventional co-precipitation method, the hydrothermal method offers higher reaction temperature and pressure, creating a more favorable environment for the growth of LDHs nuclei, improving the structural stability and performance of LDHs. For instance, N.A. Kamal, et al. prepared MgAl/NiAl/ZnAl LDH through an alkali-free hydrothermal method. They utilized the “memory effect” to reconstruct the structure through a process of “precipitation-calcination-hydrothermal rehydration” [67]. This product has a high degree of crystallinity and large grain size. Compared with the traditional alkali precipitation method, the hydrothermal method not only avoids product contamination but also significantly increases the grain size and specific surface area of LDH [68].

The ion exchange method utilizes the exchangeability of ions between the layers of LDHs for preparation. Muráth, S., et al. demonstrated that the reaction of a solution containing target ions with the prepared LDHs can enable the exchange of target ions into the interlayer of LDHs. For example, when preparing organic anion-intercalated LDHs, a solution containing organic anions is mixed with LDHs and stirred under specific conditions. The organic anions will exchange with the original anions between the LDHs layers, thereby obtaining the organic anion-intercalated LDHs [65]. This method can regulate the interlayer structure of LDHs, introduce ions or molecules with specific functions, and endow new properties to LDHs. It has significant application value in the preparation of LDHs materials with specialized functions to meet the diverse needs of various biomedical fields.

Moreover, the microwave-assisted synthesis technology has successfully prepared advanced nanocomposites with superior performance, such as NiAl layered double hydroxide (LDH)/reduced graphene oxide (RGO) [69] or high-performance NiFe layered double hydroxide (LDH)/polyaniline (PANI) and other nanocomposite materials [70]. Through the rapid and uniform heating by microwave, the NiAl-LDH nanosheets can be uniformly loaded on the surface of RGO, effectively suppressing the agglomeration of graphene, and its specific surface area and pore volume are higher than that of pure LDH. In addition, the NiFe-LDH produced by in-situ growth in the PANI network can form a porous structure, and the resulting product exhibits excellent

performance. Meanwhile, the introduction of new materials into LDH not only enhances the electrical conductivity of the material and accelerates charge transfer, but also increases additional pseudo-capacitance, making it a highly promising electrode material for supercapacitors.

Finally, homogeneous precipitation method and ultrasonic-assisted methods are also frequently used in the preparation of LDHs [71]. [72], The former forms LDHs by slowly generating a precipitate agent in solution, causing metal ions to participate uniformly. For example, under specific conditions, urea is hydrolyzed to produce ammonium hydroxide, which facilitates the precipitation of metal ions to form LDHs [73]. The latter employs the energy of ultrasonic radiation to accelerate the reaction rate of the metal salt solution and facilitate the formation of LDHs. Ultrasonic radiation can enhance the mass and heat transfer efficiency of the reaction, thereby obtaining LDHs with higher crystallinity and smaller particle size [74].

The preparation method of LDHs can be selected and optimized according to the type, performance requirements and the experimental conditions. During the preparation process, it is essential to control the reaction conditions, such as the ratio of metal ions, the pH of the solution, the reaction temperature, and the duration of the reaction, to ensure the production of LDHs with optimal performance.

4.2. Modification of LDHs

LDHs can be efficiently prepared using the above-mentioned methods. However, similar to many other nanomaterials, LDHs often demonstrates instability in complex physiological environments [75]. Therefore, it is essential to improve the stability of LDHs through modification [76,77]. This not only enables the attachment of ligand to the nanostructure for targeted delivery [78], but also imparts a variety of functions to LDHs, including flexibility, intracellular uptake, stability, and biocompatibility [79]. [80],

The modification process of LDHs involves several aspects, including surface modification, intercalation modification, composite modification, and morphology control. According to different application requirements and research purposes, appropriate modification methods

can be selected to optimize LDHs, as illustrated in Table 2.

This section reviews the classic and advanced synthesis strategies of LDHs, such as co-precipitation, hydrothermal synthesis, and ion exchange, as well as key modification techniques such as surface, intercalation and composite modifications. These methods collectively determine the final morphology, size, stability and biological function of LDHs. By precisely controlling the synthesis and modification parameters, the physicochemical properties of LDHs can be “customized on demand”, thus meeting the specific requirements for material performance in different disease treatment scenarios.

5. Application of LDHs in disease treatment

Oxidative stress is closely related to the development of various diseases. In-depth research on the regulatory mechanisms of oxidative stress induced by LDHs materials is conducive to the development of more effective therapeutic methods and provides a theoretical foundation for them. LDHs materials have demonstrated multiple advantages in diseases treatment.(Fig. 3)

5.1. Cancer

Malignant tumors are one of the most major diseases that seriously threaten public health and have a profound impact on global human health [93]. The tumor microenvironment possesses distinct physiological characteristics, such as hypoxia acidic pH, and elevated concentration of glutathione (GSH). These factors can influence drug absorption, distribution and metabolism of drug, ultimately diminishing the efficacy, which underscores the necessity for alternative therapeutic strategies [94]. Nano-catalytic tumor therapy, as an innovative and effective modality for cancer treatment, has been extensively developed in recent years.

Recently, nano-systems based on LDHs have garnered significant interest in the field of antitumor research due to their convenient fabrication, good biocompatibility, easy modification, and high chemical stability [95]. As a typical two-dimensional nanosheet, LDHs contains divalent and trivalent metal ions (e.g., Fe^{2+} , Fe^{3+} , Ni^{2+} , and Co^{2+})

Table 2
The modification method for LDHs.

Modification type	Concrete method	LDH Modification Example	Effectiveness Analysis	Literature examples
Surface modification	Non-covalent modifications- Biomolecular modification	LDH-BSA CS-LDH	Biomolecules bind to the surface of LDHs through non-covalent interactions, including electrostatic interactions, hydrogen bonding, and van der Waals forces to enhance biocompatibility and stability.	[81]
	Non-covalent modifications- Fluorescent molecular modification	RITC-LDH LDH-NH-Cy5.5	Fluorescent molecules, such as fluorescein and rhodamine, bind to the surface of LDHs to prepare LDHs with fluorescent labeling capabilities for bioimaging, drug tracking, etc.	[82]
	Covalent modification- Hydroxyl functionalization	FITC-LDH ANTS-LDH APTS-LDH	Utilizing the hydroxyl functional group on the surface of LDHs, other functional groups such as amino and carboxyl groups are introduced into the surface through chemical reactions.	[83]
	Covalent modification- Ligand modification	P-NiAl-LDH	Ligands with specific biological activities bind to LDHs, regulating enzyme activity and interactions with other molecules.	[84]
Intercalation modification	Organic molecular intercalation	EA-LDH DBHP-LDH	Organic molecules such as phenols are inserted into the interlayer space of LDHs to improve antioxidant properties and facilitate controlled drug release.	[85,86]
	Metal ion intercalation	MnFe-LDH FeAl-LDH	Metal ions, such as iron and manganese ions are inserted into the interlayers of LDHs to modify their properties through redox or catalytic reactions.	[87,88]
Compound modification	Composite with metal nanoparticles	Mg-M-Al LDH (M = Fe, Co, Ni, Cu, Zn)	Metal nanoparticles are combined with LDHs to enhance their mechanical properties, thermal stability, functional diversity and dispersibility, etc.	[89]
	Composite with polymer	DEX-CM- β -CD@LDH-GS MgGa-LDH-DNA	The composite materials of polymers and LDHs improved dispersion and stability, and can be used in drug delivery, tissue engineering, etc.	[90]
Morphology control	Dimension control	MgAl-LDH nanosheet CoMo-LDH nanosheet	By adjusting reaction conditions, the grain size and morphology of LDHs can be controlled to affect cytotoxicity and biocompatibility.	[91]
	Structural control	LDH-TPS LDH-OBS LDH-DBS	LDHs with varying layer spacings and crystal structures affects its ion exchange capacity and adsorption properties.	[92]

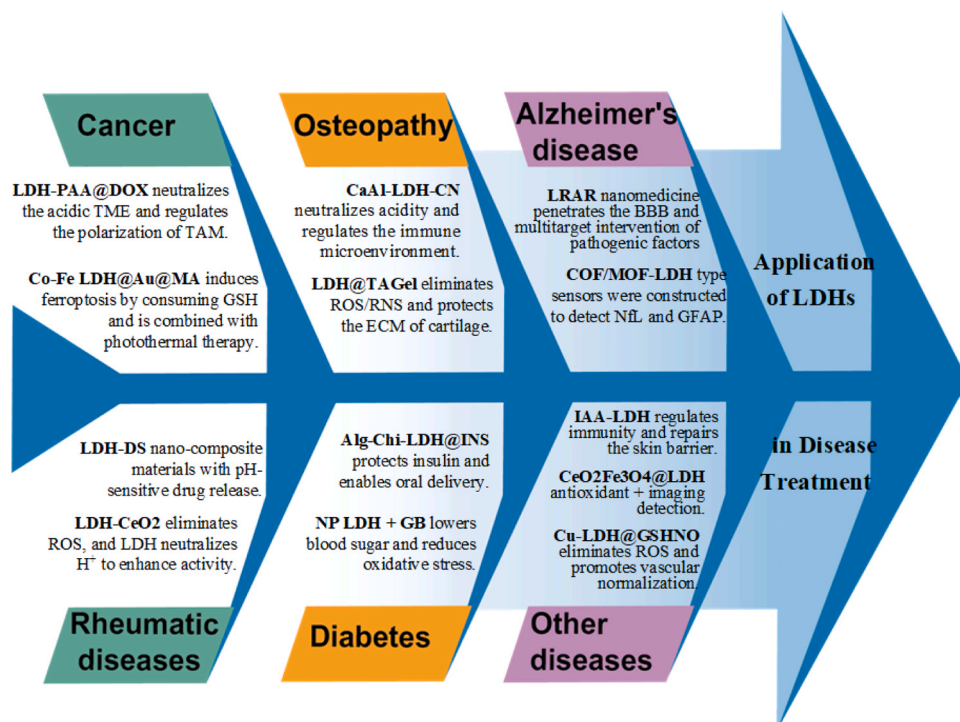


Fig. 3. The regulatory mechanism of oxidative stress induced by LDHs and their typical applications in different diseases.

that can catalyze the generation of ROS from H₂O₂ under specific conditions. These ROS induce oxidative stress in tumor cells and destroy intracellular biomolecules such as lipids, proteins, and DNA, ultimately leading to the death of tumor cells. For example, Pan, Q., et al. prepared Fe/Ni-LDH using metal salts containing Fe³⁺ and Ni²⁺ as precursors (Fig. 4a). Iron (Fe) atoms strongly interact with nickel (Ni) atoms in Fe/Ni-LDH, showing significantly enhanced ROS catalytic activity. A large number of hydroxide ions (·OH) and superoxide radicals (O₂^{·-}) are generated for chemo-dynamic therapy. *In vitro* and *in vivo* experiments have demonstrated that Fe/Ni-LDH biocatalysts serve as a potent nanoplatform for inhibiting tumor proliferation and killing tumor cells (Fig. 4b-d) [96].

