Nanoscale

REVIEW

View Article Online
View Journal | View Issue

Cite this: *Nanoscale*, 2025, **17**, 4958

Carbon dots derived from organic drug molecules with improved therapeutic effects and new functions

Zhao-Fan Wu, [a] Xiao-Xiao Luo, [a] Xiao-Feng Shi,[b] Bao-Juan Wang,[a] Hao-Wen Sun,[a] Zhao-Nan Sun,[a] Yuan-Qing Mao*[b] and Huan-Ming Xiong *[a]

Received 28th October 2024,
Accepted 17th January 2025

DOI: 10.1039/d4nr04467c

rsc.li/nanoscale

Carbon dots (CDs) are new types of fluorescent nanomaterials with particle diameters of 1~10 nm and have excellent photoluminescence (PL) properties, good biocompatibility, simple preparation methods and numerous raw materials; consequently, they are promising in the biomedical field. In recent years, to overcome drug resistance and toxic side effects of traditional organic drugs, the synthesis of CDs from drug molecules has become an effective strategy, which produces CDs with the same therapeutic effects as the raw drugs and even possessing new properties. At present, many CDs derived from organic drugs have been developed, which can be classified according to their sources such as antibiotics, anti-inflammatory drugs, and guanidine drugs. This article focuses on the progress of the above-mentioned drug-derived CDs compared with their drug precursors in terms of therapeutic efficacy, enhanced performance and new additional functions, with special attention to the structure–activity relationship between the drug precursors and the CD-based therapeutic agents. It demonstrates the feasibility of designing new drug-derived CDs for clinical applications, summarizes the shortcomings and research gaps of the existing work, and provides a reference for related work in the future.

1. Introduction

Carbon dots (CDs) are a vital member of the fluorescent nanomaterial family. Due to their high biocompatibility, stable luminescence, high quantum yield, and carbon-based structure, CDs are widely used in the biomedical field, including cell imaging, antibacterial, anti-oxidation, and anti-cancer activities.[1–4] CDs are usually spherical nanoparticles with diameters of 1~10 nm, and their internal carbon atoms have hybrid sp^2 or sp^3 structures.[5–7] The raw materials used to produce CDs are extremely diverse, involving numerous organic substances and natural biomasses.[7–11] The obtained CDs not only exhibit different fluorescence colors but also many other tunable properties and functions.[12,13] The preparation routes for CDs are usually categorized into bottom-up and top-down strategies. The former has become the most adopted strategy in recent years because it is more convenient to carry out by chemical synthesis and it can produce multifunctional CDs with adjustable compositions and structures.[14,15] Just by microwave, hydro/solvothermal, or reflux treatment, CDs with very high PL quantum yields can be obtained in a short time, and some CDs can even be extracted from natural products like tea.[16–19] When the production of CDs was low in the early years, their biomedical applications were limited to fluorescent probes, detection reagents, drug delivery carriers, *etc.*[20–22] Recently, large-scale synthetic methods for CDs have emerged gradually, and the obtained nanoparticles still have uniform sizes.[23–26] Among these methods, solid phase synthesis without solvents usually results in higher yields, reducing the cost of CDs.[27–29] Therefore, the biomedical application of CDs can be explored in a broader range of areas.

The most important property of CDs is photoluminescence. By adjusting the chemical structure of raw materials, synthetic methods, and reaction conditions, the fluorescence emission wavelengths can be flexibly adjusted, covering all bands from the ultraviolet to the near-infrared region, resulting in multicolor and brilliant multi-color fluorescence.[30–33] CDs with short-wave emission often have absorption peaks in the UV band, allowing their use as additives in products such as masks, skin care items, sunscreens, and textiles.[34–38] CDs that emit in the visible wavelength range can be used for LED lighting, high-

