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Review of lipoic acid: From a clinical therapeutic agent to various emerging biomaterials

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ABSTRACT

Lipoic acid (LA), an endogenous small molecule in organisms, has been extensively used for the highly efficient clinical treatment of malignant diseases, which include diabetes, Alzheimer's disease, and cancer over the past seven decades. Tremendous progresses have been made on the use of LA in nanomedicine for the development of various biomaterials because of its unique biological properties and highly adaptable structure since the first discovery. However, there are few reviews thus far, to our knowledge, summarizing this hot subject of research of LA and its derived biomaterials. For this purpose, we present herein the first comprehensive summary on the design and development of LA and its derived materials for biomedical applications. This review first discusses the therapeutic use of LA followed by the description of synthesis and preclinical study of LA-derived-small molecules. The applications of various LA and poly (lipoic acid) (PLA)-derived-biomaterials are next summarized in detail with an emphasis on the use of LA for the design of biomaterials and the diverse properties. This review describes the development of LA from a clinical therapeutic agent to a building unit of various biomaterials field, which will promote the further discovery of new therapeutic uses of LA as therapeutic agents and facile development of LA-based derivates with greater performance for biomedical applications.

1. Introduction

Lipoic acid (LA), IUPAC name: 5-(1,2-dithiolan-3-yl) pentanoic acid, is a natural occurring dithioheterocyclic compound that was first isolated from liver by Reed in 1951(Reed et al., 1951). The activity of LA is mainly based on the disulfide heterocyclic ring in its structure, where the two neighboring sulfur atoms repel each other at a rather high electron density, leading to the strong reductive property of LA.

LA has two optical isomers: bioactive (R)-isomer [R-LA or (+) LA] and (S)-isomer [S-LA or (-) LA]. The R-isomer exists in nature, while the S-isomer is mainly prepared by chemical methods. The reduced LA is called dihydrolipoic acid (DHLA). Brookes successfully determined the

Abbreviations: Aβ, β-amyloid peptide deposition; ATP, adenosine triphosphate; CMX-2043, α-N-[(R)-1,2-dithio-lane-3-pentanoyl]-L-glutamyl-L-alanine; C4LA, Calix[4]arene LA; CDs, carbon dots; DHL-TauZnNa, (N-[6,8-dimercaptooctanoyl]-2-aminoethane-sulfonate zinc complex; DTT, 1,4-dithio-D,L-threitol; DHLA, dihydrolipoic acid; EMT, epithelial-mesenchymal transition; EDC, carbodiimide activation; GSH, glutathione; GLUT, glucose transporter; HA, hyaluronic acid; LA, lipoic acid; LPO, lipid peroxide; MDA, malondialdehyde; MDDSs, multivalent drug delivery system; NOS, nitric oxide synthase; PDH, pyruvate dehydrogenase; PI3K, phosphatidylinositol-3-kinase; PMs, polymer micelles; PDT, photodynamic therapy; QDs, quantum dots; R/R AML, relapsed/refractory acute myeloid leukemia; T1DM, type 1 diabetes; TAN, N-hydroxy succinimide; TKN, thioketal nanoparticle; TEAEs, treatment-related adverse events; TM, thiophanate-methyl; AD, Alzheimer's disease; BBB, blood-brain barrier; CPI-613, 6,8-Bis-benzylsulfanyloctanoic acid, devimistat; CLS, cross-linked liposome; DHL-HisZnNa, N-(dihydrolipoyl)-l-histidinate zinc complex; DN, Diabetic neuropathy; DMXAA, 5-methylethonone-4-acetic acid; DIB, 1,3-diisopropenylbenzene; EPR, enhanced permeability and retention; FAD, flavin adenine dinucleotide; GSSG, oxidized glutathione; HNK, bond magnolol; IRS1, insulin receptor substrate-1; KGDH, α-ketoglutarate dehydrogenase; MCI, mild cognitive impairment; mPEG, methoxy-poly(ethylene) glycol; NDDS, nanomedicine delivery system; PKB, protein kinase B; PLA, poly (lipoic acid); PGMA, polymethyl methacrylate; PTAs, photothermal agents; PTT, photothermal therapy; ROS, reactive oxygen species; SAMs, self-assembled monolayers; T2DM, type 2 diabetes; TCA cycle, tricarboxylic acid cycle; UV, ultraviolet; VE, α-tocopherol; VC, ascorbate.

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absolute configuration of LA as R in 1983(Brookes et al., 1983). Elliott made asymmetric synthesis under the induction of chiral auxiliary reagent for the first time and successfully synthesized R-α-LA(Elliott et al., 1985). Presently, chemical synthesis is the principal method to produce LA: (1) chemically catalyzed asymmetric synthesis method starting from achiral raw materials(Kaku et al., 2010; Sudalai, 2001); (2) chiral resolution methods starting from racemic intermediates(Bose et al., 2006; Purude et al., 2015); (3) asymmetric synthesis methods starting from commercial chiral raw materials(Chavan et al., 2015).

The disulfide ring of LA was reduced to give dihydrolipoic acid (DHLA). Studies demonstrated that both LA and DHLA have strong antioxidant properties and form a synergistic effect in the body(Dos Santos et al., 2019; Farhat and Lincet, 2020). The redox potential reflects that LA/DHLA (−0.32 V) takes more advantages than glutathione (GSH)/oxidized glutathione (GSSG) (-0.24 V) and cystine/cysteine (−0.22 V) in providing antioxidant protection. The antioxidant effect of LA/DHLA stems from the following aspects: (1) scavenging reactive oxygen species (ROS) such as ·OH, ·NO, ·ROO; (2) chelating metal ions such as Hg^{2+}, Mn^{2+}, Pb^{2+}, Cu^{2+}, Fe^{2+}, Zn^{2+}; (3) regenerating endogenous antioxidants such as GSH, ascorbate (VC) and α-tocopherol (VE). Hence, LA/DHLA is called "omnipotent antioxidant" in redox reaction in human body. The effect of antioxidation also lays the foundation for its application in the treatment of malignant diseases.

LA is widely distributed in cell membrane, cytoplasm and extracellular space of all cells, especially in mitochondria, where it is most densely distributed. As an important cofactor of mitochondrial multienzyme complexes involved in tricarboxylic acid cycle (TCA cycle) in energy metabolism, such as pyruvate dehydrogenase (PDH), α-ketoglutarate dehydrogenase (KGDH), and flavin adenine dinucleotide (FAD), which can regulate the stability and redox dependence of multienzyme complexes. However, it is worth noting that LA acts only when it binds to a specific enzyme subunit (E2) through covalent binding. In summary, LA is a substance that plays a key role in mitochondrial activity, coordination of energy metabolism, etc., and the excellent properties of LA have clearly aroused the curiosity of researchers.

Current research on LA derivates is divided into two categories in biomaterials: small molecules and supramolecular polymers. Small molecule derivatives of LA are widely developed and used in the treatment of various cancers(Hiratsuka et al., 2013; Philip et al., 2019), cardiovascular diseases(Kates et al., 2015) and chemotherapy-induced alopecia(Sagawa et al., 2019). At present, several kinds of small molecules have been tested in clinical trials, including 6,8-Bis-benzylsulfanyloctanoic acid (CPI-613), N-(dihydrolipoyl)-l-histidinate zinc complex (DHL-HisZnNa) and α-N-[(R)-1,2-dithio-lane-3-pentanoyl]-L-glutamyl-L-alanine (CMX-2043) and so on. Among them, CPI-613 is considered to be the most promising drug based on mitochondrial targeting drug (Zachar et al., 2011). The mechanism is to damage mitochondrial metabolism and inactivate PDH and KGDH. CPI-613 is extremely effective in xenograft tumor growth inhibition trials, including pancreatic cancer(Gao et al., 2020), lung cancer(Lycan et al., 2016), ovarian adenocarcinoma(Bellio et al., 2019), and so on. Reasonable preclinical and clinical studies results provide accordance for their clinical advance.

Besides being small molecular drugs, the extremely simplified amphiphilic molecular structure of LA personates an important role in the field of biomaterials. Firstly, the hydrophobic core formed in the hydrophobic segment in aqueous solution is convenient for the preparation of shell-core micelles(Li et al., 2009; Richter et al., 2021) and nanogels(Li et al., 2016). The disulfide bond on the terminal pentane can be available as a ligand to modify the surface of specific functional materials. Secondly, self-assembled monolayers (SAMs) formed by covalent bonding with the surface of the material can protect materials on the one hand. On the other hand, carboxyl groups provide more opportunities to graft different active functional groups (Muro et al., 2012; Zhang et al., 2011). In addition, the disulfide bond is fairly easy to fracture and repolymerize under the facile preparation method, and various biomaterials can be synthetized by utilize the potential reaction sites of carboxyl groups(Chen et al., 2020; Choi et al., 2021; Zhang et al., 2018). In general, the special and simple structure of LA provides unlimited possibilities for the creation of novel substances to provide an opportunity in the construction of drug delivery carriers, self-repairing materials, biological detection, sensing platform, wearable and flexible pressure sensors, and other fields.

In this review, we summarized the application of LA from endogenous small molecules to biomaterials (Fig. 1). We first introduced the physiological role of LA in cells to highlight how it exerts curative effect in mainstream diseases as an endogenous small molecule. Secondly, we begin to describe the application of LA in the construction of biomaterials with excellent functions. Small chemical molecules with excellent activity derived from the basic structure of LA and their clinical experimental progress are presented in detail, followed by the perspectives and outlooks of pharmaceutical chemistry field. Last emphasis is placed on how LA is skillfully applied to biomaterials to achieve extreme improvement in all aspects of material properties.

2. Therapeutic usage of LA

LA, as a coenzyme factor, participates in mitochondrial energy metabolism and is considered to be the most effective natural antioxidant (Fig. 2). The remarkable electrophilic ability and free radical reaction capability of LA are realized through its five-membered disulfide bond ring. Substantial basic studies have implied that LA can stimulate an array of cellular actions, such as the ROS scavenger, the chelating agent for metal ions, the regeneration of other endogenous antioxidants, and anti-inflammatory factors(Deore et al., 2021; Fiedler et al., 2021; Hajizadeh-Sharafabad and Sharifi Zahabi, 2020; Spain et al., 2021; Zeng et al., 2021). Both LA and DHLA can scavenge (1) ·OH, ·NO, ·ONOO and other free radicals in the body; (2) hydrogen peroxide, hypochlorous acid and other substances that are prone to free radicals. The antioxidant activity of LA is also verified as a model drug in biomaterials. Liu et al. simulated tumor microvascular environment with triglyceride-gelatin hydrogel on microfluidic chip and co-cultured glioma cell line U87 and human umbilical vein endothelial cells. The results *in vitro* showed higher selectivity of LA to U87 cells than that of human umbilical vein endothelial cells, which confirmed that LA had strong antioxidant capacity(Liu et al., 2017). Its intrinsic activity provides a basis for clinical application, including diabetes, Alzheimer's disease, cancer (Fig. 3).

2.1. LA for diabetes

LA mainly acts on type 1 (T1DM) and type 2 (T2DM) diabetes. T1DM is characterized by absolute insulin deficiency. LA plays a therapeutic role in T1DM by affecting insulin metabolic pathway, glucose uptake and glycogen synthesis. LA enhances glucose metabolism by increasing the activity of insulin receptor kinase (IR), insulin receptor substrate-1 (IRS1), phosphatidylinositol-3-kinase (PI3K) and protein kinase B (PKB), which mediates the displacement of glucose transporters GLUT1 and GLUT4 to the plasma membrane of the cell(Moini et al., 2002; Smith et al., 2004; Tibullo et al., 2017; Yaworsky et al., 2000). The antioxidant properties of LA are used to scavenge the ROS caused by amylin and to inhibit the deposition of amylin in islets and cellular toxicity which is one of the markers of T2DM(Azzam et al., 2018). Therefore, in clinical treatment, regular intake of LA through diet or nutritional supplements can prevent and treat T2DM. Diabetic neuropathy (DN) is one of the serious complications of T1DM and T2DM, which can involve the central and peripheral nerves. LA for injection is currently used clinically in the treatment of sensory abnormalities caused by diabetic neuropathy for more than 30 years in Germany.