Li, S., et al. utilized cobalt nitrate hexahydrate (Co(NO₃)₂·6 H₂O) and iron nitrate nonahydrate (Fe(NO₃)₃·9 H₂O) to prepare Co-Fe LDH nanosheets using co-precipitation method. The cobalt (Co) and iron (Fe) elements in its structure act synergistically, using hydrogen peroxide (H₂O₂) in tumor microenvironment to undergo Fenton or Fenton-like reactions, producing ROS such as hydroxyl radicals (·OH) [97]. It is worth noting that the surface chemical engineering of two-dimensional single-element materials (Xenes) has provided a new direction for tumor photodynamic therapy. Two-dimensional H-Germanene has expanded its band gap to 1.65 eV through H-termination surface modification, becoming a new type of inorganic photosensitizer that can generate singlet oxygen (¹O₂), and has good biodegradability and potential for cancer treatment [98]. This strategy can achieve efficient synergy with the characteristics of LDHs. H-germanene can be loaded onto the surface or interlayer of LDHs through electrostatic interaction or interlayer insertion, and by taking advantage of the pH sensitivity of LDHs, targeted release can be achieved at the tumor site. Meanwhile, the ROS catalyzed by LDHs and the photodynamic therapy mediated by H-germanene form a synergistic effect, further amplifying oxidative stress damage and enhancing the tumor-killing efficiency.

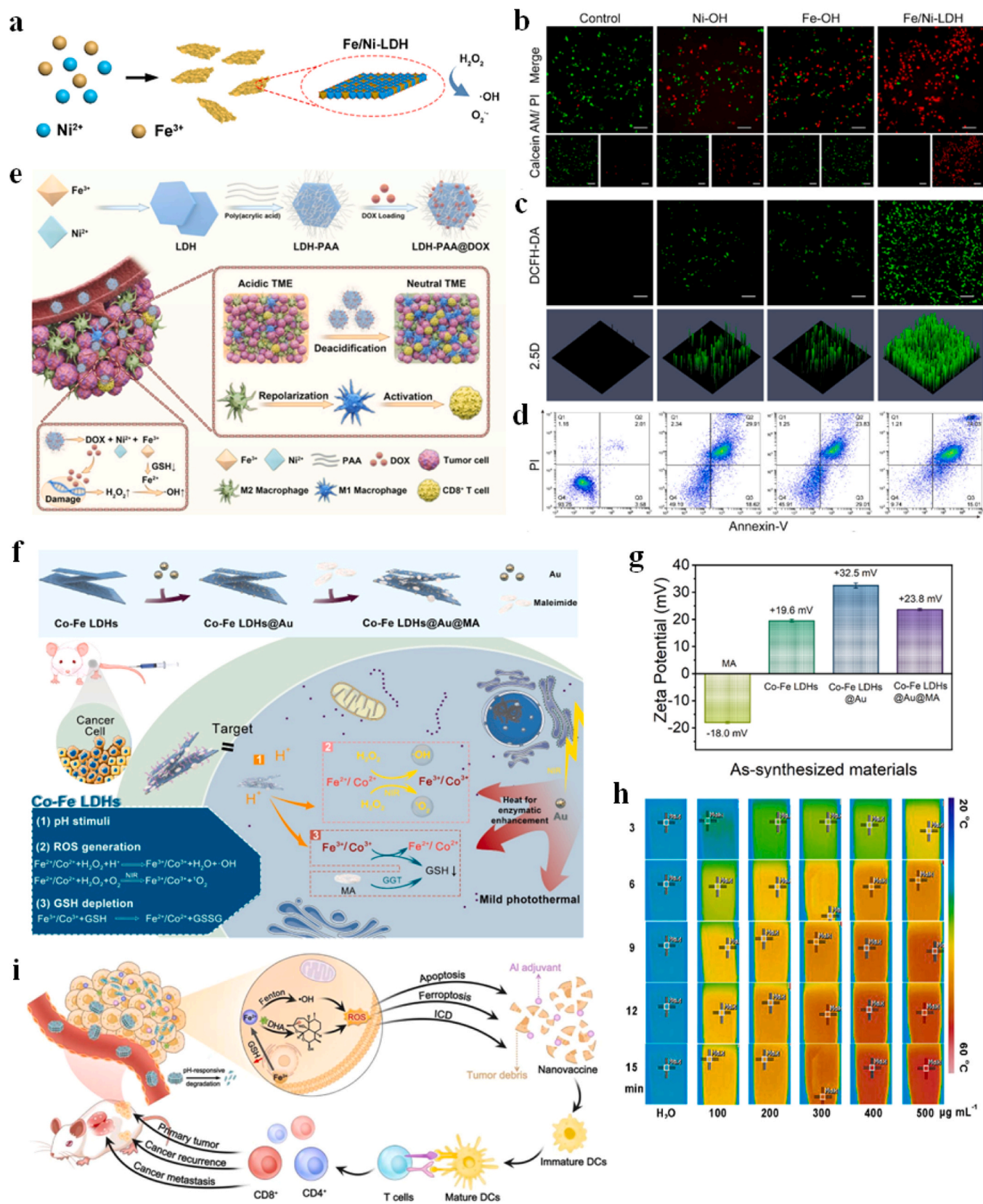
This reaction is particularly effective in the tumor microenvironment (TME), as the acidic environment is conducive to the catalytic reaction of LDHs. Moreover, LDHs have the ability to regulate acid and base, which can neutralize the acidic environment within tumor cells and improve the pH value of the tumor microenvironment [99]. Moreover,

tumor-associated macrophages (TAM) play a crucial role in tumor immunity, and its polarization state is closely related to tumorigenesis and progression. Chen, C., et al. developed a novel polyacrylic acid (PAA)-coated, adriamycin (DOX)-loaded layered double hydroxide (LDH) nanosheets (NSs). LDH-PAA@DOXNSs demonstrate excellent deacidification ability to neutralize acidic TME and regulate the polarization state of TAM. Repolarization of TAMs to the M1 phenotype promotes the secretion of anti-inflammatory cytokines and chemokines by TAMs, activates the immune system, and enhances the anti-tumor immune response (Fig. 4e) [100]. Meanwhile, the release of metal ions by LDHs can also act as an immune stimulant, activating antigen-presenting cells (APCs) and CD8⁺ T cells to enhance anti-tumor immune responses [101].

In addition, high concentration of GSH serves as a crucial antioxidant in tumor cells, which can scavenge ROS and protect the cells from oxidative damage. Therefore, consuming GSH, disrupting the antioxidant defense system of tumor cells to elevate ROS level have a significant cytotoxic effect on tumor cells. Meanwhile, the depletion of GSH and intracellular redox imbalance also promote ferroptosis [102]. For example, it was discovered that the Co-Fe LDHs nanosheets facilitated the in situ electrostatic adsorption of gold nanoparticles (Au NPs) and maleimide (MA) to form an integrated sandwich structure (Co-Fe LDHs@Au@MA nano-enzymes). This configuration undergo redox reactions with GSH, and MA disrupts the supply of glutathione, depletes GSH levels [97], thereby induces ferroptosis to inhibit tumor growth (Fig. 4f-h) [103].

Finally, some LDHs materials, such as FeAl-LDH and LDH-PAA@DOX, can release metal ions such as iron and aluminum ions in acidic environments, jointly initiating the immune response against tumors and inhibiting cancer recurrence and metastasis (Fig. 4i). Among them, T1-weighted magnetic resonance imaging (MRI) effect of iron (Fe) can serve as a contrast agent in MRI for the diagnosis and therapeutic monitoring of tumors [101]. Through MRI imaging, the size, location, and morphological changes of tumors can be observed in real time, providing valuable guidance for the treatment.

In summary, depending on the type of tumor, LDHs can be utilized alone or in combination for catalytic oxidative therapy, depletion of



(caption on next page)

Fig. 4. a) Schematic diagram of Iron/Nickel-layered double hydroxide (Fe/Ni-LDH) synthesis. Fluorescent images stained with calcein AM (green, live cells) and propidium iodide (PI) (red, dead cells) b), ROS level stained by dichloro-dihydro-fluorescein diacetate (DCFH-DA) c), and Flow cytometry assessment of cell death by Annexin V-FITC/PI staining d) of UMRC-6 renal cell carcinoma cell line (UMRC-6 cells) after treating with Fe/Ni-LDH. (Scale bar = 100 μ m). Copyright (2023) Elsevier. e) The construction of polyacrylic acid-coated, doxorubicin-loaded layered double hydroxide nanosheets (LDH-PAA@DOX NSs) and the schematic diagram of tumor elimination by LDHs deacidification-mediated immunotherapy and DOX-enhanced chemotherapy. Copyright (2023) Elsevier. f) Schematic diagram of design and preparation of cobalt-iron layered double hydroxide loaded with gold nanoparticles - maleimide composite nanozyme (Co-Fe LDHs@Au@MA nanozymes). g) Zeta potential of maleimide (MA), Co-Fe LDHs, Co-Fe LDHs@Au, and Co-Fe LDHs@Au@MA. Data were displayed as mean $\pm$ S.D. (n = 3). h) Thermal infrared images of Co-Fe LDHs@Au@MA solutions exposed to an 808 nm laser irradiation at different time. Copyright (2023) Elsevier. i) A cancer nano-vaccine based on FeAl-Layered double hydroxide framework for reactive oxygen species-augmented metallo-immunotherapy. Copyright (2024) ACS. (a) Reproduced and adapted with permission from ref [96]. (b) Reproduced and adapted with permission from ref [100]. (c) Reproduced and adapted with permission from ref [97]. (d) Reproduced and adapted with permission from ref [101].

GSH, modulation of the tumor microenvironment, and in synergy with biological imaging guidance to enhance the therapeutic effect.

5.2. Rheumatic diseases

Rheumatoid arthritis (RA) is a chronic progressive autoimmune inflammatory disease. Patients with advanced RA experience severe pain and joint discomfort, which brings considerable challenges to daily life and diminishes quality of life. Currently, first-line drugs for RA include antirheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), and corticosteroids [104]. However, the long-term use of these drugs results in a significant reduction in therapeutic effects and is often accompanied by side effects [105]. For example, the use of non-steroidal anti-inflammatory drugs (NSAIDs) demonstrates excellent efficacy in a short period, it can lead to severe gastrointestinal reactions and peptic ulcers [106]. Corticosteroids can lead to metabolic disorders and even damage to the immune system [107]. In addition, current treatments fail to achieve the desired therapeutic effect due to the neglect to the immune balance and acidity regulation at the lesion site, resulting in continuous destruction of the joints [108]. Therefore, the elimination of ROS-induced anti-inflammatory M2 polarization of macrophages, combined with anti-inflammatory immune modulation and acid neutralization, can serve as an effective and relatively safe treatment for RA while simultaneously promote bone repair.