[a]*Department of Chemistry and Shanghai Key Laboratory of Molecular and Catalysis and Innovative Materials, Fudan University, Shanghai 200438, P. R. China. E-mail: hmxiong@fudan.edu.cn*
[b]*Shanghai Key Laboratory of Orthopaedic Implants, Department of Orthopedics, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, 639 Zhizaoju Road, Shanghai 200011, P. R. China. E-mail: MAOYQ1975@sh9hospital.org.cn*

resolution cell imaging, textile fiber dyeing, pattern encryption and anti-counterfeiting.[39–43] CDs with sensing characteristics can be used to detect the content of specific substances according to the fluorescence intensity, monitor the intracellular microenvironment, and analyze disease markers *in vitro*.[44–46] When combined with intelligent fluorescence colorimetric software, they can be used to develop intelligent detection platforms for water quality, pesticide pollutants, toxic gases, harmful food additives and other substances.[47–49] If the fluorescence emission of CDs occurs in the red or near-infrared region, they are more suitable for *in vivo* animal imaging where a certain penetration depth is required.[50,51] Such CDs are more suitable to be designed as tumor tissue targeting reagents, guide for surgical resection of tumors, or drug-carrying fluorescent reagents to track the release process of drugs *in vivo*, so as to facilitate visual observation of drug effects.[52–56] In addition to their fluorescence properties, CDs exhibit many other characteristics, such as catalytic effects as nano-enzymes for biomedical therapy, antibacterial or antioxidant effects,[57–60] and photothermal or photodynamic effects for killing bacteria or cancer cells.[56,61] Therefore, it is convenient to develop integrated diagnostic and therapeutic medical platforms based on multifunctional CDs.[50,62]

In recent years, researchers have synthesized various CDs using natural drugs and clinical drugs as carbon sources. Chinese herbal medicine has a long history, with various formulations, mild properties and few side effects.[63] CDs derived from Chinese herbal medicine not only exhibit effects similar to traditional Chinese medicine, but also have fluorescence properties. Such "glowing Chinese medicine" can be used for both treatment and imaging at the same time. So far, there have been some reviews on Chinese herb-derived CDs, which discussed their application in antibacterial, hypoglycemic, hemostasis, anti-cancer and anti-inflammatory areas.[8,64] However, due to the complex ingredients of Chinese herbs, the active ingredients and chemical structures are unknown, so it is difficult to study the structure and structure–activity relationship of Chinese herb-derived CDs. In contrast, some recent reports declare that after the carbonization of organic drug molecules, the original chemical structures and groups with therapeutic effects partly remain in the products, so that the as-prepared CDs still have the same therapeutic effect as the raw drugs. Moreover, CDs can also improve the water solubility of drugs and reduce side effects, highlighting the new advantages and application potential of CDs as new types of nanodrugs. To our knowledge, there is no review on the development of such CDs derived from organic drug molecules so far. This article reviews CDs derived from organic drugs and their biomedical applications in the past several years, as displayed in Fig. 1, with a focus on the relationship between the precursor structures of drug molecules and the medicinal effects after polymerization and carbonization. In addition, this review will highlight the advantages of CDs compared with raw medicine, explore the value of CDs as a new type of alternative medicament, and summarize the synthesis methods of CDs from drug-active molecules, so as to provide ideas for the development of novel CDs derived from drug-active molecules.

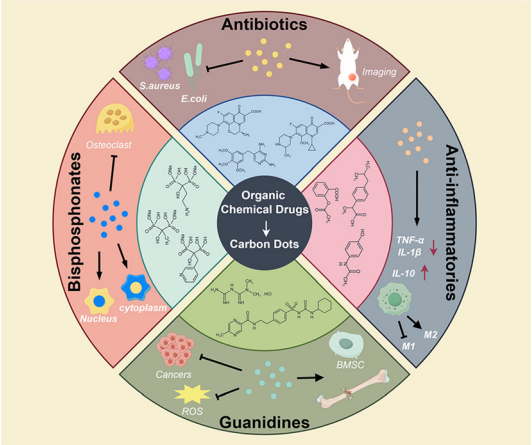

Fig. 1 Schematic diagram of CDs derived from various drug molecules and their applications in the treatment of diseases.