2.2. LA for Alzheimer's disease

To date, patients with mild to moderate Alzheimer's disease (AD)

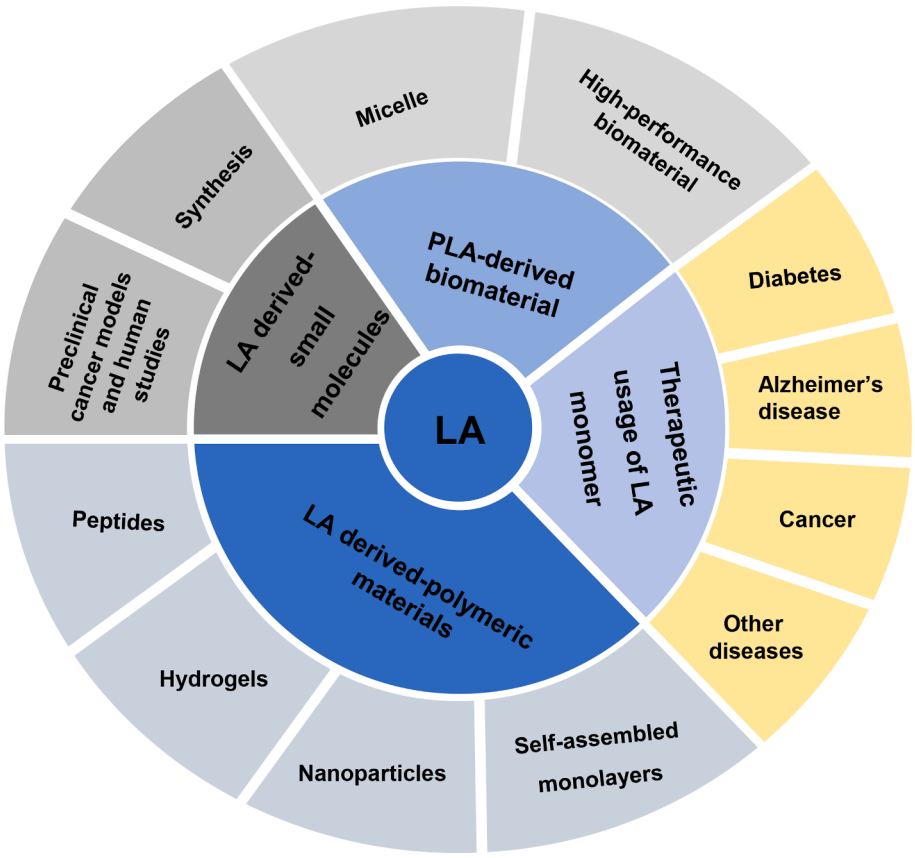

Fig. 1. Schematic illustration of the application of LA from a clinical therapeutic agent to various emerging biomaterials.

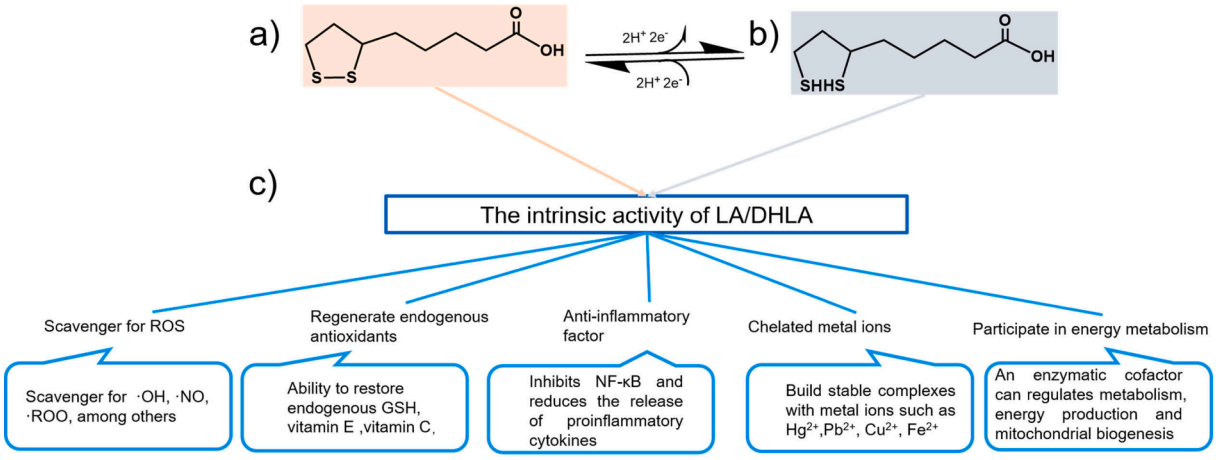

Fig. 2. The chemical structure of (a) LA and (b) DHLA (reduced form), and (c) the intrinsic activity of LA/DHLA.

were treated with cholinesterase inhibitors in approved AD treatments (donepezil, rivastigmine, and galantamine) (Stefano et al., 2011). Interestingly enough, LA helps increase glucose uptake and metabolism, and the final product of glucose metabolism is acetyl-CoA(Holmquist et al., 2007; M. Rosini et al., 2011). Acetyl-CoA is a pivotal catalyst for the synthesis of acetylcholine, which acts as the main component of neurotransmitter in synaptic transmission, and plays a role in transmitting nerve excitement. Harsh et al. performed [1-^{13}C] glucose infusion on 13-month-old triple transgenic mice (3xTg-AD mice model) followed by an ex vivo ^{13}C NMR to found that the mice had low glucose metabolism, and successfully reverse this low metabolic state after treating LA(Sancheti et al., 2014).

Metal ions such as iron, copper, zinc, and aluminum haven bee reported to participate in the pathogenesis of AD(Wang and Wang, 2016). The metabolic disorder of metal particles has great toxicity to the nervous system which affects neuronal metabolism to cause oxidative stress and eventually lead to cell death(Oddvar et al., 2013). As we all know, LA is a general-purpose antioxidant with both fat-soluble and water-soluble properties which can easily cross to BBB reach any part of the cell and provide comprehensive treatment. Lovell et al. reported that LA can protect hippocampal neurons in primary culture from both Aβ peptides and Fe/H_2O_2 mediated toxicity. The metal chelating properties of LA may enhance the extraction of Aβ peptides from cortical areas (Lovell et al., 2003). Fonte et al. successfully dissolved amyloid β with a

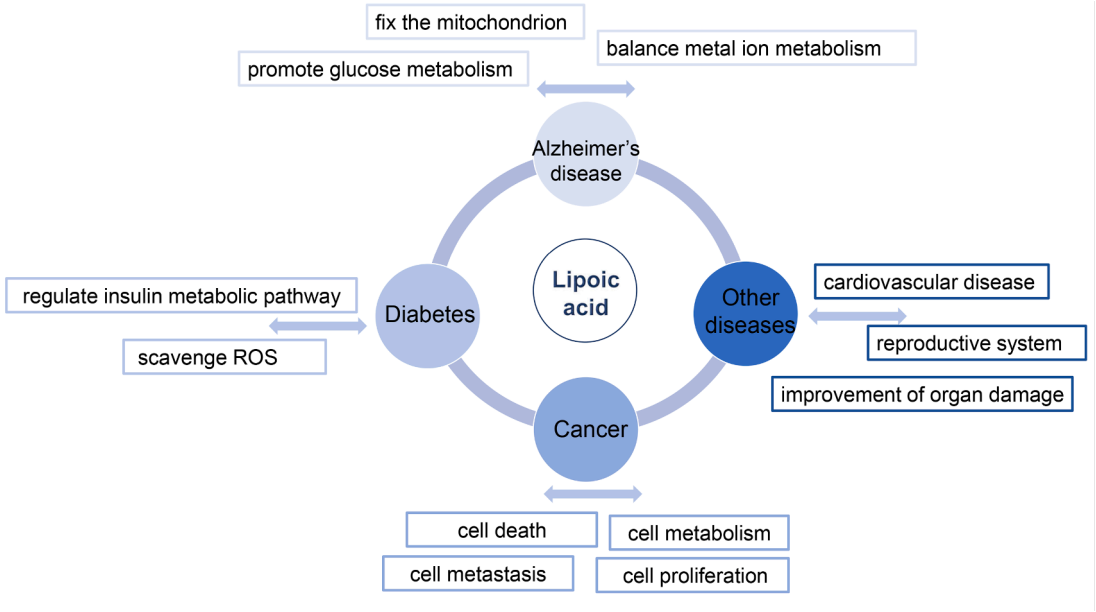

Fig. 3. Schematic illustration of the therapeutic usage of LA.

transition metal ion chelator, and found in a mouse model of AD that LA can enhance the extraction of amyloid β from the frontal cortex(Fonte et al., 2001). Besides, mitochondria are the main source of the production of ROS. Extensive studies shown that mitochondrial dysfunction is one of the important factors in the pathogenesis of AD by generating ROS(Calvo-Rodriguez and Bacskai, 2021; John and Reddy, 2021; Pradeepkiran and Reddy, 2020). The damage of neuronal mitochondria in patients with AD has been recognized for decades. According the comparison of the same age group, many abnormalities of mitochondrial metabolism were found in the neurons of patients with AD, which caused an increase in ROS production and a decrease in energy storage, resulting in neurodegeneration(Moslemnezhad et al., 2016). Mitochondria which play a fundamental role in the regulation of intracellular bioenergy may be the key to the pathogenesis of AD. In this sense, LA may fix mitochondrial function by acting as a cofactor of mitochondrial enzyme complex and anti-oxidant to achieve the treatment of AD.

2.3. LA for cancer

Enough basic experimental studies have proved that LA possess positive significance in the treatment of cancer. The basic anti-tumor mechanisms of LA are as follows:

(1) Induction of apoptosis and proliferation; Dozio et al. found that LA treatment can reduce the proliferation of MCF-7 cells, which may be due to inhibition of Akt pathway, up-regulation of cyclin-dependent kinase inhibitor p27kip1, and change of apoptosis-related protein Bax/Bcl-2 ratio(Dozio et al., 2010). This phenomenon was observed in FaDu(K. Van de Mark et al., 2003), HepG2(Jiang et al., 2015), and Hey8A(Vig-Varga et al., 2006) cells. With regard to ROS, Moungjaroen et al. confirmed that H460 human lung cancer cells were incubated with 100 μM LA for 24 h, an increase in ROS levels was observed, leading to the down-regulation of the mitochondrial anti-apoptotic protein Bcl-2, and finally triggering the mitochondrial apoptosis pathway(Moungjaroen et al., 2006).

(2) Inhibition of epithelial-interstitial transformation; Jeon et al. (Min et al., 2015) found that the abundance of cadherin in thyroid cancer cells treated with LA increased, while activated β-catenin and vimentin involved in mesenchymal phenotypic invasion and tumor progression decreased accordingly. In cancer stem cells that was proved to drive tumor progression and metastasis, the expression of these markers also decreased after LA treatment(Phiboonchaiyanan and Chanvorachote, 2017). Correspondingly, EMT induced the decrease of mRNA expression of transcription factors Snail and Twist in thyroid cancer cells. In breast cancer cell lines MCF-7 and MDA-MB-231 pretreated with LA and then irradiated, Tripathy et al.(Tripathy et al., 2018) observed that LA can not only increase the sensitivity of cells to ionizing radiation but also inhibit radiation-induced EMT.