According to the research of Fu, H., et al., LDHs can reduce the intracellular ROS concentration by regulate the immune microenvironment in rheumatic diseases due to its inherent properties. For example, nano-cerium dioxide loaded Mg-Al layered double hydroxide (LDH-CeO₂), where CeO₂ exhibits activities similar to superoxide dismutase (SOD) and catalase (CAT), is capable of effectively scavenge ROS (Fig. 5b, c). In the microenvironment of RA, LDH-CeO₂ enhances the antioxidant activity of CeO₂ by neutralizing excess H⁺ ions, thereby reducing intracellular ROS levels, promoting macrophage polarization toward the anti-inflammatory M2 phenotype and reducing the secretion of pro-inflammatory cytokines, such as interleukin-6 and tumor necrosis factor- α . Additionally, this decrease in ROS levels enhances the release of anti-inflammatory cytokines, including interleukin-10 (Fig. 5a,d,e) [109]. Through its immunomodulatory effect, LDHs help alleviate the inflammatory response, reduce joint damage, and inhibit the progression of disease.

The above-mentioned studies also found that metal ions in LDHs, such as Mg²⁺ in the positively charged MgAl-LDH, play an important role in the treatment of rheumatic diseases. In patients with RA, increased osteoclast activity leads to bone erosion, while inhibited osteoblast activity impairs bone repair [110]. Magnesium ions (Mg²⁺) released by LDHs not only synergistically promote macrophage polarization by reducing ROS levels, but also has the function of inhibiting osteoclast formation and promoting osteoblast activity. This is of positive significance for effectively alleviating joint inflammation and injury, improving joint function, and the long-term management of the disease.

Due to its unique layered structure, LDHs can serve as a therapeutic drug carrier to load multiple drugs, such as anti-rheumatic drugs. Additionally, surface modifications can be employed to achieve targeted delivery to the lesion site. Lin, S., et al. demonstrated that dextran sulfate

(DS) can be incorporated into LDHs by solution method. Through electrostatic interaction, the insertion of DS molecules into the interlayers of LDHs leads to the formation of LDH-DS nanocomposites with unique structures. Modified LDH is pH-sensitive and can utilize the acidic RA microenvironment to achieve precise release of the drug, increase the drug concentration in the lesion and enhancing the therapeutic effect (Fig. 5f,g) [56]. This targeted drug delivery can minimize the distribution of drugs throughout the body, lower the toxic side effects on healthy tissues and organs, and enhance the safety and effectiveness. Meanwhile, the layered structure of LDHs endows it with slow-release property, maintaining a stable drug concentration. This sustained-release property can decrease the frequency of drug administration and enhance the convenience compared to traditional dosage forms.

5.3. Osteopathy

Bone plays a vital protective and supportive role in the human body. Self-repair and remodeling are the fundamental physiological and biological characteristics of bones. However, these abilities will diminish when the bone defect exceeds a certain threshold, which is common in bone-related diseases such as osteoporosis, osteoarthritis, bone tumors, and bone infections [111]. With the advancement of nanotechnology, layered double hydroxides (LDHs) have showed great promise significantly in the treatment of bone diseases due to the open layered structure and adjustable metal ion composition, multiple bioactive properties, as well as effective drug loading and delivery capabilities [112,113].

Osteoporosis is a global chronic bone disease characterized by progressive bone loss and a decline in bone quality, which significantly increases the risk of bone fragility. In clinical practice, the treatment of osteoporosis primarily focuses on the inhibition of bone injury caused by osteoclasts, while ignoring the role of immune cells in the progression, resulting in a significant reduction in therapeutic efficacy [114]. Therefore, it is crucial to establish an effective immunotherapy, approach for osteoporosis based on the synergistic effects of acid neutralization and immune microenvironment regulation for the treatment.

In the treatment of bone tumors, LDHs can serve adjuvants for the enhanced anti-tumor immunotherapy by neutralizing acid substances in the tumor microenvironment, inhibiting the autophagy pathways of tumor cells, and modulating tumor-associated macrophages and T cells. Fu, H., et al. discovered that LDHs are weakly alkaline and can neutralize the local acidic microenvironment of osteoporosis and reduce the erosion of bone tissue caused by hydrogen ions. Meanwhile, it promotes the polarization of macrophages to M2 type, secretes anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF- β), inhibits the activity of T helper 17 cells, and regulates the immune microenvironment and reduces the inflammatory response [115]. For example, Ca-Al LDH prepared through homogeneous alkalization was functionalized with the bone-targeting moiety calcein to form CaAl-LDH-CN (CALC) nanosheet, which possesses both acid-neutralizing and immunomodulatory functions. The nanosheets degrade in acidic environments, releasing calcium ions and neutralizing excess hydrogen ions [116]. It inhibits osteoclast activity

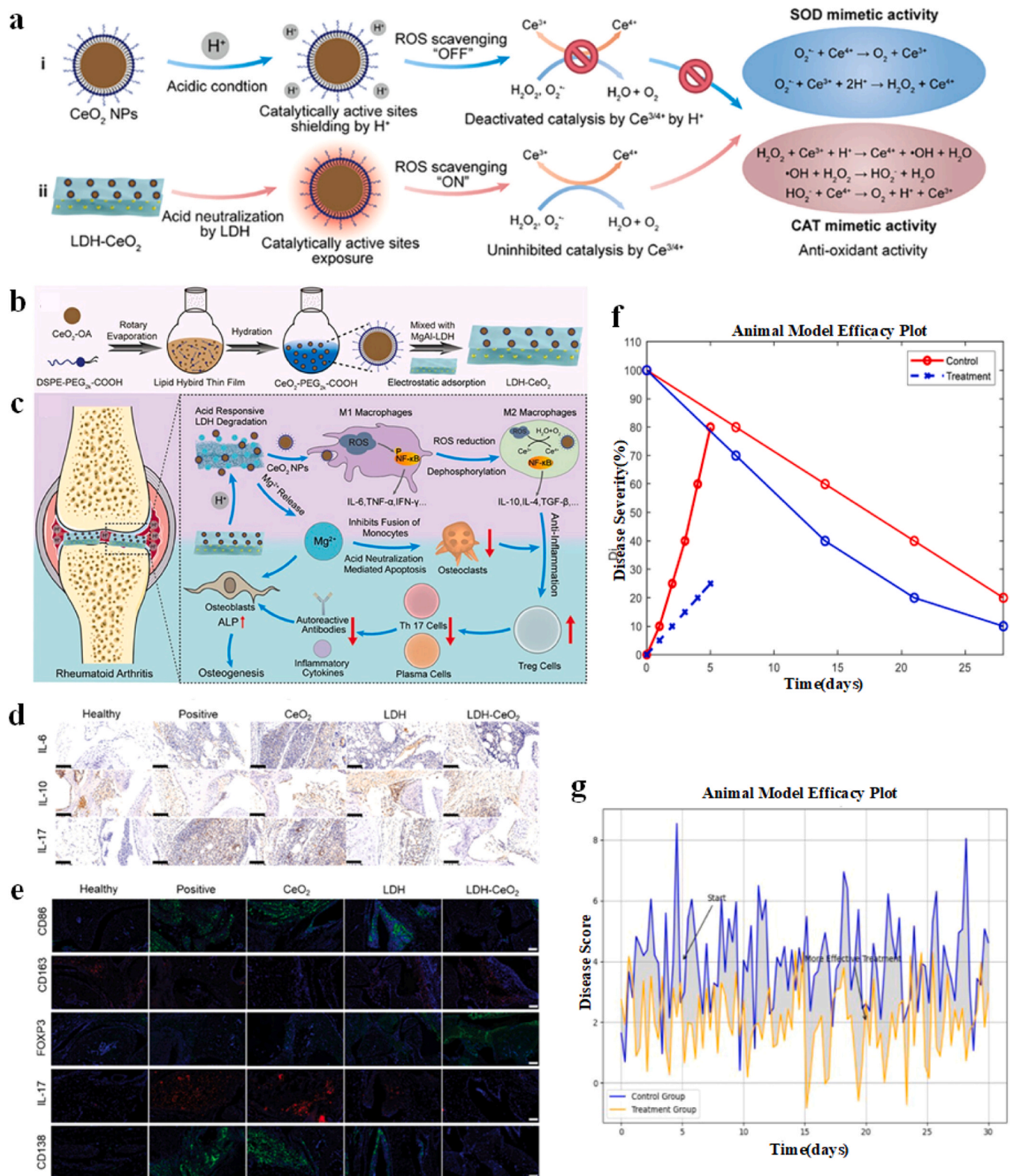


Fig. 5. a) Mechanism of ROS scavenging ability of cerium dioxide nanoparticles (CeO_2 NPs) assisted by acid neutralization of LDHs. b) Preparation of nanocatalytic LDH- CeO_2 for RA therapy. c) Mechanism of LDH- CeO_2 in treating RA. d) Immunochemical staining images of cytokine (IL-6, IL-10, and IL-17) expressions in joints. Scale bar: 100 μm . e) Immunofluorescence staining (CD86: green, CD163: red, FOXP3: green, IL-17: red, CD138: green) images of the joints for monitoring activities of immune cells after different treatments. Scale bar: 50 μm . Copyright (2024) John Wiley and Sons. f) Therapeutic efficacy of dextran sulfate-loaded layered double hydroxide (LDH-DS) nanocomposites in Adjuvant-Induced Arthritis (AIA) Rats. g) Lower severity of adjuvant induced arthritis (AIA) treated with LDH-DS nanocomposites than the control group treated with free methotrexate (MTX) nanomaterials (wave plot). Copyright (2024) Elsevier.

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and activates the c-Maf transcription factor, inducing macrophage polarization to the M2 type and promoting bone formation (Fig. 6a). In animal models of osteoporosis, LDHs can significantly increase bone density and bone volume fraction, reduce bone tissue loss, and improve bone structure. For example, magnesium alloys coated with Mg-Fe LDH can enhance bone regeneration and osseointegration, increase new bone formation, and improve the mechanical properties of bone [117]. Osteoarthritis (OA) is a chronic disease with high morbidity and clinical burden. It is characterized by the progressive and irreversible deterioration of articular cartilage, as well as persistent inflammatory response. However, most clinical medications used in the treatment of OA primarily alleviate symptoms without addressing the fundamental pathology [118]. To alleviate this issue, Kolasinski, S. L., et al. developed an inflammatory response vector and prepared LDH@TAGel nanogels by encapsulating LDHs within TAGel formed by cross-linking gelatin with tannic acid (TA) [119].