2. CDs derived from organic drug molecules

Among the various advantages of CDs, one interesting feature is that some inherent properties of the precursors can be inherited and retained by the newly synthesized CDs. The abundance of sources of CDs has led scientists to wonder what kinds of products could be produced if synthetic drug molecules were used as precursors. This unique phenomenon provides a strong incentive for preparing CDs using drugs with targeting or therapeutic effects. Another interesting feature is that some newly synthesized CDs exhibit enhanced properties of the original precursors, as well as reduced toxicity of the drug. Moreover, drug-derived CDs often display new functional properties such as fluorescence emission, sensing capability, ability to overcome drug resistance, drug loading and anticancer activity. These features can complement the effects of the precursor molecules and play a synergistic role in disease treatment and biological imaging. As listed in Table 1, CDs derived from several drug categories are summarized, such as antibiotics,[65–74] anti-inflammatory drugs,[75–80] guanidine drugs,[81–87] disease-specific drugs,[88,89] *etc.*, involving the inherited chemical structures or functional groups from precursors, improved pharmaceutical efficacy, new functions, *etc.*

2.1 CDs synthesized from antibiotics

Antibiotics refer to a class of secondary metabolites produced by microorganisms (including bacteria, fungi, and actinomycetes) or higher animals and plants during their life processes with anti-pathogenic or other activities, which can interfere with the developmental functions of other living cells.[90,91] Commonly used antibiotics in clinical practice include extracts

Table 1 The raw materials, synthesis methods, applications and characteristics of CDs reviewed in this paper derived from organic molecular drugs

Materials	Organic drug molecules	Synthesis methods	PL wavelength/nm	Application	Advantages over raw materials	New function and performance	Ref.
g-CDs	Ciprofloxacin hydrochloride	Hydrothermal	432	Antibacterial agent and a sensitive pH and Al(III) nanosensor		Fluorescence sensing properties	65
C-CDs and Cu-C-CDs	Ciprofloxacin	Hydrothermal	445, 440	Antibacterial drugs	More water-soluble	Fluorescence properties and excellent biocompatibility	66
F-CDs	Levofloxacin hydrochloride	Hydrothermal	428	Nano-bactericides		Fluorescence and producing ROS without light	67
LCDs	Levofloxacin	Hydrothermal	510	Antibacterial medicine	Improved antibacterial activity and water solubility	Low drug resistance	68
Co-Lvx-CDs	Levofloxacin and vitamin B12	Hydrothermal	460–494	Antibacterial applications	Enhanced antibacterial activity	Excellent photoluminescence (PL) properties	69
CDs and r-CDs	Levofloxacin	Hydrothermal	480	Advanced dynamic information encryption	Different phosphorescence color	Time-dependent phosphorescence colors	70
M-CDs	Neutral red and levofloxacin	Microwave	642	Live-cell imaging of granule dynamics	More water-soluble	RNA-targeting and red-emissive	71
CDs	Amoxicillin and sodium carbonate	Hydrothermal	303	An effective fluorescent probe for monitoring benzidine		PL property and sensing	72
M-CDs	Expired amoxicillin	Hydrothermal	510	Evaluate total antioxidant capacity (TAC) in human serum samples	Accelerate decomposing H_2O_2 to form $^{\bullet}OH$	Nanozymes with peroxide-like activity	73
AMO-CDs	Amoxicillin	Microwave-assisted	475	Antibacterial effects, toxic Hg^{2+} detection, and ultra-sensitive determination of methanol in edible alcoholic beverages	Greatly improved water-soluble and antibacterial properties	Sensing properties	74
FACDs	Aspirin	Microwave	432	Bioimaging and anti-inflammation	Increased anti-inflammatory effects	Fluorescence and cellular imaging	75
AACDs	Adenosine and aspirin	Hydrothermal	410	Direct osteogenic differentiation of hBMSCs	More effective osteogenic differentiation and lower cytotoxicity	Fluorescence and higher cellular retention	76
AspCDs	Aspirin	Hydrothermal	410	Imaging agent and anti-inflammatory replenisher	Visualization of drug distribution	Fluorescence and drug-loading properties	77
DCDs	Citric acid, ammonium fluoride and dexamethasone	Hydrothermal	430	Anti-inflammatory, osteogenesis, and osteoimmunomodulatory	Improved ROS removal capability	Sustained bone immune regulation and cell imaging	78
CDs	Dexamethasone and 1,2,4,5-tetraaminobenzene (TAB)	Microwave	500, 580	Ratiometric imaging of formaldehyde in living cells		Sensitive formaldehyde sensing capability	79
G-CDs	Acetaminophen and ethylenediamine	Hydrothermal	507	$MnO4^{-}$ detection and fluorescent anti-counterfeiting		Solid state fluorescence and fluorescent ink	80
G-CDs	Citric acid, DDA and PHMG	Heat with stirring	393	Treatment of pneumonia caused by Gram-negative bacteria	Fight drug-resistant bacteria without causing new resistance	Different antibacterial mechanism	81
M-CDs	Metformin hydrochloride and citric acid	Hydrothermal	445	Treating periodontitis	More effectively promote osteogenesis of rBMSCs	Enhance periodontal bone regeneration	82
Met-CDs	Citric acid and metformin	Metformin	440	Targeted bioimaging and chemotherapy of tumors	Integrated tumor imaging and therapy	Fluorescence and bioimaging	83
MMCDs	Methylene blue (MB) and metformin	Hydrothermal	642	Lysosome-targeted PDT cancer therapy	Enhanced ROS generation efficiency	Red fluorescence and imaging	84