(3) Regulation of tumor metabolism. The Warburg effect was discovered as early as the 1920 s. LA acts as a cofactor for PDH and activates PDH activity by inhibiting pyruvate dehydrogenase kinase. PDH can catalyze the conversion of pyruvate to acetyl-CoA, thereby preventing the production of lactic acid. Focusing on the high metabolism of cancer cells and suppressing the aerobic cycle may contribute to anti-cancer effects. Feuerecker et al. (Feuerecker et al., 2012) demonstrated in various cancer cell lines that adding a certain dose of LA can inhibit the formation of lactate and the proliferation of tumor cells. It also was found that daily LA treatment can delay tumor growth in a mouse transplantation model of SkBr3 tumor cells.

2.4. LA for the improvement of organ damage

LA adjuvant therapy can improve organ damage caused by conventional therapeutic drugs. Clinical medicine treatment induced side effect resulting in damage to normal tissues. The serious normal tissue toxicity caused by the frequently used antineoplastic such as cyclophosphamide (Mythili et al., 2007), cisplatin(El-Beshbishy et al., 2011), and doxorubicin(El-Sayed et al., 2017) limits the expansion of clinical treatment. Another example is methotrexate as an anti-metabolite for the treatment of tumors and rheumatoid arthritis, often accompanied by severe liver damage(Fayez et al., 2018). Radiotherapy has unhealthy complications in the later stage of treatment, which seriously affect the therapeutic effect(Kim et al., 2020; Said et al., 2020). The damage of normal tissues is partially associated with drug therapy resulting in inflammatory reactions and oxidative stress induction. Recently, to find new drugs that can neutralize or reduce side effect in clinical treatment is the immediate task. As a powerful antioxidant, LA can effectively regulate the level of antioxidant enzymes and prevent inflammation and oxidative stress. The El-Sayed's team compared the single-dose doxorubicin group with the group treated with LA and doxorubicin, and found that the latter could reduce nephrotoxicity, proving that LA treatment reduced the increase of biomarkers of inflammation, oxidative stress, and apoptosis in rats(El-Sayed et al., 2017). Long-term radiation therapy can

ultimately lead to temporary or even permanent tissue damage. The addition of the antioxidant LA to the treatment process is beneficial to improve this damage. Said'group found that LA is effective in reducing testicular dysfunction mediated by ionizing radiation in rats(Said et al., 2020). The severe damage caused by clinical treatment can lead to aggravation of the disease or forced withdrawal of drugs is fatal for patients. It is worthwhile to consider using LA which has been fully verified *in vivo* and *in vitro* as an adjuvant to improve or prevent side effects caused by treatment.

2.5. LA for other diseases

Many clinical basic studies reported the application of LA in other diseases, such as cardiovascular disease, reproductive system related disease, and organ replacement related diseases(Ambrosi et al., 2016; Ambrosi et al., 2018; Makvandi et al., 2019; Truong and Gardner, 2017). In terms of cardiovascular disease, LA has been demonstrated that possess therapeutic effects in various *in vivo* models related to redox imbalance: ischemia and reperfusion(Ding et al., 2021), heart failure(Li et al., 2020a) and hypertension(El Midaoui et al., 2019). Recently, several studies have increasingly highlighted the impact of LA in reproductive system, such as pregnancy, sperm cell, and oocyte. For example, Nasr-Esfahani's group reported that LA can play a protective role in improving sperm quality and maintaining sperm function by reducing sperm lipid peroxidation and increasing antioxidant enzyme activity(Makvandi et al., 2019). Gardner's group found that LA also can reduce the level of ROS in oocytes, thereby increasing its total antioxidant capacity and ultimately enhancing the developmental potential of oocytes(Truong and Gardner, 2017). The antioxidant and anti-inflammatory effects of LA also was demonstrated to be protective in organ replacement in not only several animal experimental models but also humans(Ambrosi et al., 2018). Ambrosi's group reported that LA for the treatment of organ donors and recipients with simultaneous kidney and pancreas transplantation showed protective effect on short-term outcomes(Ambrosi et al., 2016). Additionally, LA is considered safe and effective anti-obesity drug, which has been reported to reduce weight in obese adults, children and adolescents(El Amrousy and El-Afify, 2020; Huerta et al., 2015; Nong et al., 2017).

3. Synthesis and preclinical study of LA derived-small molecules

Both LA and DHLA are pharmacophores with unique antioxidant properties. Based on its chemical and biological properties, LA is an attractive modified molecule, and its derivates with excellent activity show potential pharmacological effects.

3.1. Synthesis of LA derived-small molecules

LA is prone to oxidation, desulfurization, polymerization, amide condensation, and esterification. It is soluble in organic solvents and insoluble in water. The active carboxyl group of LA is chemically combined with clinical drugs by esterification. In a series of identical reports, it has been demonstrated that the chemical combination of LA with a variety of clinical therapeutic drugs such as scopolamine(Connell et al., 2016), edaravone(Connell et al., 2014), paclitaxel(Falah et al., 2019), apocynin(Tarek et al., 2015), andrographolide acid(Yao et al., 2012; Zhang et al., 2009), and oxoisoaporphine(Chen et al., 2014), showed better therapeutic efficiency than either of the two compounds alone in disease models. Chen' group synthesized the oxoisoaporphine-LA hybrids which significantly improved the learning and memory ability of Aβ42 transgenic Drosophila. The compound had been proved could inhibit AD-related neurotoxicity by regulating cholinergic system and weakening the neurotoxicity induced by Aβ42(Chen et al., 2014). Andrographolide-LA-1 which was derived from andrographolide acid and LA through esterification was found to be a major inflammatory transcription factor, significantly reducing the inflammatory response of inflammatory bowel disease(Moeinian et al., 2019; Yang et al., 2016) (Fig. 4a). Andrographolide LA 1 is at least 10 times more potent than Andrographolide in inhibiting the activation of RIN-m nuclear factor-κB (Yao et al., 2012). And the underlying mechanism of Andrographolide LA 1 is still being sought.

LA, with instability and poor solubility, is difficult to be applied in clinic. It is extremely important to construct a novel substance with excellent physical and chemical properties and therapeutic effect by changing the structure of LA. In addition to chemically combining clinical drugs with LA, some derivates obtained by introducing metal ions or modifying other groups to change the structure of LA molecules. As early as in 1994, Cronan et al. synthesized a LA derivative called selenolipoic acid by replacing two sulfur atoms with selenium. Unexpectedly its biological properties were unaltered to incorporate into the α-ketoacid dehydrogenase complexes of growing cells(Jordan and Cronan, 2002; Reed et al., 1994). Based on this pioneer work, Xu et al. developed a green and high-yield selenolipoic acid synthetic route and further accessed different groups at the carboxyl terminus to screen a LA derivative with high inhibitory efficiency in MCF-7, HL-60 and HeLa cancer cell lines(Xu et al., 2013). Considering the high effectiveness of LA is in ischemia-reperfusion injury as well as into the brain, intravenous administration of a single selenium analogue may be useful in the treatment of stroke, spinal cord injury, and myocardial infarction. Encouraged by the excellent experimental results of the previous researchers, more and more new substances derived from LA are being synthesized. Seigo et al. synthesized a highly stable antioxidant DHL-HisZnNa (N-(dihydrolipoyl)-l-histidinate zinc complex)(Kono et al., 2012) (Fig. 4b) and DHL-TauZnNa (N-[6,8-dimercaptooctanoyl]-2-aminoethane-sulfonate zinc complex)(Hiratsuka et al., 2013) (Fig. 4c), which both has cytotoxic and anti-proliferative effects on human colorectal cancer cell line HT-29 *in vitro* and *in vivo*. Beeuwkes's group obtained the CMX-2043 (α-N-[(R)-1,2-dithio-lane-3-pentanoyl]-L-glutamyl-L-alanine) by partial condensation of natural and non-natural amino acids with carboxylic acid of LA(Kates et al., 2014) (Fig. 4d). CMX-2043 is more effective in reducing cardiac ischemia-reperfusion injury in rats than LA(Baguisi et al., 2016). The most promising derivates of LA is compound CPI-613 (6,8-Bis-(benzylsulfinyl)octanoic acid) (Zachar et al., 2011) (Fig. 4e). CPI-613 is a pioneering drug that can selectively inhibit the function of tumor cell mitochondria, which is obtained by symmetrically grafting benzylthio group on reduced dithiolane ring by Bingham's team(Zachar et al., 2011).

Another source of LA derivatives is a kind of metabolite in biological artifacts. As LA is well known as a noted antioxidant molecule, some researches have been conducted on its biological metabolites deservedly. Schupke's group investigated the changes in the products of LA during metabolism in detail, based on an on-line liquid chromatography/tandem mass spectroscopy assay, which identified LA and a total of 12 metabolites(Schupke et al., 2001). Szeląg et al. further demonstrated an antioxidant mechanism of LA metabolite sequential proton loss electron transfer in polar media and hydrogen atom transfer in vacuum(Szeląg et al., 2012). The metabolites of LA include 2,4-dimethylthio-butyric acid (BMTBA) and tetranor-dihydrolipoic acid (tetranor-DHLA). Kwiecień et al. found that both tetranor-DHLA and BMTBA observably reduced the inflammatory response in fermentase-induced peritonitis and in the carrageenan-induced hind paw edema models in mice(Kwiecień et al., 2013). Clearly, more efforts should be devoted to the work on LA metabolites, which could be used to direct the rational design and development of any LA-based new compounds for better properties and performance.

The change of LA explored by the researchers originated from LA monomers and innovated in the introduction of different chemical groups. Excellent toxicity experiments at the cellular level verify that small molecular derivatives of LA can pave the way for follow-up biosafety experiments and further work. The easily modified characteristics of LA, which provide a solid foundation for subsequent innovative research.

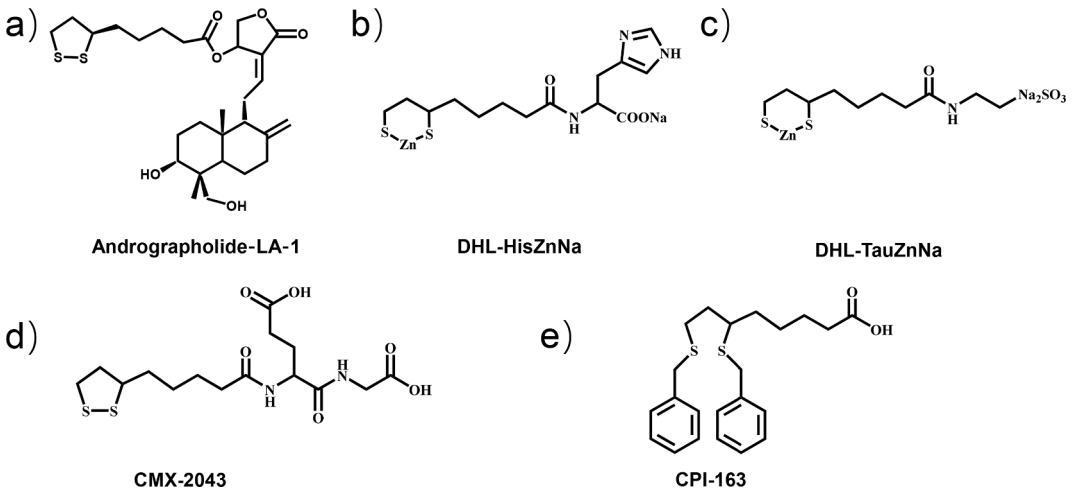

Fig. 4. Molecular structure of typical LA derivates.

3.2. Preclinical cancer models and human studies of LA derived-small molecules

At present, as shown in Table 1, there are already a variety of derivatives that are undergoing or have completed clinical trials. The clinical trials of some derivatives have obtained inspiring results. Phase II clinical trial of a new antioxidant DHL-HisZnNa in the prevention of chemotherapy-induced alopecia (CIA) caused by anticancer drugs in breast cancer patients was finished. Applying 1% DHL-HisZnNa on the scalp does not prevent CIA, but the results also show that it can promote the recovery of CIA(Sagawa et al., 2019).