LDH@TAGel nanogels possess anti-inflammatory and antioxidant properties, it is capable of scavenging free radicals, including reactive oxygen species (ROS) and reactive nitrogen species (RNS). This action helps to reduce the oxidative stress damage to chondrocytes and decrease the expression of inflammatory factors such as interleukin-1 β (IL-1 β) and tumor necrosis factor- α (TNF- α), thereby mitigating the destruction of cartilage tissue caused by inflammatory responses (Fig. 6b). Moreover, LDH@TAGel can act directly or synergistically with other bioactive molecules (e.g., tannins, strontium ions, etc.) to restore the extracellular matrix (ECM) secretion function of damaged chondrocytes, reduce the expression of matrix metalloproteinases, and inhibit the apoptosis of chondrocyte [120]. By promoting the proliferation and differentiation of chondrocytes, as well as the synthesis and repair of ECM, it helps restore the structure and function of articular cartilage (Fig. 6c, d).

Based on the nano-sheet structure of LDHs, which features stability and dispersibility, the photothermal agent is introduced into the structure of LDH. Through the thermal effect, it induces apoptosis of tumor cells and achieves a highly efficient anti-tumor effect. For instance, Shi, J. J., et al. selected graphene oxide (GO) and chitosan (CS) to modify Mg-Al LDH through freeze-drying, and prepared nacre simulated GO/LDH/CS layered scaffolds. The incorporation of GO as a photothermal agent allowed the scaffold to generate effective tumor-killing energy when exposed to near-infrared (NIR) light irradiation (Fig. 6e,f) [121].

In bone infection models, LDH-based nanomaterials can effectively inhibit the growth and reproduction of bacteria, reduce the spread of infection, attenuate the inflammatory response, and promote wound healing and bone tissue repair [111]. [117]. For instance, Li, W., et al. modified Mg-Fe LDH with ascorbic acid (AA) through co-precipitation to form AA@LDH, which exhibits antimicrobial properties and bone regeneration functions [122]. In the acidic microenvironment where bacteria located, AA@LDH undergoes degradation, facilitating the pro-oxidative transformation of ascorbic acid and generating substantial amounts of ROS, thereby leading to significant bacterial mortality (Fig. 6g, h). In a neutral environment, AA@LDH gradually releases Mg²⁺ and ascorbic acid, which can directly induce the differentiation of stem cells into osteoblasts and promote the bone repair process by modulating the immune microenvironment. By simultaneously controlling bacterial infections reducing inflammation, and inducing tissue regeneration, it minimizes the complications associated with bone infections.

Some emerging strategies also offer new directions for addressing these issues related to orthopedic implant infections [123]. For instance MOF nanoparticles can regulate redox homeostasis and activate antibacterial immunity [124]. Silica-copper nanosheets enhance the bactericidal efficiency through the synergistic effect of photothermal and chemical kinetics and have excellent biocompatibility [125]. While NK cell mimics (NKMs) efficiently eliminate intracellular bacteria by loading perforin and B-lactamase through redox-responsive carriers, and

their efficacy is superior to that of clinical antibiotics [126]. These strategies are highly consistent with the characteristics of LDHs, achieving targeted delivery of functional components through pH responsiveness, and the release of antibacterial metal ions. These synergistic effects further enhance the therapeutic effects on biofilm infections and intracellular infections, providing diverse solutions for drug-resistant bone infections.

In summary, LDHs play a significant role in the treatment of various bone-related diseases, including acid neutralization and immunomodulation for osteoporosis, anti-inflammatory and antioxidant treatment, cartilage repair for osteoarthritis, immune enhancement and targeted therapy in bone tumors and antibacterial and pro-repair applications in bone infections. Especially when combined with emerging redox regulation, immune activation, photothermal catalytic synergy and intracellular antibacterial strategies, the application prospects of LDHs in orthopedic implant-related refractory bone infections are even more promising.

5.4. Diabetes

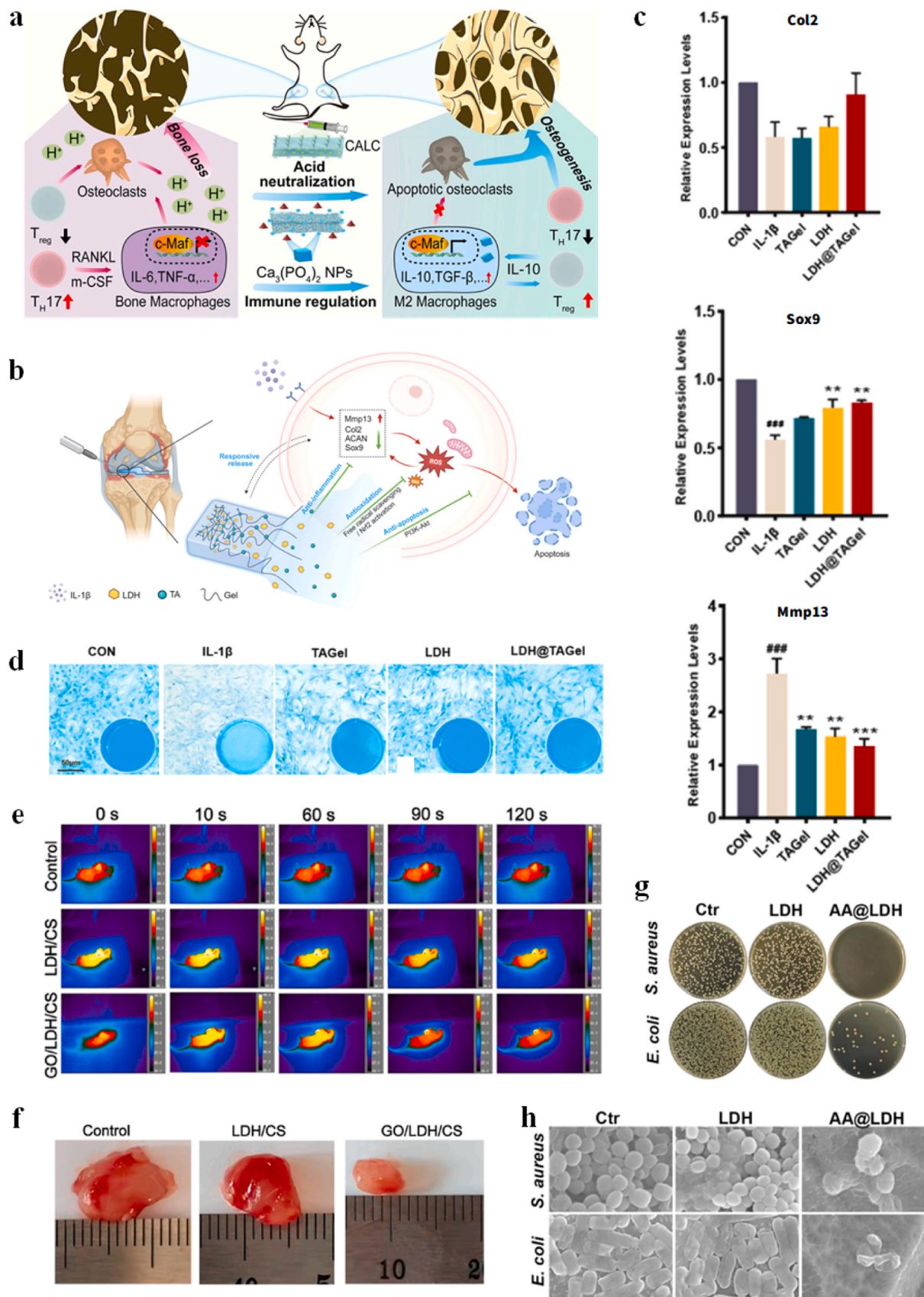
Diabetes is a widespread chronic metabolic disorder characterized by elevated blood glucose levels. Over 420 million people worldwide are affected, and more than one million deaths each year, and the incidence of early deaths continues to rise [127].

Diabetes not only affects overweight people and the elderly, a study by the Indian Council of Medical Research (ICMR) revealed that over 96,000 children have been diagnosed. Therefore, consistent and accurate monitoring of blood glucose levels is essential for effective diabetes management [128]. In this context, the precise treatment of diabetes is urgently needed, and there is an increasing demand for non-invasive, highly sensitive, reliable, and cost-effective glucose sensing technologies.

Since LDHs are an inorganic material with a layered structure, they have demonstrated significant advantages in the field of diabetes treatment. Insulin can be incorporated into LDHs through electrostatic interactions, hydrogen bonding, and other mechanisms to form stable nanocomplexes, precisely delivering insulin to targeted locations [129]. This complex has a stable structure, which endow it to resist the acidic environment of gastric acid and the action of various digestive enzymes. It can also protect insulin from rapid degradation, facilitates controlled release, improves its bioavailability, and addresses the limitations of traditional subcutaneous insulin injections. Pang, H., et al. prepared insulin-loaded LDHs nanocomposites (Alg-Chi-LDH@INS) with chitosan (Chi) and sodium alginate (Alg) double coating (Fig. 7a). *In vitro* experiments showed that the complex provides partial protection for insulin, thereby slowing its release in simulated gastric fluid. Moreover, the complex was found to bind stably to insulin in both simulated intestinal fluid and the physiological environment. *In vivo* experiments demonstrated that after oral administration of Alg-Chi-LDH@INS to diabetic mice, resulted in blood glucose levels was significantly reduced, indicating the potential of LDHs as an effective insulin carrier for oral delivery (Fig. 7b, c) [130].

Moreover, LDHs can also be combined with small molecular drugs such as glibenclamide. By inserting drug molecules into the interlayer of LDHs or adsorbing them onto the surface, a stable complex can be formed. This approach can address the issue of poor water solubility, reduce drug degradation, thereby increasing the effective concentration of the drug in the body and enhancing the therapeutic effect [131]. Damasceno Leão, A., et al. discovered that the combination of glibenclamide (GB) and organically modified LDHs nanoparticles (NP LDH + GB) effectively reduced blood glucose levels in diabetic rats and normalized their blood glucose values (Fig. 7d). Meanwhile, the nanoparticles did not have any significant adverse effects on body weight, water intake, or feed consumption in rats, and they also reduced oxidative stress in vascular tissues.

It is worth mentioning that two-dimensional materials are utilized



(caption on next page)

Fig. 6. a) Schematic diagram of typical osteoporosis characteristics (left) and the microenvironment regulation by calcein-functionalized calcium-aluminum layered double hydroxide (CaAl-LDH-CN) (CALC) (right). Copyright (2022) ACS. b) Graphical abstract of the layered double hydroxide encapsulated in tannic Acid-Gelatin cross-linked hydrogel (LDH@TAGel) treatment mechanism for OA. c) The mRNA levels of Collagen Type II (Col2) (I), SRY-Box Transcription Factor 9 (Sox9) (J), and matrix metalloproteinase 13 (Mmp13) (K) in different groups analyzed by reverse transcription quantitative polymerase chain reaction (RT-qPCR). d) Alcian blue staining results depicted by macroscopic images and optical microscopy images. Copyright (2024) Elsevier. e) Thermal images and statistical results indicated the effects of near-infrared (NIR) light irradiation on the local temperatures of nude mice. f) Tumor images and statistical analysis after two weeks. Copyright (2022) Elsevier. g) Representative culture images of bacterial colonies and the corresponding bacterial colony counting. h) SEM morphologies of *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*) after different treatments. Copyright (2025) Elsevier.

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for both enzymatic and non-enzymatic glucose sensing because of their exceptional stability, large surface area, and cost-effectiveness. The large specific surface area of LDHs offers numerous sites for the adsorption and reaction of glucose. The plentiful active sites on its surface can specifically interact with glucose, facilitating the electro-oxidation of glucose [132]. Moreover, the excellent catalytic properties of LDHs can accelerate the rate of electro-oxidation reactions. When combined with other materials that possess electrical properties (such as two-dimensional (2D) materials and metal nanoparticles, etc.), LDHs can form an efficient electron transport channel, which further improves the conductivity, sensitivity, and selectivity of the sensor, enabling effective and accurate monitoring of glucose concentration in biological systems.

Among these materials, nickel-based nanostructures have advantages, such as cost-effectiveness in non-enzymatic glucose sensors. nickel-cobalt layered double hydroxide (NiCo-LDH), as a high-performance non-enzymatic glucose sensor material, has garnered significant attention due to its excellent catalytic activity for electrochemical glucose oxidation [133]. For example, Qin, B., et al. combined NiCo-LDH with MoS₂ or MXene to construct novel glucose sensors CML (CC/MoS₂/NiCo LDH) and CMXL (CC/MXene/NiCo LDH). These sensors possess outstanding characteristics including a wide response range, ultra-low detection limit and high sensitivity, enabling effective monitoring of glucose levels in human sweat and offering a novel technological approach for non-invasive blood glucose monitoring (Fig. 7e) [134]. Park, J. Y., et al. modified NiFe LDHs on the surface of CuO nanowires (NWs) through potentiostatic electrodeposition. The prepared NiFe LDHs-CuO NWs sensor is capable of detecting glucose in human serum with a range of up to 8 mM. This sensor demonstrates high selectivity and reliability, with a relative standard deviation of less than 1.56 %, effectively distinguishing between non-diabetic and diabetic states, providing significant value for the monitoring and management of diabetes mellitus (Fig. 7f-i) [135].

In conclusion, LDHs have positive significance in improving blood sugar control in diabetes through multiple pathways such as promoting insulin absorption, exerting antioxidant effects, and constructing glucose sensors.

5.5. Alzheimer's disease

Alzheimer's disease (AD) is characterized by the continuous degeneration of neuronal function and the deterioration of myelin sheaths in the brain as individuals age [136]. It is a progressive and persistent neurodegenerative disease that affects approximately 300–350 million people worldwide [137]. Early diagnosis is essential for slowing the progression of AD and improving the quality of life of patients. By early detection, the progress of the disease can be managed to some extent.

It has been found that early diagnosis of AD can be achieved by detecting the expression of neurofilament light chain (NfL) biomarkers and glial fibrillary acidic protein (GFAP) in cerebrospinal fluid or blood [138]. Li, L.Y., et al. prepared COF/MOF-LDH composites by adding multivalent terbium metal-organic frameworks (Tb-MOFs) and cobalt-aluminum layered double hydroxide (CoAl-LDH) into a synthesized system of triazine covalent organic frameworks (triazine-COFs) using a one-pot method. And the LDH/MOF-COF composites were

prepared by adding Tb-MOF and triazine-COF into the synthesis system of CoAl-LDH through the hydrothermal method. (Fig. 8ab). These two composites were utilized as electrode modification materials to develop a label-free electrochemical immunosensor for the ultra-sensitive detection of NfL. (Fig. 8cd) [136]. Liu, L. L., et al. loaded copper nanoclusters (Cu NCs) onto 3D layered double hydroxide (3D-LDH) to form Cu NCs@3D-LDH. Utilizing its exceptional electrochemiluminescence (ECL) properties, a biosensor was constructed to detect the biomarker glial fibrillary acidic protein (GFAP) in the serum of patients associated with Alzheimer's disease (Fig. 8e) [139], achieving the early detection of AD.

The above-mentioned biosensing technology based on LDH-related composite materials provides crucial support for the early and precise diagnosis of AD. The core value of early diagnosis lies in ensuring the time window for subsequent treatment and intervention. Given the complexity of the pathogenesis of Alzheimer's disease (AD) and the limitations of single-target treatments, researchers have further leveraged the unique advantage of LDH materials that can carry multiple active components to develop dual-target nanomedicines, in order to achieve precise intervention of the pathogenic factors of AD.

One important feature of AD is its complex pathogenesis, which involves multiple causative factors. Given the unsatisfactory therapeutic effects of single-target, researchers are dedicated to developing dual-targeted nanomedicines. Since LDH nanoparticles can load both drugs and genes simultaneously, Zhang, L. X., et al. incorporated rutin and β -amyloid precursor protein cleavage enzyme 1 (BACE1) or glycogen synthase kinase 3 β (GSK3 β) onto LDH [140]. And the surface of drug-loaded LDH (LR) was coated with biomolecule bovine serum albumin (BSA). Then, by cross-linking the neuron-targeting peptide RVG29 and the blood-brain barrier (BBB)-targeting peptide Ang2 to bovine serum albumin (BSA) using a sulfosuccinimidyl 4-(N-maleimidomethyl) cyclohexane-1-carboxylate (Sulfo-SMCC) cross-linker, LDH-Rutin-RVG29-Ang2 (LRAR) was prepared. The modified nanomedicines can effectively cross the blood-brain barrier (BBB). RVG29 can facilitates the recognition and targeting of these nanomedicines to neurons through nicotinic acetylcholine receptors (nAChRs), thereby enhancing their accumulation in the brain and improving neuronal uptake efficiency [28,141]. In the brain, rutin promoted the degradation of amyloid-beta (A β) plaques and inhibited the overactivation of microglia. Correspondingly, siRNAs down-regulated the expression of BACE1 or GSK3 β , thereby reducing A β production and inhibiting the over-phosphorylation of tau protein. This dual-targeted therapy achieved multi-faceted interventions on the pathogenic factors of AD (Fig. 8f).

5.6. Other diseases

LDHs have a diverse application in the treatment of skin diseases, retinal disorders, cardiovascular conditions, etc.

In the treatment of atopic dermatitis (AD), layered double hydroxide nanohybrids (IAA-LDH) loaded with indole-3-acetic acid (IAA) were prepared by incorporating IAA into the interlayer of the LDHs [142]. IAA-LDH induced macrophage polarization, promoted the proliferation of M2-like macrophages, inhibited the activation of M1-type macrophages, and reduced the release of pro-inflammatory factors. IAA-LDH

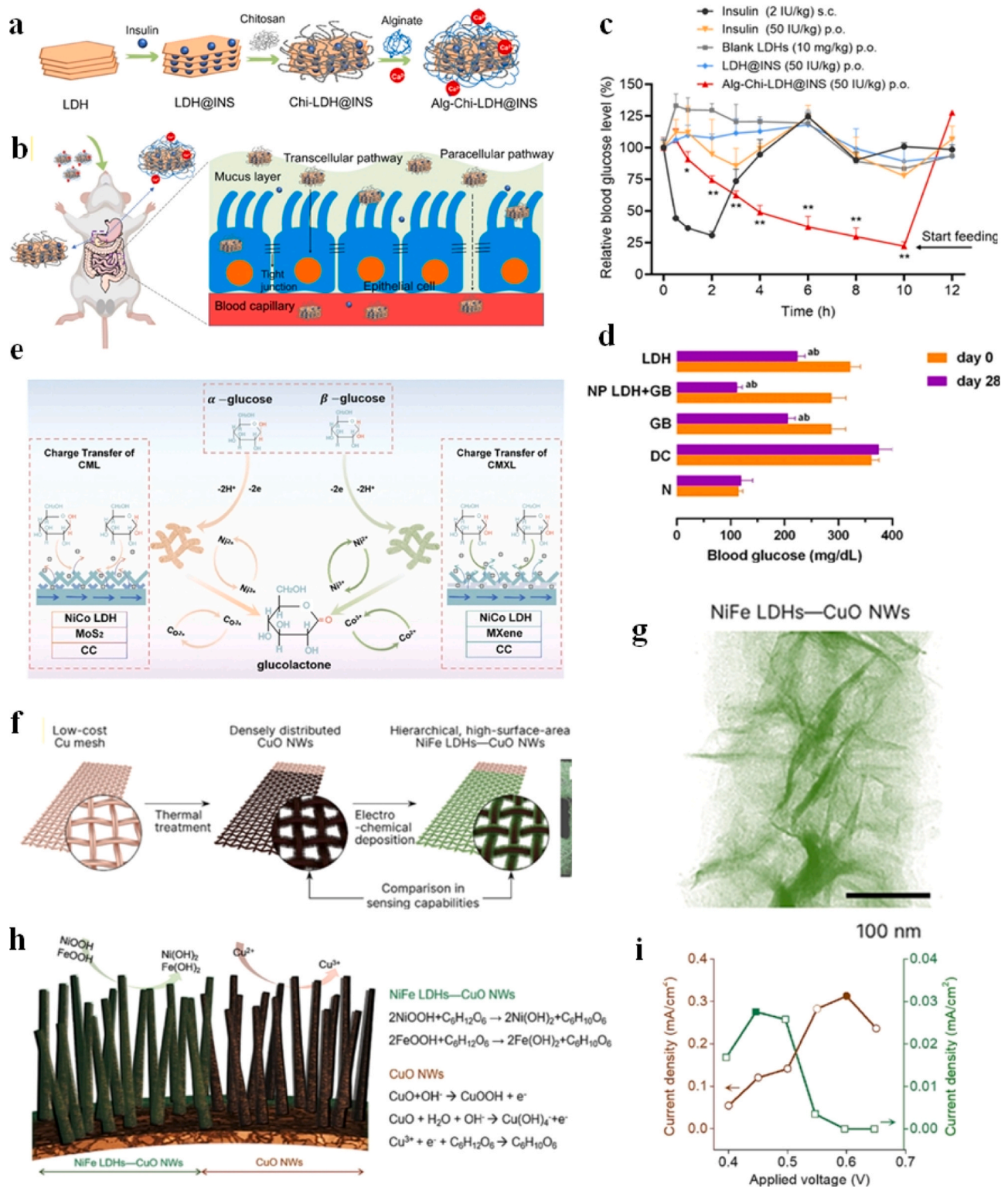


Fig. 7. a) The synthetic process of sodium alginate-chitosan-layered double hydroxide/insulin (Alg-Chi-LDH@INS) nanocomposites. b) The oral delivery of insulin through Alg-Chi-LDH@INS for diabetic treatment. c) *In vivo* hypoglycemic effect. Copyright (2024) Springer. d) Blood glucose values of different groups LDH after 28 days of treatment: normal rats (N), diabetic control (DC), glibenclamide (GB), LDH, organically modified layered double hydroxide nanoparticles combined with glibenclamide (NP LDH + GB). Copyright (2023) Elsevier. e) Schematic diagram of the operation mechanisms of glucose sensors of carbon cloth/molybdenum disulfide/nickel-cobalt layered double hydroxide (CML) and carbon cloth/MXene/nickel-cobalt layered double hydroxide (CMXL). Copyright (2025) Elsevier. f) The design of the Nickel-Iron layered double hydroxides-copper oxide nanowires (NiFe LDHs-CuO NWs) glucose sensor. g) TEM image of NiFe LDHs-CuO NWs. h) Structural schematic diagram of NiFe LDHs-CuO NWs sensor. i) Sensitivity of the CuO NWs and NiFe LDHs-CuO NWs calculated via the cyclic voltammetry (CV) or amperometric response under various applied voltages. Copyright (2024) Elsevier.