CMX-2043 has currently completed preclinical safety studies and Phase I clinical trials. The experimental results are based on 40 volunteers showing that none of the volunteers who received doses of 20 mg, 60 mg, and 150 mg of CMX-2043 reported serious treatment-related adverse events (TEAEs). There were no TEAEs at the highest dose of 300 mg, which was 15 times that at the lowest dose of 20 mg(Kates et al., 2015). Low toxicity in the preclinical safety study and the void of TEAEs in the Phase I trial support further studies of CMX-2043 in human efficacy trial.

CPI-613, a non-redox active derivative of LA, is a new type of fatty acid ester analogue developed as a potential anticancer drug. The mechanism of CPI-613 is to destroy the mitochondrial metabolism of cells and block the activities of PDH and KGDH, thereby preventing either glucose or glutamine-derived carbon from entering the TCA cycle (Vasan et al., 2020; Zachar et al., 2011), showing the effective anticancer effect on human non-small cell lung cancer and pancreatic cancer *in vivo* xenotransplantation model. CPI-613 has been used in many clinical trials along with other clinical drugs like FOLFIRINOX (a four-drug combination of fluorouracil, leucovorin, irinotecan, and oxaliplatin), topotecan and mitoxantrone. The results of clinical trials for various diseases show that CPI-613 is an up-and-coming clinical medication. In a previous phase I trial, modified FOLFIRINOX combined with devimistat was given to 18 patients with metastatic pancreatic cancer at the maximum tolerable dose, and there was an objective response rate of 61%, including a complete response rate of 17%(Alistar et al., 2017). Therefore, the evaluation of efficacy and safety of devimistat (CPI-613) combined with modified FOLFIRINOX and FOLFIRINOX in patients with pancreatic metastatic adenocarcinoma is undergoing phase III clinical trial, known as AVENGER500(Philip et al., 2019). In the early corresponding phase I/II clinical trial with devimistat in combination with high-dose cytarabine and mitoxantrone for relapsed/refractory acute myeloid leukemia (R/R AML), the complete remission/complete remission with incomplete hematologic recovery rate of elderly patients treated with 2000 mg/m^2 was 52%(Pardee et al., 2018). From this, a phase III clinical trial for R/R AML is in progress(Pardee et al., 2019). Phase II clinical trial of CPI-613 combined with topotecan in the treatment of relapsed or refractory small cell lung carcinoma has been completed. The 12 patients who participated in the clinical trial did not see a complete or partial response, of which 11 (92%) died with the median survival time was 4.3 months (range 1.2 to 18.2 months)(Lycan et al., 2016). Throughout the trial, CPI-613 alone was considered to be lack of therapeutic efficiency, but patients who given topotecan after CPI-613 showed treatment response. Therefore, CPI-613 in combination with a topoisomerase inhibitor in patients in the further research is

Table 1
Typical examples of LA derived-small molecules for clinic trial study.

Drugs	Indication	Phase	Results	Ref.
Devimistat, modified FOLFIRINOX	pancreatic metastatic adenocarcinoma	phase III clinical trial	ongoing	(Philip et al., 2019)
Devimistat, Cytarabine, Mitoxantrone	relapsed/ refractory acute myeloid leukemia	phase III clinical trial	ongoing	(Pardee et al., 2019)
CPI-613, Topotecan	relapsed or refractory small cell lung carcinoma	phase II Clinical Trial	eleven patients (92%) died with median overall survival of 4.3 months (range 1.2 to 18.2 months)	(Lycan et al., 2016)
DHL-HisZnNa	against anticancer agent-induced alopecia in breast cancer	phase II clinical trial	all 101 patients developed grade 2 alopecia, this drug may promote recovery from Chemotherapy-induced alopecia	(Sagawa et al., 2019)
CPI-613	advanced hematologic malignancies	phase I clinical trial	4 achieved an objective response and 2 others achieved prolonged stabilization of disease (29%)	(Pardee et al., 2014)
CMX-2043	Ischaemia-reperfusion injury	phase I clinical trial	no serious adverse events were reported in a placebo-controlled, sequential dose escalation Phase I clinical trial.	(Kates et al., 2015)

indispensable. In advanced hematological malignancies, a phase I clinical trial was conducted using the first-in-class anti-mitochondrial metabolism drug CPI-613. Among the 21 evaluable patients with undergone heavily pretreatments, 4 patients achieved objective responses, and 2 reached prolonged stable conditions, and the overall clinical benefit rate is 29%(Pardee et al., 2014). Based on the data that CPI-613 targets mitochondria to destroy cancer cells and further block carcinogenic signals, clinical experiments have been shown that it is meaningful to combine it with clinical therapeutic drugs.

At present, completed or ongoing clinical trials have demonstrated that the structural modification of LA is extremely rewarding creation. In the near future, perhaps we can see that small molecules derived from LA will enter the medical-market.

4. LA derived-polymeric materials for biomedical applications

In addition to being modified to form small molecules with bioactivity, LA is also widely used in polymeric materials. LA not only provides better stability to biomaterials, but also increases the versatility of biomaterials.

4.1. Preparation of LA derived-polymeric materials

Due to the unique structure, LA is both hydrophilic and lipophilic. Hydrophilic carboxylic acid groups can be easily grafted onto the side chains of natural polymers through esterification and amide condensation reactions. The hydrophobic segment creates a structure with rapid drug release, stability and reduction reaction for the nanomedicine drug delivery system (NDDS)(Fang et al., 2020; Peng et al., 2021; Richter et al., 2021). LA and DHLA also can form SAMs on the surface of metal nanoparticles and dots through covalent bonding, thereby providing such materials with better stability and functional diversity(Bhardwaj et al., 2020; Muro et al., 2012; Wang et al., 2021b). Finally, LA undergoes ring-opening polymerization (ROP) under simple conditions, such as ultraviolet (UV), heat, and the obtained PLA gradually emerges in the field of biomaterials(Li et al., 2020b; Liu et al., 2019; Yang et al., 2018).

4.2. Nanoparticles

Nanoparticles can enhance significantly the transportation efficiency of drugs in the human body. Drug-loaded nanoparticles can actively target and attack cancer cells or other diseases via intravenous administration.

4.2.1. Nanoparticles in tumor therapy

In the treatment of cancer, the *in vivo* cancer nanomedicine delivery system (NDDS) includes five stages: internal circulation (C), tumor accumulation (A), penetrate into the tumor (P), internalization by tumor cells (I) and intracellular drug release (R) (Fig. 5). The high therapeutic efficacy and favorable prognosis require that the nano-system efficiently completes the full CAPIR cascade *in vivo*(Sun et al., 2014). NDDS own the advantages of better stabilization, higher drug loading, and safety. In addition to passively targeting tumors through enhanced permeability and retention (EPR) effect, active targeting can also be introduced by ligand modification, resulting in higher drug concentration at tumor sites and lower toxicity compared with systemic administration. And compared with normal tissue cells, the concentration of redox substances, the type and quantity of enzymes, pH value, and temperature of tumor microenvironment are quite different. How to combine these features to achieve targeted, rapid and complete drug release in tumor cells has aroused widespread interest. The redox properties of LA can be regarded as a tool in future NDDS to accurately regulate the release of drugs in an "on-off" manner in accordance with clinicians' prescriptions.

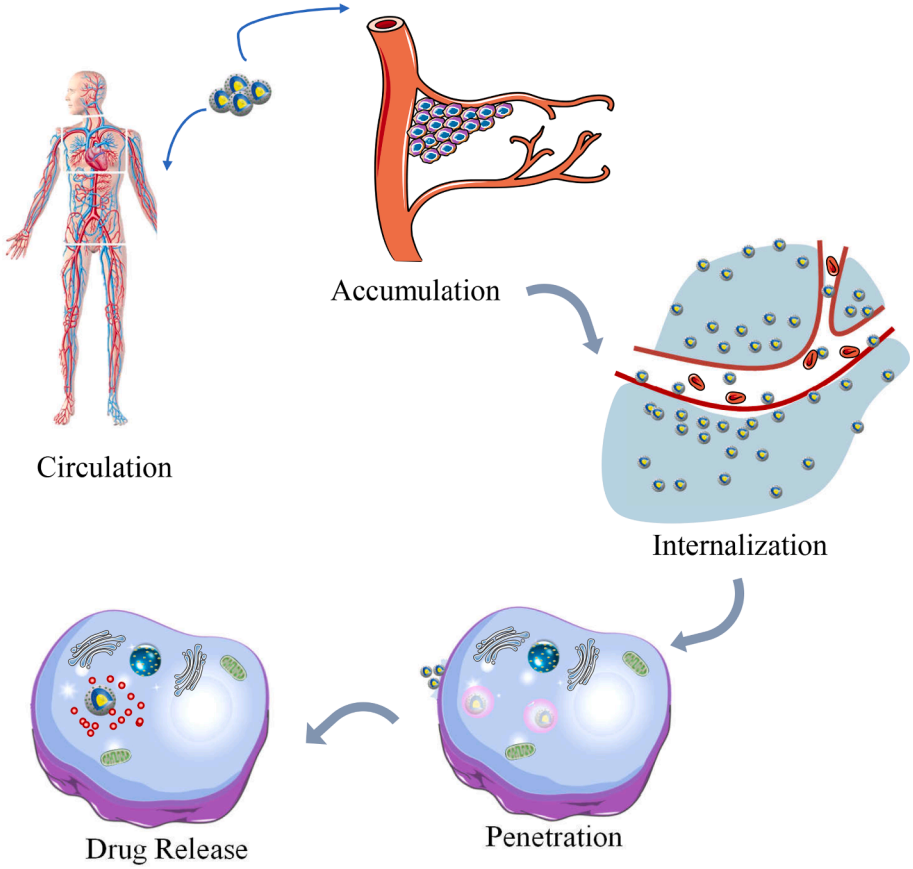

Fig. 5. *In vivo* delivery process of NDDS.

4.2.1.1. Redox shell crosslinked micelle. Reduction-responsive nuclear cross-linked NDDS have been widely used in the field of intracellular drug release. The methods of disulfide crosslinking nanomicelle are generally divided into two categories: (1) the crosslinking agent containing disulfide bifunctional groups added after polymer assembly; (2) the polymer side chains of nanomicelle contain sulfhydryl groups or disulfide bonds, which can be oxidized to form stable crosslinking through self-assembly. The carboxyl group in the LA can be used as the side group of core-shell micelles to modify natural or synthetic polymers, while the disulfide bond is easy to break at high GSH concentration. Moreover, the rupture of disulfide bond in tumor cells promotes the consumption of GSH, which provides a considerable solution to reverse the drug resistance of tumors. In 2009, Zhong's group reported that LA was modified by dextran side chain to obtain reduction sensitive reversible cross-linked drug nanoparticles, which takes into account the advantages of extracellular stability and intracellular reduction trigger rapid drug release. The nanoparticle exerts a high inhibitory effect on the proliferation of cervical cancer cell Hela and leukemia cell K562(Li et al., 2009). Wherein lipoyl rings are opened at the disulfide bond under the catalysis of 1,4-dithio-D,L-threitol (DTT) to form a preferential linear disulfide polymer. The hydrophobic core of the carrier is connected into a whole to enhance the stability of the nano-drug carrier. In the reduction environment of high GSH concentration of cancer cells, the disulfide bond of the micelle is destroyed, and then the carrier was cleaved to release doxorubicin. And the drug release rate and anti-tumor effect are better than those without cross-linking(Li et al., 2009) (Fig. 6a). Zhong et al. additionally reported reversibly crosslinked hyaluronic acid (HA) nanoparticle with both reduction sensitivity and active targeting of CD44 receptor based on HA-Lys-LA conjugates for DOX delivery. This nanoparticle can rapidly gather depending on actively target tumor cells expressed by CD44 receptor, and lose stability under reduction conditions, making drug accumulation effectively reverse drug resistance in tumor cells(Zhong et al., 2015) (Fig. 6b). In order to be used in the clinical market, we need to find a better skeleton with better biocompatibility.