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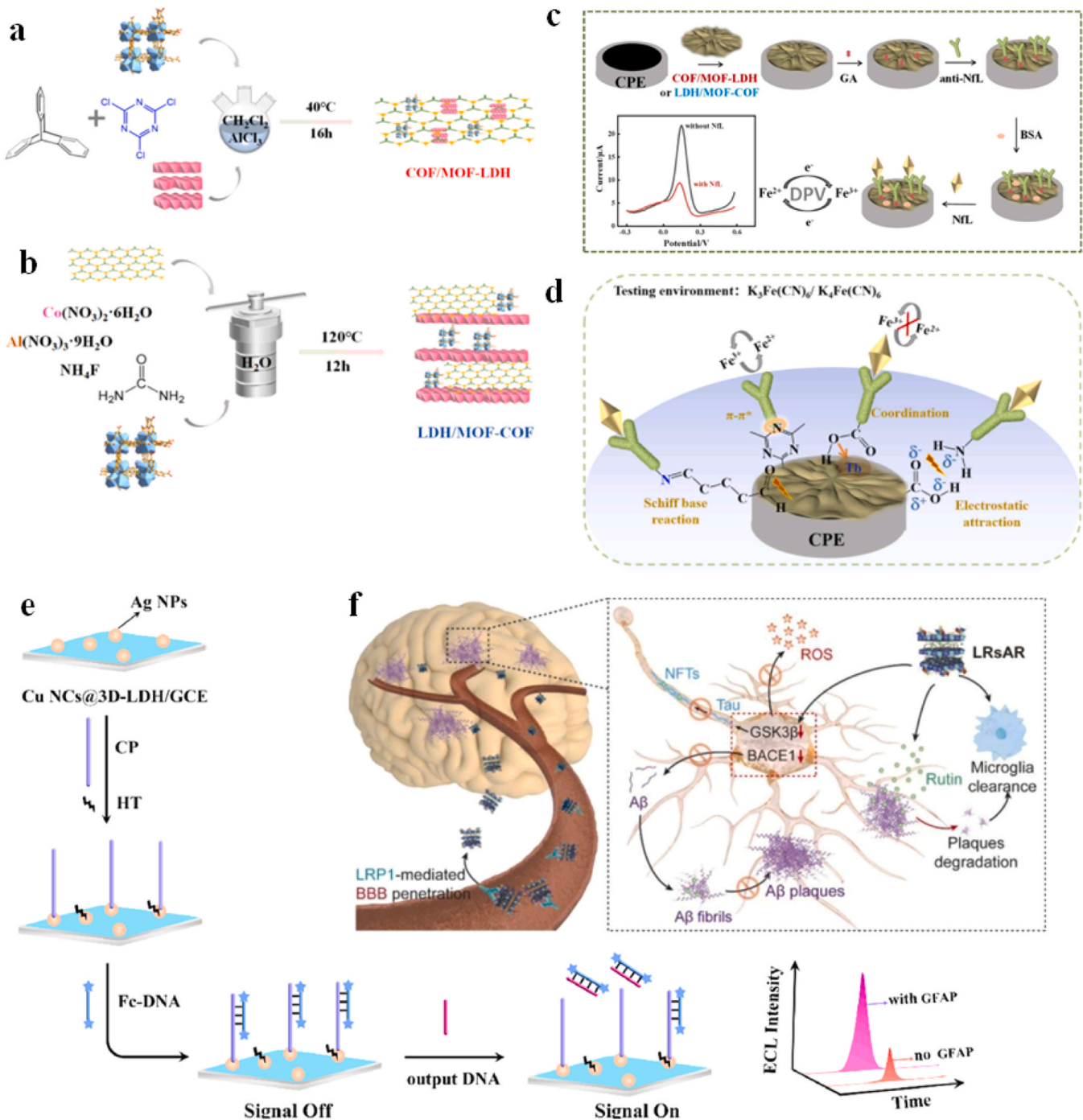


Fig. 8. Construction process of covalent organic framework/metal-organic framework-layered double hydroxide (COF/MOF-LDH) a) and LDH/MOF-COF b) and COF/MOF-LDH or LDH/MOF-COF immunosensors for detecting neurofilament light chain (NfL) c). d) The interaction between COF/MOF-LDH and the anti-NfL. Copyright (2024) Elsevier. e) The assembled steps and signal response principle of Electrochemiluminescence (ECL) biosensor. Copyright (2024) Elsevier. f) Therapeutic mechanism of layered double hydroxide-rutin-RVG29-Ang2 (LRsAR) nanomedicine. Copyright (2023) Elsevier.

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can also reduce intracellular ROS levels, exert antioxidant effect and mitigate oxidative stress damage. In addition, IAA-LDH can alleviate AD symptoms by regulating immune response, reducing immunoglobulin E (IgE) levels, and decreasing mast cell infiltration (Fig. 9ab). Both *in vitro* and *in vivo* experiments showed IAA-LDH was non-toxic to cells, demonstrating good biocompatibility. Besides, IAA-LDH was modified with targeting molecules such as RVG29 and Ang2, which can specifically recognize and bind to cells of AD lesions, achieving targeted drug

delivery and enhances therapeutic effects. (Figure 9 cd).

In the treatment retinal vascular disease, copper-containing layered double hydroxide (Cu-LDH) nano-enzymes was combined with nitric oxide donors (GSHNO) to form the nanoreactor Cu-LDH@GSHNO. This nanoreactor exhibited superoxide dismutase (SOD) and catalase (CAT) cascade enzyme-like activities, catalyzing the substrate to produce oxygen and facilitating the release of glutathione (GSH) and nitric oxide (NO) [143]. This cascade SOD-CAT catalytic capability can effectively

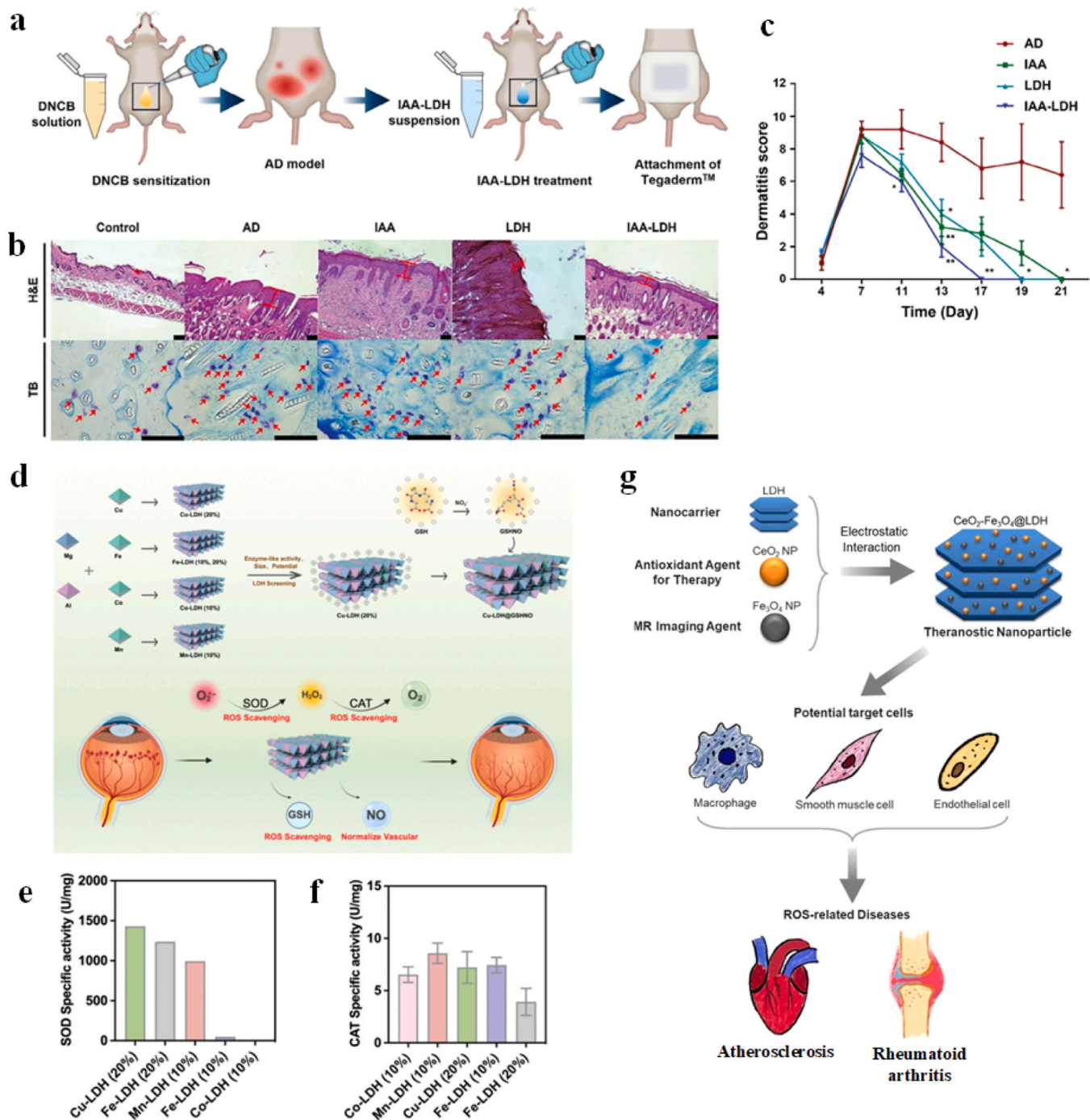


Fig. 9. a) Schematic diagram of 2,4-Dinitrochlorobenzene (DNCB)-induced atopic dermatitis (AD)-like model in BALB/c mice. b) Representative histological images of skin tissue sections: Hematoxylin and Eosin (H&E)-stained and Toluidine Blue (TB)-stained, scale bar: 100 μ m. c) Dermatitis scores derived from the cumulative individual symptom scores. Copyright (2023) John Wiley and Sons. d) The preparation process of copper-containing layered double hydroxide/glutathione-nitric oxide donor (Cu-LDH@GSHNO) and the therapeutic mechanism on oxygen-induced retinopathy (OIR). e, f) Superoxide Dismutase (SOD)-like and Catalase (CAT)-like activities of LDHs nanocomposites. Copyright (2024) John Wiley and Sons. g) Schematic diagram of therapeutic functions of cerium dioxide-iron tetraoxide/layered double hydroxide ($\text{CeO}_2\text{-Fe}_3\text{O}_4\text{/LDH}$) nanocomposites and their potential applications in ROS-related diseases. Copyright (2019) ACS.

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eliminate intracellular ROS, alleviate oxidative stress injuries, inhibit the inflammatory response and reduce the expression of inflammatory factors, such as vascular endothelial growth factor (VEGF). Meanwhile, the release of NO from Cu-LDH@GSHNO can promote vascular normalization, improve the ischemic and hypoxic conditions of the retina, and restore vascular function (Fig. 9e-g). For vivo experiments, Cu-LDH@GSHNO demonstrated excellent biosafety, without toxic side

effects on cells and significant tissue damage. It possesses both antioxidant properties and the ability to restore vascular function, allowing it to address retinal vascular diseases from multiple aspects and enhance therapeutic effects.

In the treatment of cardiovascular diseases, LDHs nanocomposites were coated with metal oxide nanodots, such as cerium dioxide (CeO_2) and iron tetraoxide (Fe_3O_4) to produce $\text{CeO}_2\text{-Fe}_3\text{O}_4\text{/LDH}$, which exert

two primary functions: antioxidation and imaging (Fig. 9h) [144]. CeO₂ NPs in CeO₂-Fe₃O₄@LDH nanocomposites exhibit antioxidant properties. First, the rapid transition between the oxidation states of Ce³⁺ and Ce⁴⁺ on the surface of CeO₂ allows the nanocomposite to effectively reduce intracellular ROS levels, inhibit cellular damage and inflammatory responses associated with the overproduction of ROS, exerting therapeutic effect to cardiovascular diseases. Second, the diagnosis and monitoring of cardiovascular disease are critical to effective treatment. Fe₃O₄ NPs in the nanocomposite serve as magnetic resonance imaging (MRI) contrast agents, providing T2-weighted imaging contrast. In the *in vitro* macrophage experiment, macrophages were incubated with various concentrations of CeO₂-Fe₃O₄@LDH nanocomposite. MRI detection revealed that the T2 contrast signal was enhanced with the increase of Fe concentration. The MRI signals of the cells can be clearly detectable when the Fe concentrations 0.027 mM. This enhancement could facilitate the labeling and tracking of macrophages *in vivo*, allow for real-time monitoring of the developmental processes of

cardiovascular disease and provide a crucial foundation for effective treatment plans.

In summary, LDHs can effectively treat dermatological, retinal, and cardiovascular diseases through various mechanisms of action. In the future, LDHs are expected to become an important drug carrier and therapeutic tool for these diseases.

This section presents a large number of examples to specifically demonstrate the remarkable efficacy of LDHs in the treatment of various oxidative stress-related diseases such as cancer, rheumatic diseases, bone disorders, diabetes, and Alzheimer's disease. Its therapeutic mechanisms are diverse, including generating ROS to kill tumors, eliminating ROS to combat inflammation, serving as an intelligent carrier for targeted drug/gene delivery, and regulating the immune microenvironment, etc. These applications have fully demonstrated the significant potential of LDHs in improving drug efficacy, achieving synergistic treatment, and promoting the integration of diagnosis and treatment through precise regulation of oxidative stress. The core

Table 3

Summary of LDHs treatment strategies and key results.

Disease type	LDH base material	The mechanism of oxidative stress regulation	Treatment strategy	Core treatment outcome	Literature examples
Cancer	Fe/Ni-LDH	Promote the production of ·OH from H ₂ O ₂ (Fenton-like reaction), and enhance the oxidative stress of tumor cells.	Chemical kinetics therapy	It effectively kills UMRC-6 cells both <i>in vitro</i> and <i>in vivo</i> , and inhibits the proliferation of tumor cells by up to 99 %.	[96]
	Co-Fe LDHs@Au@MA	Consumption of GSH to disrupt the antioxidant defense system and, in combination with the photothermal effect to amplify the ROS damage.	Chemical kinetics therapy and Photothermal therapy and ferroptosis	Through the synergistic effect of plasmon energy transfer and defect-directed charge capture, the tumor inhibition rate reached as high as 75.34 %.	[97]
	LDH-PAA@DOX	Neutralize acidic TME, enhance drug activity, and regulate TAM polarization (M2→M1).	Chemotherapy , immunotherapy, and acid-reducing treatment	Activate CD8 ⁺ T cells, enhance anti-tumor immunity, and achieve tumor ablation.	[100]
Rheumatic diseases	LDH-CeO ₂	The Ce ³⁺ /Ce ⁴⁺ cycle removes O ₂ ^{·-} and H ₂ O ₂ , and LDH neutralizes H ⁺ ions to enhance the antioxidant activity.	Anti-inflammatory treatment, and immunomodulation to achieve bone repair	Significantly alleviated symptoms of joint swelling and bone erosion, and regulation of the immune microenvironment.	[109]
	LDH-DS	Interstitial dextran sulfate (DS) sustained-release and acid environment-responsive release to reduce ROS-mediated cartilage damage.	Targeted and acid-triggered sustained-release	Significantly reduced arthritis scores and ankle joint thickness, the effect was superior to that of free MTX treatment.	[56]
Osteopathy	CaAl-LDH-CN (CALC)	Neutralize the local acidic microenvironment, inhibit the production of ROS, regulate the polarization of macrophages, thereby regulate the balance between Treg and Th17 cells.	Immune regulation therapy	Increase bone density and bone volume fraction (significantly rising from 6.2 % to 10.7 %), improve bone structure, and inhibit bone loss.	[116]
	LDH@TAGel	Remove ROS/RNS and inhibit the damage to chondrocytes caused by oxidative stress.	Anti-inflammatory and antioxidant therapy (for osteoarthritis)	Protect the ECM of cartilage, reduce the expression of Mmp13, and promote the expression of Col2/Sox9.	[119,120]
	AA@Mg-Fe LDH	The ROS produced can kill bacteria in an acidic environment, and slowly releases active ingredients in a neutral environment, thereby alleviating oxidative stress.	Antibiotic treatment and bone regeneration (bone infection)	Effective elimination of <i>S. aureus</i> , significant increases in both new bone volume and bone density, as well as the synergistic effect of infection control and bone regeneration.	[122]
Diabetes	NiCo-LDH/MoS ₂ (CML Sensor)	High catalytic activity promotes glucose electro-oxidation and precisely captures ROS-related metabolic signals.	Non-invasive blood glucose monitoring	Wide response range and extremely low detection limit, enabling efficient monitoring of sweat glucose.	[133,134]
	Alg-Chi-LDH@INS	Protect insulin from degradation, regulate intestinal oxidative stress, and enhance bioavailability.	Oral insulin delivery therapy	The blood sugar level dropped by approximately 50 % within 4 h.	[130]
Alzheimer's Disease	COF/MOF-LDH	Based on electrochemical signal amplification, precise detection of biomarkers related to oxidative stress.	Early diagnosis (biological sensing)	Ultra-sensitive detection of NfL, facilitating early screening of Alzheimer's disease.	[136]
	LDH-Rutin-RVG29-Ang2 (LRAR)	Rutin eliminates ROS and inhibits excessive activation of microglia, while siRNA reduces Aβ production.	Dual-targeted synergistic therapy (integrated diagnosis and treatment)	Penetrate the blood-brain barrier, promote the degradation of Aβ plaques, and improve cognitive function.	[28,141]
Atopic dermatitis	IAA-LDH	Reduce the cellular ROS level, inhibit the activation of M1 macrophages, and regulate the immune response.	Immune regulation therapy (for atopic dermatitis)	Reduce IgE levels and mast cell infiltration, repair the skin barrier, and lower the dermatitis score.	[142]
Retinal vascular diseases	Cu-LDH@GSHNO	The SOD-CAT cascade enzyme activity eliminates ROS and releases NO to promote vascular normalization.	Antioxidant therapy and vascular repair (for retinal diseases)	Inhibit the formation of retinal neovascularization and improve the ischemic and hypoxic state.	[143]
Cardiovascular diseases	CeO ₂ -Fe ₃ O ₄ @LDH	CeO ₂ removes ROS, while Fe ₃ O ₄ was used for MRI imaging.	Antioxidant therapy and imaging monitoring (cardiovascular diseases)	Reduce the cellular ROS level, inhibit the inflammatory response, and achieve targeted tracking of macrophages.	[144]

treatment outcomes for various diseases can be summarized in Table 3:

6. Summary and discussion

6.1. Progression and importance of LDHs in disease

In this review, we provide a thorough and comprehensive summary of recent advancements in LDH-based nanomaterials for the treatment of oxidative stress-related diseases. First, the categorization of diseases induced by oxidative stress and the influencing mechanisms were elaborated. Then, the advantages and research progress of LDHs nanomaterials used in the biomedical field are discussed based on their structure and composition. Subsequently, the synthesis and surface modifications are described in a systematic manner. Finally, the advancements in LDH-based nanomaterials for the regulation of oxidative stress in disease therapy are discussed in depth:

- (1) In cancer therapy, LDH-based nano-systems can catalyze the generation of ROS from hydrogen peroxide, regulate the polarization of tumor-associated macrophages, deplete intracellular glutathione to induce ferroptosis, thereby enhancing anti-tumor immune response. (2) For rheumatic diseases, LDHs participate in regulating the immune microenvironment, reduces the concentration of intracellular ROS, promotes the polarization of macrophages toward the anti-inflammatory M2 phenotype, and diminishes the inflammatory response. Meanwhile, the metal ions it contains, such as Mg^{2+} , possess the functions of inhibiting the formation of osteoclast and promoting the activity of osteoblast to alleviate rheumatoid joint injuries. (3) In the treatment of bone disease, LDHs can neutralize local acidity, regulate the immune microenvironment, increase bone density, and improve osteoporosis. Its anti-inflammatory and antioxidant properties protect chondrocytes and restore the structure and function of articular cartilage, thereby achieving good therapeutic effects in osteoarthritis. For bone tumors, LDHs not only facilitate the targeted delivery and controlled release of antitumor drugs but also exhibit photothermal and photodynamic properties. These characteristics can be utilized as an immunotherapeutic adjuvant to regulate immune responses. In addition, LDH-based nanomaterials can inhibit the growth and reproduction of bacteria, promote wound healing and bone tissue repair, and can be utilized in the treatment of bone infections and other bone diseases. (4) Due to the large specific surface area and excellent catalytic properties, LDHs can be combined with other materials to construct high-performance glucose sensors, achieving efficient and accurate detection of glucose concentrations in biological organisms. Meanwhile, LDHs can serve as a carrier for insulin and other diabetes drugs to enhance the efficacy. (5) LDHs can be utilized to develop biosensors for the early detection of biomarkers associated with Alzheimer's disease. In addition, LDHs nanoparticles can simultaneously load drugs and genes to prepare dual-targeted nanomedicines for multi-targeted intervention against the pathogenic factors of AD. Besides, LDHs also offer effective therapeutic strategies in the treatment of some other diseases, providing innovative treatment concepts.