LA plays another role in the micelles of photodynamic therapy (PDT) and photothermal therapy (PTT). The introduction of LA also solves the problem of some photothermal agents (PTAs) which are hard to be loaded into micelles because of physical or chemical properties. The hydrophobic IR780, a derivative of indocyanine green, is one of the PTAs. High crystallinity and strong π-conjugated chemical structure hinder the viable preparation of IR780 micelles. Li's group combined with computer simulation and introduced another biocompatible small molecule into the micelle to regulate the interaction energy between

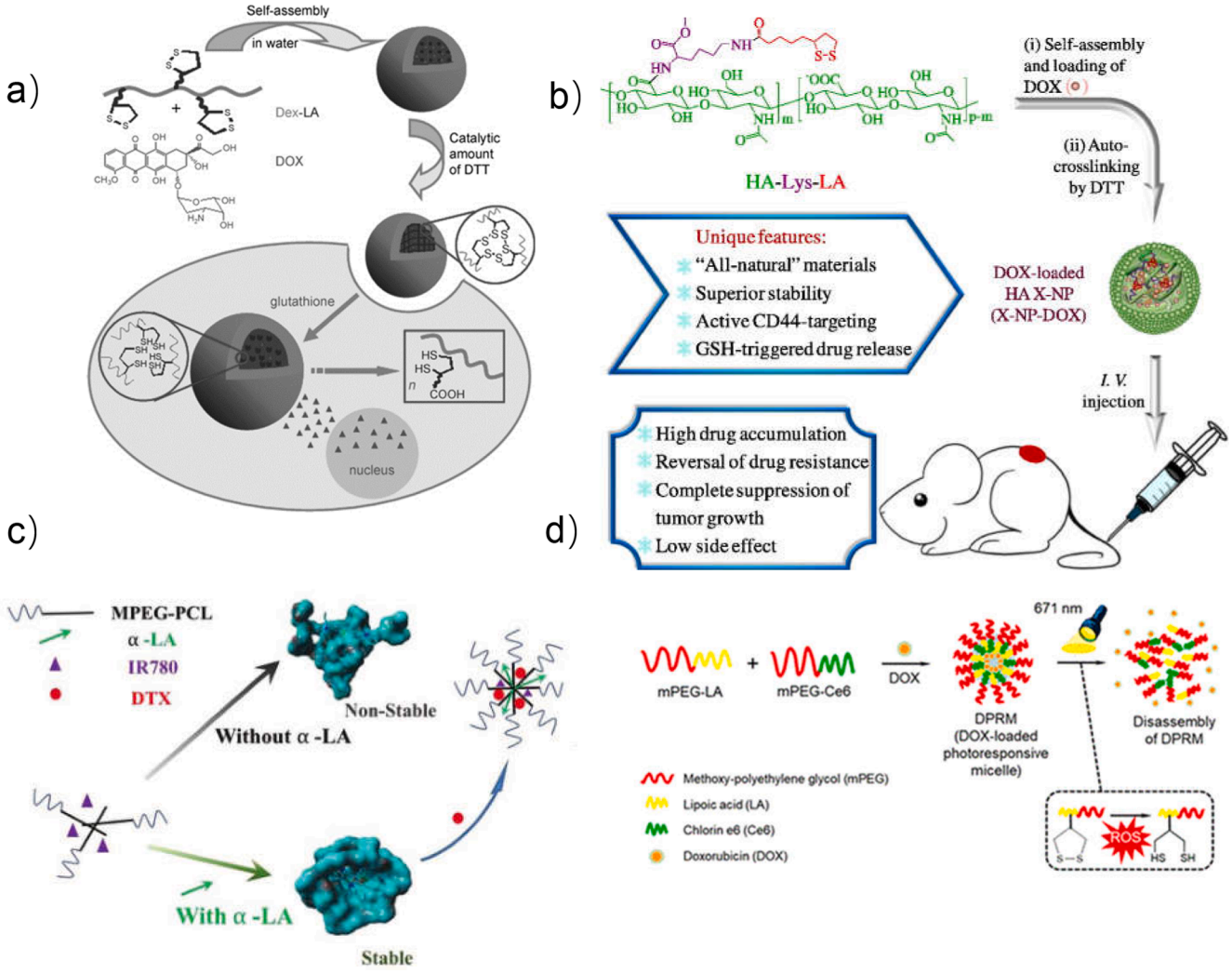

Fig. 6. a) Illustration of reversible redox-shell cross-linked micelles obtained by coupling LA to dextran. Adapted with permission from Ref(Li et al., 2009). Copyright 2009, Elsevier. b) HA nanoparticles (HA X-NPs) based on disulfide crosslinking can target CD44 and reverse drug resistance. Adapted with permission from Ref (Zhong et al., 2015). Copyright 2015, Elsevier. c) The introduction of LA can enhance the stability of micelles to facilitate the loading of hydrophobic drugs. Adapted with permission from Ref(Li et al., 2018). Copyright 2018, Royal Society of Chemistry. d) Scheme of the PD-L1-AuNP-DOX with light-triggered DOX release at tumor sites. Adapted with permission from Ref(Kim et al., 2018). Copyright 2018, American Chemical Society.

IR780 and amphiphilic block polymer molecules. The results showed that the introduction of LA increased the loading capacity of IR780 compared with polymer molecules without LA. DTX/IR780 co-loaded micelles had excellent tumor growth inhibition effect in the treatment of breast cancer model in nude mice bearing tumor for 42 days(Li et al., 2018) (Fig. 6c). Photosensitizer can switch energy to the surrounding oxygen and generate singlet oxygen with robust activity. LA as a redox sensitive substance, disulfide bond breakage will occur in the case of high GSH concentration or ROS. Rapid release of chemotherapeutic drugs in the presence of a sharp increase in singlet oxygen compared to the conventional tumor microenvironment. Kim'group designed DOX loaded photoresponsive micelles (DPRMs) based on the combination of PS (chlorin e6, Ce6) and LA conjugated methoxy-poly(ethylene) glycol (mPEG). LA and Ce6 were covalently combined with mPEG to form a single composite system. The redox sensitive aliphatic ring of mPEG-LA was brought into DPRMs to induce light-mediated reduction (Fig. 6d). In the nude mouse model of CT-26 tumor, in contrast with laser irradiation and chemotherapy alone, the tumor of mice treated with DPRMs under

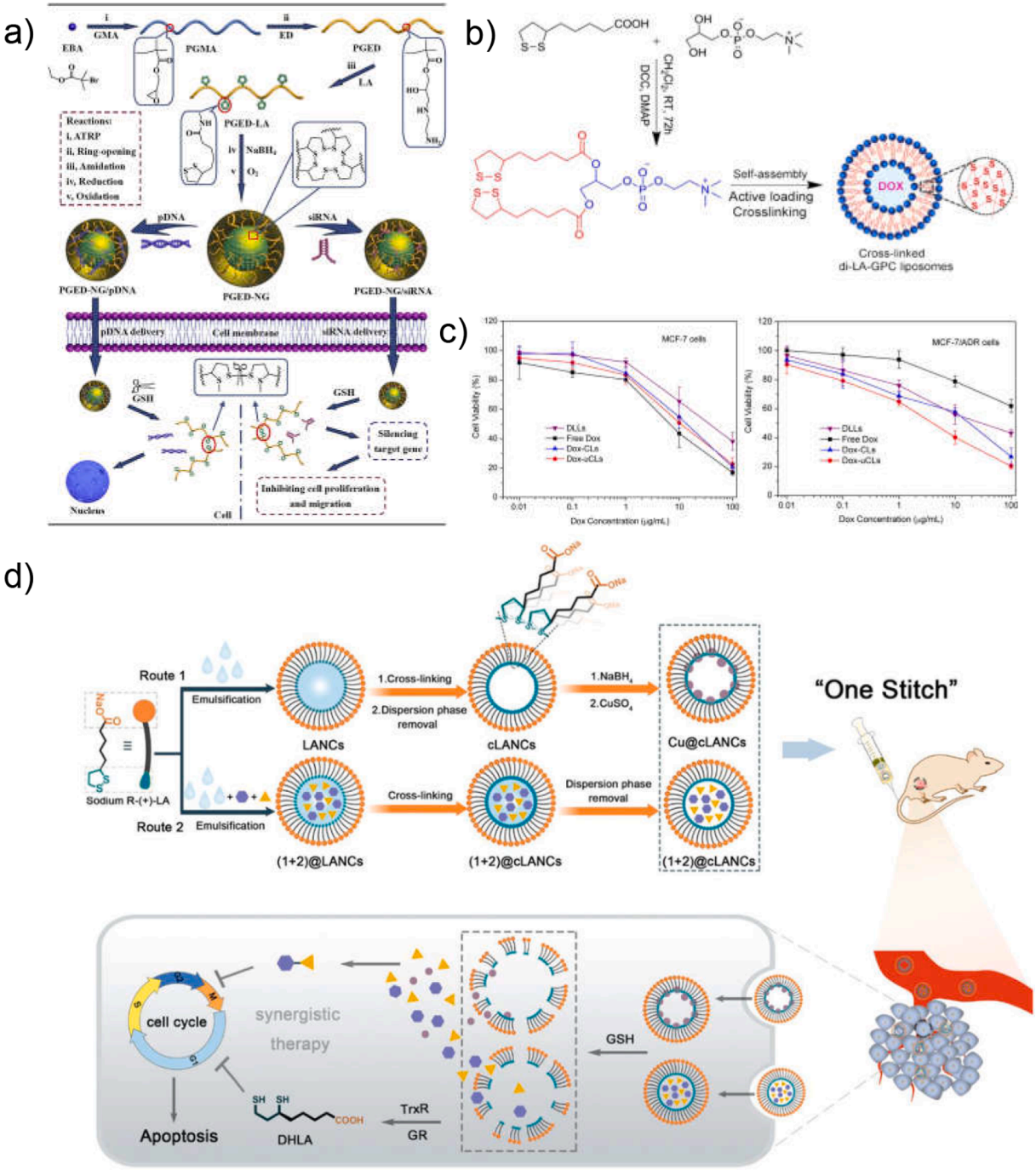

Fig. 7. a) Schematic diagram of the synthesis of cationic nanogels (PGED-NGs) cross-linked by α-LA and the loading of pDNA and siRNA. Adapted with permission from Ref(Li et al., 2016). Copyright 2016, Elsevier. b) Synthesis, self-assembly, active loading of Dox and cross-linking of di-LA-PC conjugate. Adapted with permission from Ref(Ling et al., 2019). Copyright 2019, Elsevier. c) Inhibitory effect of different experimental groups on the viability of MCF-7 cells and MCF-7 / ADR cells. Adapted with permission from Ref(Ling et al., 2019). Copyright 2019, Elsevier. d) Schematic illustrations of the nanocapsule based on the cross-linked LA with two-component bioorthogonal nanosystem for the treatment of human colorectal tumor. The exfoliated LA maintains its anticancer activity, thus enhancing the anticancer effect of drugs synthesized in situ. Adapted with permission from Ref(Wang et al., 2021a). Copyright 2021, Elsevier.

laser irradiation showed considerably greater tumor growth inhibition efficiency (Kim et al., 2018).

4.2.1.2. Nanogel. Nanogel is a kind of functional polymer material with a three-dimensional network structure and has good swelling properties in water(Soni et al., 2016). Nanogel as an ideal drug delivery system shows a broad application prospect in the delivery of chemotherapeutic drugs, protein drugs and gene drugs in biomedical fields. Li et al. believe that the multifunctional nanogels prepared by simple polyion complexation and cross-linking methods are expected to become a promising drug-carrier system for targeted delivery(Li et al., 2016). The transportation and delivery of DNA and RNA for therapeutic purposes is a particularly challenging field. A balance needs to be found between high binding capacity, biocompatibility and drug release. Utilizing ethylenediamine-functionalized low-molecular-weight polymethyl methacrylate (PGMA) as the main segment, successfully synthesized a series of cationic nanogels with LA crosslinking reagents (PGED-NGs). The introduction of LA not only provides the characteristic of sensitivity to reduction reaction, but also improves the stability and circulation time (Fig. 7a). The cationic nanogel effectively encapsulates pDNA and siRNA, and exhibited highly efficient nucleic acid delivery and excellent abilities for inhibiting the growth of hepatocellular carcinoma cell HepG2(Li et al., 2016).

4.2.1.3. Liposome. Liposomes have been recognized as one of the most promising drug delivery systems after years of research since they were first discovered in 1963. Doxil® as the first PEGylation liposome preparation of doxorubicin was approved by FDA in 1995(Duggan and Keating, 2011). The phospholipid bilayer of liposomes is similar to biological membranes, with favorable biocompatibility and weak carrier toxicity. The discrete aqueous spaces and internal aqueous core contained in liposomes can encapsulate hydrophilic, lipophilic drugs, proteins, and other macromolecules. Stimulus-responsive liposomes are very popular because of their specific and selective drug release, potentially lower side effects, and reversion of cell resistance. On the grounds of the significant difference of redox environment the extra- and intra- cells and the overexpression of GSH in tumor cells, the disulfide bond of LA can be considered as the responsive linker. Liposomes were formulated by connecting hydrophilic substances at the carboxyl end of LA as the hydrophilic layer of the phospholipid bilayer, and the cross-linked disulfide bonds could be regarded as the hydrophobic layer. Ling et al. prepared a novel disulfide cross-linked liposome (CLS) by facial esterification of LA and glycerophosphorylcholine(Ling et al., 2019) (Fig. 7b). CLS encapsulates doxorubicin stably in vesicles, and highlights its potential to reverse drug resistance through the inhibitory effect on the proliferation of doxorubicin-resistant MCF-7/ADR cells. More importantly, it was found that CLS was more effective than free Dox and DLL with the same dose in nude mice carrying human breast carcinoma xenograft(Ling et al., 2019) (Fig. 7c). Maiti and his colleagues(Maiti et al., 2018) introduced two new tocopherol-based molecular entities and LA covalently coupled through ester bonds to synthesize two new α -tocopherol LA conjugates (TL1 and TL2). Both conjugates are able to form stable, serum-tolerant, biocompatible and reduction-responsive nanovesicles. TL1 and TL2 release 50% and 40% DOX respectively under the condition of GSH, the natural biological reducing agent of cells. The efficiency of doxorubicin delivery and the effectiveness of inhibiting cell proliferation of the two vesicles in doxorubicin-resistant HeLa cells were higher than those of doxorubicin alone.

4.2.1.4. Potential therapeutic enhancement of dissociation of LA in NDDS. NDDS hold bright future in clinical therapeutics in cancer chemotherapy. However, the carrier itself turns into redundant substance in the biological body with the delivery task is completed. The clinical application prospects of NDDS are severely limited because the poor curative effect, as well as higher cytotoxicity in the body. LA and DHLA can induce apoptosis in various cancer cell lines, while having almost no effect on normal cells. In a series of NDDS with the structure of LA mentioned above, LA and DHLA may still retain the bioactivity when it breaks in the tumor microenvironment. In recent years, Zhang's team reported a series of new drug container of cross-linked LA vesicles constructed solely from biogenic (R)-(+)-LA(Liao et al., 2019; Wang et al., 2021a; Yang et al., 2021). After the drug was released in target tissues, the carrier was no longer a redundant substance, but degraded into DHLA with a strong synergistic anticancer effect *in vivo* and *in vitro* (Fig. 7d)(Wang et al., 2021a). The results showed that cross-linked LA vesicles downregulated anti-apoptotic Bcl-2 protein and upregulated the level of caspase-3 protein, which confirmed that cell death was triggered by pro-oxidant mechanism through mitochondrial pathway. Perhaps it is a choice to enhance the synergistic effect when LA is applied to the NDDS.

4.2.2. Nanoparticles in the treatment of other diseases

Besides the extensive use of LA and its derivatives for cancer therapy, LA-based nanoparticles have been applied in antibacterial therapy and antioxidation. Stefano et al. adulterated levodopa and dopamine with LA, respectively, to obtain four multifunctional adjuvants with antioxidant properties. Sustained release of levodopa was observed following oral administration of the adjuvant drug in the presence of gastrointestinal enzymatic digestion and exhibited antioxidant effects, which could improve free radical damage and reduce dopamine concentrations in the brain(Stefano et al., 2006). Luo et al. synthesized LA-modified chitosan nanoparticles. The grafting of LA improved the anti-E. coli effect of chitosan as evidenced by the inhibition circle and growth curve (Luo et al., 2019). Interestingly, chitosan-coated LA nanoparticles could be used as a nutritional supplement to improve the passage of LA through the human gastrointestinal tract. Quester et al. demonstrated that LA encapsulated in chitosan nanoparticles can cross the intestinal barrier by atmospheric pressure intestinal technique(Quester et al., 2022). Therefore, proper inclusion of LA in a balanced diet may have a preventive effect on diseases such as cardiovascular disease, diabetes and obesity.

4.3. Hydrogels

The reasonable design of hydrogels with mechanical flexibility, self-healing ability, the similarity to biological soft tissues and electrical conductivity have attracted recent attention in strain sensing, environmental monitoring, body health monitoring, object tracking, intelligent equipment, and so on. Xiong et al. constructed a qualified pH "off-on" signal switch in chemical and biosensors by combining DHLA-modified silver nanocomposites with agarose hydrogels. The range of pH change measured by fluorescence sensor is 4.0–8.0, which can be competent to monitor pH change during bacterial growth and metabolism(Xiong et al., 2016). Li's group functionalized LA at the end of Pluronic F127 (PEO_{99}-PPO_{65}-PEO_{99}) and prepared "one-component, multi-response" hydrogels by photo crosslinking. F127-LA hydrogel has thermal response and reductive response, as well as self-healing properties under UV irradiation. The cytocompatibility assay using L929 mouse fibroblasts showed that F127-LA had no adverse effect on cellular metabolic activity(Song et al., 2019).

4.4. Peptide

Generally, peptides incorporation endows the resulting peptide-decorated conjugates with various functions, such as enhanced targeting and therapeutic effects. An elegant integration of LA and peptides has been highlighted to exert a synergistic effect in antibacterial, detection of cell numbers, and anti-aging. A notable example is the use of LA as not only a link for peptide modification, but also a co-drug to enhance the activity of the conjugated peptide. Yao et al. prepared LA-Bac8c conjugates by introducing LA as a hydrophobic ligand of fatty

acids for the natural antimicrobial peptide Bac8c. The minimal inhibitory concentration (MIC) value of LA-Bac8c against staphylococcus aureus (MRSA) was lower than Bac8c alone because LA-Bac8c exhibited better degradation activity against the formed or forming biofilms, disrupting the integrity of bacterial membranes and leading to leakage of material inside the bacteria(Zhou et al., 2020). Chai et al. obtained a potential adjuvant with anti-melanogenic and anti-aging properties by linking LA to the pentapeptide Lys-Thr-Thr-Ly-Ser(Lu et al., 2013). The resulting LA-peptide conjugates were non-toxic to normal cells at high concentrations and stimulated collagen biosynthesis in fibroblasts more effectively than the pentapeptide.

4.5. Self-assembled monolayers

SAMs provide opportunities for an in-depth understanding of the relationship between structure, performance and various interface phenomena at the molecular and atomic levels(Casalini et al., 2017). SAMs can not only improve the physical and chemical properties of the material surface, but also can use SAMs as a medium to graft other functional groups on the surface of materials. Up to now, the widely used model is mercaptan/metal SAMs, a class of SAM systems first used for self-assembly. Significantly, SAMs formed with carbon dots, as a new type of carbon nanomaterials, do not involve the use of heavy metals in the preparation process, and have high biocompatibility and low cytotoxicity. And the sulfhydryl compounds is generally HS-$(CH_2)_n$-X (functional group)(Zhao et al., 2019). Obviously, LA accords well with the general structure of SAMs, and can exert good results with simple chemical modification. SAMs are prepared by using the strong interaction between the surfaces of monolayer materials. SAMs modified with LA can be found in the fields of biosensors, biotechnology, chemical sensors, and molecular electronics. The reactive carboxyl functional group of LA facilitates the rapid and stable grafting of the sensor. In the past decade, SAMs modified by LA has developed rapidly as an examination of biological sample in biosensors and chemical sensors(Casalini et al., 2017; Zhao et al., 2019).

4.5.1. SAMs formed on the surface of quantum dots

Quantum dots (QDs) are promising labeling agents and sensing platform. In order to promote the integration between QDs and biological systems, a common strategy is cap/ligand exchange, replacing the natural cap with hydrophilic bifunctional ligands with strong coordination on the metal surface to form SAMs to enhance stability and reach multiple functions(Aldeek et al., 2015; Wang et al., 2015; Zhu et al., 2015). As a commonly used ligands with multiple thiol group, such as LA, under various biological conditions, greatly improve the colloidal stability of QDs than those monothiol or other weakly coordinating groups (Fig. 8a). One end of the bifunctional ligand contains an anchor group for coordination to the surface of the nanocrystal and a