Therefore, it is essential to continue the research about the regulation of oxidative stress induced by LDHs, which is conducive to a deeper understanding of their action mechanisms in the complex environment *in vivo*. It brings new therapeutic hope to numerous patients suffering from diseases related to oxidative stress and broadens the scope of biomedical materials in the field of disease treatment.

6.2. Current challenges

Although numerous studies have demonstrated the significant

potential of LDHs in biomedical applications, further in-depth research and the establishment of rigorous standards are still required to advance LDHs toward clinical applications and commercial production. The clinical application of LDHs materials still needs to address the following key issues:

(1) Standardization of the preparation process

The synthesis methods, such as co-precipitation and hydrothermal methods, are highly sensitive to reaction conditions (such as the ratio of metal ions, pH values, temperature, etc.). This leads to the uneven particle size distribution of LDHs, significant morphological variations, and challenges in controlling the stability of surface modifications, such as targeting ligands and drug loading [145]. Such performance fluctuations between batches will directly affect the reliability of clinical efficacy. Moreover, as laboratory synthesis is typically conducted in small batches, scaling up for production can lead to changes in the mass and heat transfer efficiencies within the reaction system, which may further exacerbate performance differences. Furthermore, the current synthesis methods are costly (such as high-purity metal salts, complex modification reagents, etc.), which makes it difficult to meet the large-scale production requirements for clinical use and limits their commercialization [146].

(2) Potential biological activity

The current research primarily focuses on the drug carrier functions and oxidative stress regulatory roles of LDHs to achieve the eliminating of ROS and regulation of macrophage polarization. However, there is insufficient exploration of other potential biological activities of LDHs, including the regulation of stem cell differentiation and interactions with the immune system [147]. For instance, the specific target sites and signaling pathways of LDHs composed of different metal ions in various disease microenvironments (such as tumors, rheumatoid arthritis) have not been fully elucidated. This may lead to the ambiguity of the therapeutic mechanism, affect the precise verification of the therapeutic efficacy, and restrict the expansion of its application [148]. Therefore, further exploration of the potential biological activities of LDHs can provide more directions for their application in complex *in vivo* environments.

(3) Biological safety

Although existing studies have shown that LDHs have certain biocompatibility, the clinical translation requires verification of their long-term safety for use. This includes whether it induces an immune responses (such as antibody production, complement activation), as well as potential toxicity to the hematopoietic system and reproductive system [149]. For instance, biological molecules modified on the surface of LDHs (such as BSA and chitosan) may trigger allergic reactions [150]. Additionally, the continuous release of metal ions from LDHs can interfere with intracellular signaling pathways, which may lead to abnormal cell proliferation. Therefore, more work is needed to reveal the safety of LDHs *in vivo* under different environmental conditions.

(4) Targeting and precise controlled-release

Although LDHs can target to the lesion site through surface modification with ligands such as RVG29 and Ang2, the complexity of the *in vivo* environment may significantly reduce the targeting efficiency. For instance, the heterogeneity of the tumor microenvironment can impede the penetration of LDHs, leading to an insufficient enrichment rate of LDHs in the tumor tissue and thus affecting the therapeutic effect. Meanwhile, the drug release rate of LDHs is regulated by various micro-environmental factors such as pH and temperature. The dynamic changes in the disease process may result in a mismatch between the controlled-release rate and the treatment requirements [151]. For instance, during the acute phase of rheumatoid arthritis, rapid release of anti-inflammatory drugs is

required, while in the remission phase, low doses need to be maintained for a long time. The existing LDHs controlled-release systems are difficult to achieve such dynamic responses, which mainly lead to insufficient efficacy or adverse side effects [152].

(5) Insufficient research on the Structure-Activity Relationship

Most existing studies have focused on the qualitative correlation between a single structural factor and a single kind of activity, but lack systematic research on the synergy of multiple factors and the quantitative prediction of activity. For instance, the proportions of metal ions, the interlayer spacing, and the types of modifying molecules have not yet been clearly understood in terms of their comprehensive influence on the ROS regulatory activity. This makes it impossible to precisely predict the performance of materials in complex physiological environments through structural design [17]. Meanwhile, the structure-activity rules across different diseases have not been established, and the structural optimization paths between LDHs that produce ROS in tumors and LDHs that eliminate ROS in inflammation is also unclear [153]. All these have hindered the standardized design and clinical application of LDHs.

In conclusion, in-depth research on the biological functional pathways and molecular mechanisms of LDHs is still insufficient, which hinders the comprehensive assessment of their biological safety and efficacy. Besides, more preclinical research and clinical trials are needed to provide a solid theoretical foundation and practical basis for its clinical application, which is also the goal of future efforts.

6.3. Solution strategies and future directions

LDHs have shown great potential in the field of oxidative stress regulation for disease treatment. In order to address the existing problems mentioned above and promote the clinical application of LDHs, some new attempts and breakthroughs are necessary.

In terms of the synthesis process, many existing synthesis methods are highly susceptible to reaction conditions, and the stability is difficult to control. To overcome the performance fluctuations between batches, a unified synthesis process guideline for LDHs needs to be established to achieve standardized production. The unified synthesis process is crucial for the assessment of clinical efficacy, while the large-scale production that meets clinical needs will further promote its commercial transformation. Meanwhile, the current synthesis methods often have problems such as unsatisfactory surface modification, low yield, and limited purity. Therefore, it is necessary to innovate in the synthetic method. For instance, the newly developed topological chemical oxidation method can efficiently prepare metal hydroxide nanosheets [154], which also expands new approaches for the synthesis of two-dimensional materials.

For the fundamental research, expanding the scope of research on the biological activities of LDHs is expected to achieve new breakthroughs in the exploration of their biological activity characteristics. For instance, F.D. Velázquez-Herrera, et al. achieved structural and performance optimization by constructing LDHs-based composites with inorganic compounds. By taking advantage of its high specific surface area to enhance the accessibility of active sites, the goal of expanding biological functions and improving stability can be achieved [155]. In addition to the existing drug carriers and antioxidant functions, the mechanism of action of LDHs in the complex *in vivo* environment can be further explored. For instance, how do LDHs with different cation compositions and particle sizes precisely regulate the behavior of immune system? L. Jia, et al. integrated the STING agonist with LDHs nano-scaffold and replaced Mg^{2+} with Mn^{2+} to form a self-adjuvant platform (MLDHs), thus breaking through the limitation of traditional nanocarriers that merely function as "delivery tools" [156]. LDHs achieve the "self-adjuvant delivery integration" through manganese (Mn) doping and a new technology that regulate the type of immune response by controlling metal ions. This provides a customizable carrier platform for precise immunotherapy of diseases such as cancer. It is expected to

promote the development of personalized immunotherapy and combination therapy strategies in the future.

With the continuous development of artificial intelligence technology, integrating artificial intelligence (AI) into the material design of LDHs is expected to rapidly screen the optimal metal ion combination (such as the proportion of $Fe^{3+}/Co^{2+}/Mn^{2+}$), the types of interlayer anions and the modification method, predict material performance, and optimize synthetic pathways through machine learning and high-throughput computing. This approach can significantly shorten the traditional research and development cycle by more than 90 % [157]. AI technology can assist in designing LDHs materials that are more suitable for clinical applications, such as more efficient drug carriers and more sensitive biosensors. It promotes the transition of LDHs from empirical trial-and-error to rational design, and accelerates the application and development of LDHs in clinical disease treatment.

Based on their controllable physicochemical properties and biological functions, it is suggested to form a new solution strategy centered on "material function customization and therapeutic mechanism innovation" for clinical research. Through the design and modification of the LDHs structure and in combination with clinical treatment requirements, an efficient diagnosis and treatment platform is constructed. For instance, W. Chen, et al. combined magnesium-aluminum LDHs nano-adjuvants with immune stimulants to create a 3D-printed "ring-shaped" carrier. It can enhance the efficiency of local temperature conduction by responding to radiofrequency electric fields, while releasing immune-stimulating molecules to activate anti-tumor immunity, achieving a dual effect of "local thermal ablation therapy and systemic immune protection" [158]. In conclusion, LDHs are expected to overcome the current challenges and become key materials for the treatment of various diseases. LDHs will be able to provide patients with more effective and safer treatment options in the future, driving significant changes in the field of biomedical materials in disease treatment.

This review systematically summarizes the latest progress of nanomaterials based on LDHs in the treatment of oxidative stress-related diseases, and critically analyzes the five core challenges currently faced: although the synthesis process is standardized, but the biological activity is still insufficiently understood. In addition, there are deficiencies in long-term biological safety, the precision of targeted and controlled release, and in-depth research on the relationship between structure and function. To address these challenges, we have proposed corresponding solutions and future directions, including establishing standardized synthesis processes, leveraging artificial intelligence to assist in material design, deepening the understanding of the biological activity and *in vivo* mechanisms of LDHs, and developing intelligent responsive delivery systems. Ultimately, to promote the transition of LDHs from basic research to clinical application, close collaboration among multiple disciplines such as materials science, biology, and medicine is necessary to fully exploit their potential as the next-generation nanoscale diagnostic and therapeutic platform.

CRediT authorship contribution statement

Zhaoxu Meng: Writing – original draft, Conceptualization. **Jun Wang:** Writing – original draft, Investigation. **Ouyang Su:** Writing – original draft, Investigation. **Yiping Mu:** Supervision, Project administration, Conceptualization. **Xiu Dong:** Supervision, Project administration, Conceptualization. **He Lian:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Zonghui Zhang:** Methodology, Investigation. **Zhou Li:** Project administration, Funding acquisition. **Lili Lu:** Visualization, Methodology. **Yake Qi:** Visualization, Methodology.

Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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