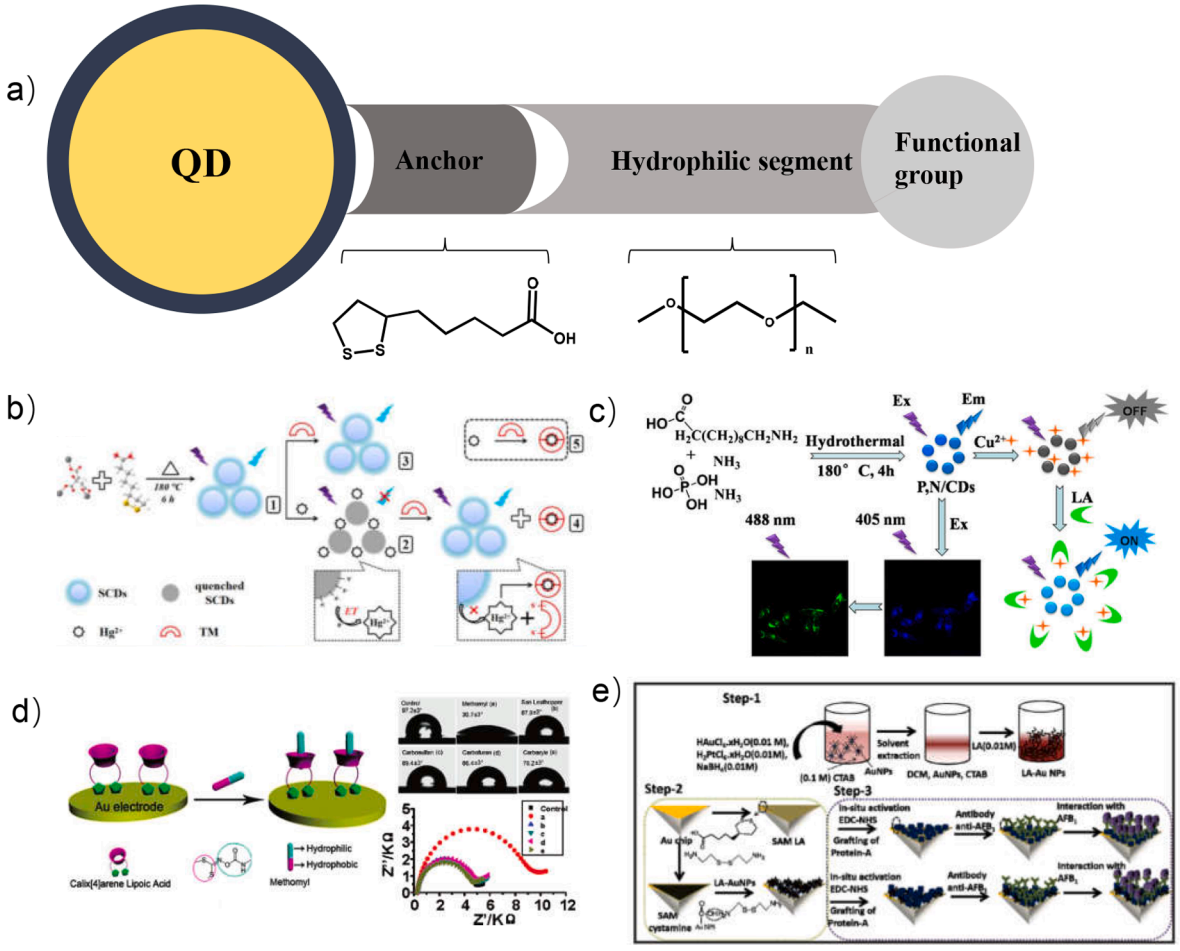

Fig. 8. a) Modular design of quantum dot surface modification. b) Schematic diagram of SCDs sensing model for detecting Hg^{2+} and TM based on the structure of LA. Adapted with permission from Ref(Wang et al., 2021b). Copyright 2021, Elsevier. c) Schematic diagram of the synthesis of P, N/ carbon dots and detection methods and cellular imaging of LA. Adapted with permission from Ref(Hu et al., 2019). Copyright 2019, Springer. d) Calix[4] arene LA immobilized it on the gold surface through self-assembly to form a self-assembled monolayer, which plays a role of detection through host–guest recognition. Adapted with permission from Ref(Zhang et al., 2011). Copyright 2011, American Chemical Society. e) Schematic diagram of different steps of multifunctional modification of biosensors. Adapted with permission from Ref(Bhardwaj et al., 2020). Copyright 2020, Elsevier.

chemically reactive group at the other end for further covalent coupling. Similarly, the modification of QDs uses this ingenious method. LA and QDs form a SAM on the surface of QDs by covalent bonding, thus obtaining stable and highly water-soluble QDs. Reactive groups at the end of the LA chain can be coupled to a potential biological function group (biotin, amine). All of the characteristics make the QDs have great application potential as a probe or carrier in imaging, diagnosis, sensing, and transmission applications. Dubertret's et al. reported that DHLA-modified QDs are more stable in the three intracellular delivery process (pinocytosis, electroporation, and microinjection) than phospholipid polyethylene glycol micelles or amphiphilic copolymers-encapsulated QDs. And the specific recognition of biotin is not affected (Muro et al., 2012). Susumu's group reported a kind of QD solutions capped with modular ligands based on LA and functional terminal groups to achieve stability over a long time and over a wide range of pH (Susumu et al., 2007).

However, thiol-terminated ligands have a negative effect on the photoluminescence properties of hydrophilic QDs. Most thiol-based ligands can be affected by photo-oxidation during prolonged storage time, causing the ligand desorption from the QD surface. Some studies combine distinct metal-coordinating groups, such as DHLA and histidine containing imidazole, together with the PEG moiety in the same ligand. This combination offers additional flexibility and solves problems of quenching and potential oxidation of thiol-based ligands (Wang et al., 2017; Wang et al., 2015).

4.5.2. SAMs formed on the surface of carbon dots

Carbon dots (CDs), a new type of photoluminescent nanomaterials was discovered in 2004, with the features of low toxicity, low cost, wide source of raw materials, excellent biocompatibility as well as distinctive physical properties(Kotta et al., 2020; Ostadhossein and Pan, 2017; Tian and Yin, 2019). The photoluminescent properties of CDs depend on different methods and raw materials, and the composition of CDs is a vital measure to understand its complex luminescence mechanism. Doped CDs is considered as a new field of carbon-based nanomaterials. The SAMs formed by heteroatom doped can effectively adjust the surface defects of CDs and change the optical properties of CDs. As a raw material, LA provides multidentate coordination groups which promote the formation of the complex and the optimization of CDs surface defects. Wang et al.(Wang et al., 2021b) found that the CDs sensing model synthesized by LA plays a key role in the detection of mercury ions and thiophanate-methyl (TM) in the environment, and the response performance is not affected by other common metal ions and pesticides. The addition of LA can not only increase the fluorescence properties of CDs by doping sulfur atoms, but also improve the stability of CDs(Wang et al., 2021b) (Fig. 8b). Besides, the prepared SCDs sensor with highly selective, sensitive, and effective in detecting Hg^{2+} and TM. The detection mechanism involves the complexes formed by LA and Hg^{2+} and the electron transfer reaction between SCDs and Hg^{2+}, causing the static fluorescence quenching of SCDs(Wang et al., 2021b).

CDs also as a fluorescent probe for the detection of LA in organisms with an excellent limit of detection. The high-sensitivity CDs prepared by researchers based on the characteristics of LA being easy to chelate with metal ions are very promising for the biological detection of LA. Hu et al. synthesized novel and efficient P, N co-doped CDs with intense blue fluorescence through a simple one-step reaction (Fig. 8c). The combination of the complex and Cu^{2+} as an "off-on" fluorescent probe for the detection of LA with high sensitivity and selectivity with the detection limit is 0.02 μM(Hu et al., 2019). Compared with the commonly used high-performance liquid chromatography, spectrophotometry, and fluorescence analysis, fluorescence probe detection of LA needs to be developed in the direction of rapid, efficient, low-cost, and environmental protection.

4.5.3. Other types of SAMs

Many functional supramolecular systems including crown ethers, cyclodextrin derivatives and calixarene can also be immobilized on the substrate surface to form SAMs. Li's research group synthesized Calix[4] arene LA (C4LA) using click chemistry and immobilized it on Au surfaces through self-assembly to form C4LA SAM (Fig. 8d). The SAM of C4LA exhibits a dual-signal response of wettability and impedance to carbamate pesticides with remarkable selectivity and sensitivity and can be used as a pesticide detection chip. And the author believes that the detection mechanism is molecular recognition through host-guest interactions(Zhang et al., 2011). Besides, many studies directly modify various detection units to SAM substrates to make biosensors. Connecting proteins/antibodies to the carboxyl-terminal functional groups of SAMs compounds by using carbodiimide activation (EDC)/succinimide (NHS), is the most commonly used method for the fabrication of biosensors. Hema et al. (Bhardwaj et al., 2020)developed ultrasensitive microfluidic surface plasmon resonance biosensor for the detection of aflatoxin B_1 in food (Fig. 8e). Multilayer chip surface was prepared using functionalized LA AuNPs deposited on SAM Au chips, followed by grafting of protein-A and immobilization of anti-AFB1antibodies. Multilayer functionalized AuNPs modified Au chip (0.01–50 nM) has been successfully utilized for aflatoxin B1 detection, which is better than bare self-assembled Au chip (1–50 nM).

5. PLA - derived biomaterial

As a macromolecular skeleton obtained by ROP of LA monomer, Poly (lipoic acid) (PLA) has been used in the construction of drug delivery carriers, self-repairing materials, wearable and flexible pressure sensors, intelligence devices and other fields.

5.1. PLA for micelle

PLA has been synthesized as early as several decades. PLA was prepared by a simple self-polymerization method and coupled with hydrophilic chain segment to improve hydrophilicity. The obtained copolymer is amphiphilic and can self-assemble into nano micelles in an aqueous solution. Furthermore, this system which can be degraded into the biocompatible by-product LA after completing the delivery task under redox conditions. This nanocarrier is used for the delivery of different types of medicine and may possess potential clinical application value. Liu's team used PLA as a nano-carrier to bond magnolol (HNK) and 5-methylethonone-4-acetic acid (DMXAA) conjugates at the carboxyl end. The disintegration of nano-drugs at the tumor cytoplasm under the high levels of GSH achieved the combination therapy of HNK and DMXAA. In the mouse 4T1 breast tumor model, the tumor inhibition rate was 93%(Liu et al., 2020). Moreover, by modifying disulfide bonds and introducing ROS response, the double response structure avoids the drug loss caused by a single response. Dual-response NDDS is sensitive to bio-related H_2O_2 and GSH and can release drugs as needed. Chen et al. used ROP to cleverly design a ROS and GSH dual responsive thioketal nanoparticle (TKN) for NDDS, succeeded in a programmable release of PTX at the tumor site(Chen et al., 2018) (Fig. 9a). The dual-stage responsive of reduction/oxidation reaction of nanoparticles indicated that the drug release rate was greatly accelerated after the addition of H_2O_2 and GSH successively (Fig. 9b). The tumor size chart clearly showed that PTX-TKNs effectively inhibit tumor growth with an inhibition rate of 65%(Chen et al., 2018) (Fig. 9c).

5.2. PLA for high-performance biomaterial

The development of high-performance polymer materials for biomedical applications is of great significance to the increasing demand of the future social development. Scientists have developed a series of polymer materials with plasticity, extensibility, self-repair, adhesion, and recyclability(Dong et al., 2015). However, complex properties and multifarious functions bring about the synthesis of polymer material with higher difficulty and cost. The key sensitive and tradeoff point is to

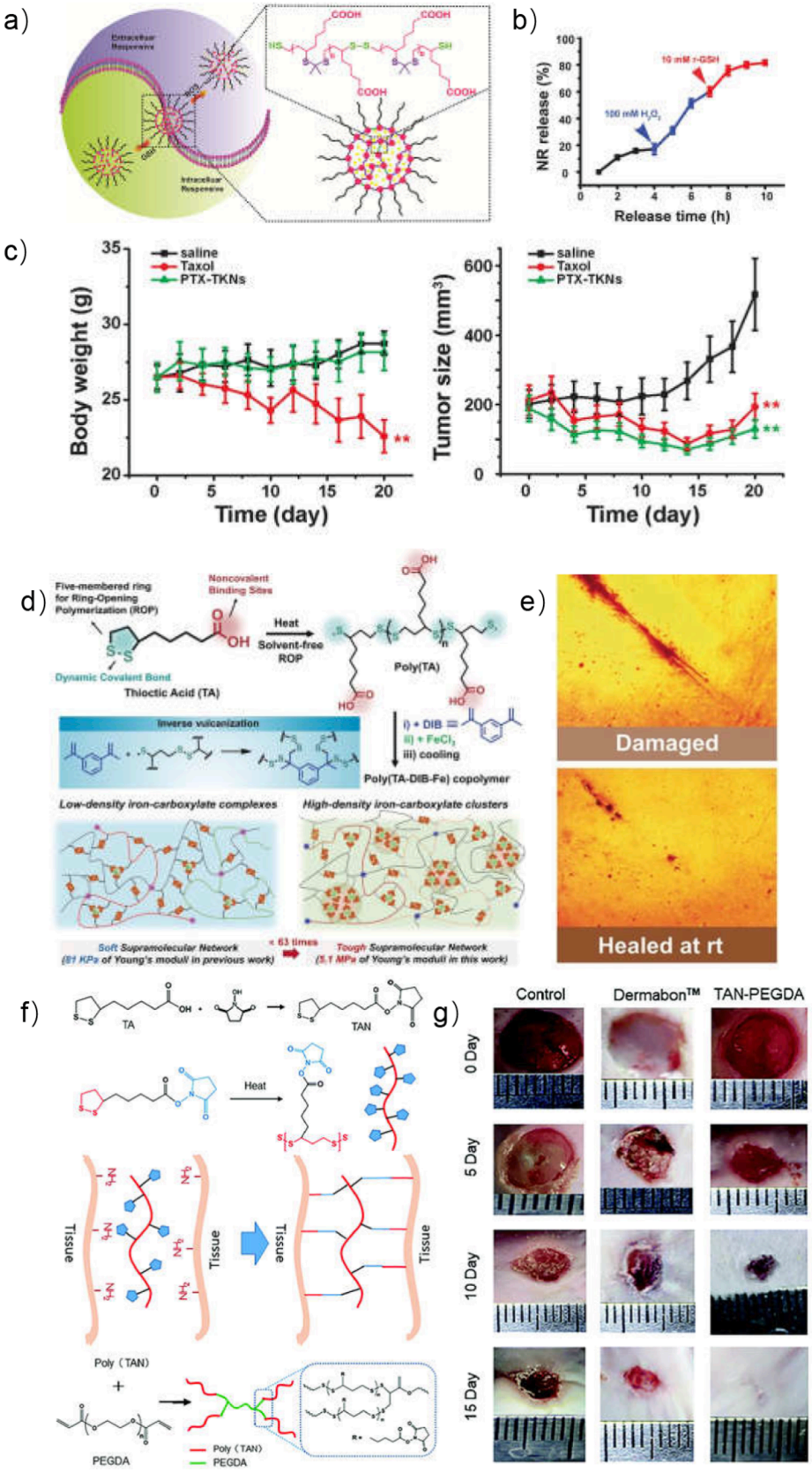

Fig. 9. a) ROS and GSH dual response nano-drug delivery system (PTX-TKNs). b) Drug release of PTX-TKNs triggered by 100 mM H_2O_2 and 10 mM GSH. c) The change curve of body weight of mice and tumor size in different groups during 20 days of treatment. Adapted with permission from Ref(Chen et al., 2018). Copyright 2018, American Chemical Society. d) Schematic diagram of synthesis of poly (LA) polymers. Iron-carboxylate complexes of different densities caused by different concentrations of Fe^{3+}. e) Auto-restoration of damaged polymers at room temperature for 24 h. Adapted with permission from Ref(Deng et al., 2020). Copyright 2020, Wiley-VCH. f) Schematic diagram of the structure of poly-TAN and the mechanism of wound healing. g) Photographs of wound healing during the 15 days of treatment. Adapted with permission from Ref(Chen et al., 2020). Copyright 2020, Royal Society of Chemistry.

reduce the complexity of the construction of materials and increase the property of material. Researchers are focusing on how to obtain polymer materials with excellent properties by simple preparation methods from readily available raw materials(Chen et al., 2012; Liu et al., 2018; Yan et al., 2018). LA exists two chemical bonds: covalent disulfide bond and non-covalent hydrogen bond of the carboxyl group. This tailor-made molecular structure makes LA a perfect raw material for constructing polymer networks in a hierarchical self-assembly fashion. Zhang et al. created a new class of thermoplastic polymers that can be formed without solvents. Using LA as the main feedstock, a cross-linked solid polymer poly (TA-DIB-Fe) was prepared by a facile blending method of molten LA liquid, 1,3-diisopropenylbenzene (DIB) and minimum $FeCl_3$, without involving external solvents. Poly (TA-DIB-Fe) copolymer can be performed as a self-healable elastomer at ambient temperatures(Zhang et al., 2018) (Fig. 9d). Nevertheless, the copolymer exhibits very low mechanical modulus (only 81 kpa), which limits the further application in high strength self-healing materials. Subsequently, Zhang et al. used evaporation-induced self-assembly technology to construct a layered sodium PLA with high crystallinity in next work(Zhang et al., 2019). Inspired by the high-strength ionic bonds in the sodium PLA material, the research team increased the concentration of Fe^{3+} in the reactant to 1% molar ratio, strictly avoiding the influence of water molecules in the air to produce a dry supramolecular network. The network shows tough mechanical strength (up to 5.1 MPa), self-repairing performance (Fig. 9e), and repeatable processing and recycling(Deng et al., 2020). The excellent performance of the polymer is attributed to four different dynamic combinations in a single network based on LA: dynamic covalent disulfide bonds, non-covalent hydrogen bonds, iron-carboxylate complexes and ionic cluster. It is conceivable that low-cost, natural product-based, biomaterial shines brilliantly in the application of self-healing materials, biodegradable devices, recyclable material, etc (Deng et al., 2020).

Poly (TA-DIB-Fe) copolymer network mentioned above has poor adhesion to tissues, high use temperature and toxic additives which limits its applications in biomedical fields. Chen'group directly used the ROP of LA to form a long polymer chain with end groups modified by N-hydroxy succinimide (TAN), making a xerogel from poly (LA) seems to solve these problems(Chen et al., 2020). Some kinds of literature confirmed that succinimidyl active esters can react with the amino groups of animal tissue proteins to form covalent bonds on the molecular chain, and found that the adhesive strength of the material with cartilage tissue was shown to be tenfold higher than that of fibrin glue(Bu et al., 2016; Strehin et al., 2010). However, the metastable properties of TAN seriously affect its applications. To improve the stability, the author grafted PEGDA to the chain segment (TAN-PEGDA), Chen's group successfully constructed a dry gel with the antibacterial effect which promote infection for wound regeneration (Fig. 9f). And in a mouse skin wound model, the wound was basically cured in 15 days under the treatment with TAN-PEGDA (Chen et al., 2020) (Fig. 9g). Huang's group reported the synthesis of tannic acid-lipoic acid (TALA) supramolecular hydrogel via ROP of LA and Michael addition reactions of thiol radical-polyphenol in the absence of toxic organic cross-linkers or heavy metal ions. The reaction can be performed in aqueous solution under mild conditions without tedious modification routes and precise chemical design, and further purification processes. In addition, TALA hydrogel also exhibits the properties of antioxidant, antibacterial activity, and adhesive, making it an ideal alternative for wound healing sutures(Chen et al., 2021).

The chemical modifiability of the carboxyl group in the side chain of PLA endows the dynamic molecular unit with huge expandable space (Zhang et al., 2022). These polymers with response to external conditions were used as functional materials in different areas, such as photo-cross-linked bottle brush polymer, surface and tissue crosslinking agent, stimulus-responsive self-healing gel, antifreeze wearable pressure sensor and so on. Bates et al. reported the dynamic photo-cross-linked bottle-brush network created by grafting LA onto the terminal group of PDMS polymers(Choi et al., 2021). The photopolymerization properties of LA under UV light in ambient conditions can additionally provide dynamic functions. After UV irradiation (365 nm), the resulting cross-linked network showed rapid repairable. Due to the existence of dynamic disulfide bond, the disulfide cross-linking network also can be degraded as needed when heated to 180 ℃ or by adding alkaline or reductive reagents.

Due to the limitation of pure water solvent, the traditional conductive hydrogel lacks the ability of moisturizing and anti-freezing, which greatly limits their application in extreme environment. Zheng et al. designed a PVA-B-TA-CNTs organic hydrogel with the ability to convert deformation into electrical signals, and possess the properties of excellent anti-freezing (-60 ℃), long-term moisturizing (30 days), perfect stability (400 cycles), conductive sensitivity ($S = 0.625\ kPa^{-1}$). This physical conversion based on pressure sensing is conducive to the development of monitoring machines that detect human movement in extreme environments(Zheng et al., 2021).

The recyclability of polymer materials is a significant feature of sustainable application in society in the future. A major challenge in biomaterial recycling need balance profit with recovery cost. Considering the cost-effectiveness of chemical recycling, the recycling features of polymer materials should be reproducible, environmentally friendly, and cost-effective. The depolymerization process of PLA needs to be in dilute solution and meets the requirement for disulfide bond breakings, such as heat, nucleophiles, and short-wavelength UV light. Zhang et al. reported a recyclable and reconfigurable poly (disulfide) polymer using LA as raw material. Both poly (TA-M) (M = Fe^{3+}, Cu^{2+}, Zn^{2+}, Ca^{2+}) elastomers and poly (TA-Na) ion networks are easily depolymerized into monomers by alkali-catalyzed cascade depolymerization in dilute solution of sodium hydroxide. The polymer can be completely depolymerized into high quality monomer, and the monomer recovery is as high as 86%(Zhang et al., 2021).

In industrial applications of polymer materials, LA is introduced to achieve functions such as high responsiveness to stimulation, environmental adaptability and self-healing. Moreover, the recyclable properties of PLA-based polymers are very important for the next generation of sustainable materials. In the frontier fields such as application-oriented designs and new material discovery, a noteworthy direction is to explore high-performance materials composed of LA and premium materials.

6. Conclusion and perspective

Definitely, both bench and bedside studies have confirmed the extensive use of LA and its derived biomaterials for biomedical applications. The high antioxidant activity of LA together with the diverse methods reported the functionalization of LA including oxidation, desulfurization, polymerization, amide condensation, and esterification enabled successful preparation of various LA-based polymers as novel biomaterials. This review made a first and timely review on the use of LA and its-derived biomaterials for biomedical applications in terms of therapeutic usage of LA, synthesis and preclinical study of LA derived-small molecules, and LA derived-polymeric materials for biomedical applications. Synthesis and application of various LA and PLA-derived-biomaterials were described in detail with an emphasis on the synthesis strategies and properties of materials. While tremendous progresses have been made on the development of various LA-based biomaterials with excellent properties and performance for biomedical applications, there still exist some critical issues that should be taken into account and addressed in future studies.

(1) Although enormous excellent and promising basic experimental results have been achieved over the past few decades, the clinical therapeutic effect of LA has not been fully demonstrated. Compared with the excellent basic experimental results of LA, LA only serves currently successfully as a drug mainly for the treatment of sensory abnormalities caused by diabetic neuropathy. In the future, based on the basic experimental results of LA, LA should be fully clinically applied for the

treatment of many other types of diseases. One approach is to use various drugs in combination. The combination of LA and clinical drugs can not only increase the curative effect, but also reduce the adverse effects of clinical drugs by the antioxidation of LA. Another approach is to chemically modify LA. At present, a series of clinical trials of the most eye-catching drug CPI-613 are under way. Looking to the coming years, the result of the phase III clinical trial of CPI-613 in patients with metastatic pancreatic adenocarcinoma (NCT03504423) will come out. Successful clinical trials targeting mitochondrial metabolism will take mitochondria to the forefront of cancer metabolism and immunemetabolism. More excellent clinical trials will inspire more researchers for continuous synthesis of small molecules with medicinal properties from LA.

(2) Biomaterials are used for artificial organs, surgical repair, diagnosis, and treatment of diseases that require no adverse effects on human tissue. But LA-derived biomaterials have only been tested at the animal level. Up to now, there have been, to our knowledge, few LA-derived-polymeric biomaterials approved for the treatment of diseases in clinic or being tested in clinical trials. To promote clinical translation, research on clinical safety, pharmacokinetics, biostability, and overall efficacy of LA-derived biomaterials remains to be deeply and comprehensively evaluated. Biomaterials are effective tools for enhancing disease treatment efficiency in the future after the above pivotal issues are addressed.

Taken together, the perfect use of LA will drive the rapid development of novel solution for efficient treatment of cancer, diabetes, AD, tissue repair and other disease treatments as well as promote the production of detection, intelligence devices.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. #These authors contributed equally.

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Shao-yang Lv: Writing-original draft, Writing-review & editing, Writing-revision. **Suisui He:** Writing-original draft, Writing-review & editing. **Xiao-li Ling**, **Yue-qin Wang**, **Cong Huang**, **Jin-rong Long**, **Jia-qi Wang**, **Yang Qin:** Data Curation. **Hua Wei:** Conceptualization, Supervision, Writing-original draft, Writing-review & editing Writing-revision. **Cui-Yun Yu:** Conceptualization, Funding acquisition, Supervision, Writing-original draft, Writing-review & editing Writing-revision.

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.

Data availability

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

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