Table 1 *(Contd.)*

Materials	Organic drug molecules	Synthesis methods	PL wavelength/nm	Application	Advantages over raw materials	New function and performance	Ref.
MFCDs	Metformin and DTSA	Hydrothermal	460	Inhibitable colorectal cancer therapy	Enhanced cancer cell lethality and excellent biosafety	Stable optical properties	85
MGA-CDs	Metformin and gallic acid	Hydrothermal	460	Glioblastoma therapy	Enhanced anticancer effect	Imaging tumor cells mitochondria and inducing ferroptosis	86
MTCDs	Metformin and tea polyphenol	Hydrothermal	506	Treatment of nonalcoholic fatty liver disease	Enhanced lipid metabolism and antioxidative ability	Imaging of cellular lysosomes	87
Alen-CDs	Alendronate	Hydrothermal	410	Effective osteoblastic differentiation induction and promotion	Improved water dispersion ability	PL properties and cellular bioimaging	88
ALEN-CDs	Alendronate (ALEN)	Microwave-assisted	400–500	For the treatment of osteoporosis	Avoid side effects such as BRONJ	Anti-inflammatory effects	89

from microbial culture media and chemically synthesized or semi-synthetic compounds. According to their chemical structure, antibiotics can be divided into quinolone antibiotics, β-lactam antibiotics, macrolides, aminoglycoside antibiotics and so on.[92,93] Although antibiotics can effectively prevent the proliferation of microorganisms and cure many diseases, they also have many disadvantages. Adverse reactions caused by antibiotics are very common. While killing pathogenic bacteria, they can also cause damage to the human body; for example, chloramphenicol, lincomycin, tetracycline, erythromycin, *etc.* can cause damage to organs during liver and kidney metabolism.[94] In addition, many antibiotics such as penicillin, streptomycin and other drugs can cause allergic reactions, which in severe cases can lead to dyspnea and shock.[95] Furthermore, the abuse of antibiotics may also lead to the emergence of drug resistance in bacteria, delaying disease treatment. At present, the problem of bacterial resistance to antibiotics is very serious, which is posing a threat to global health.[96,97] However, the development of new antibiotics is time-consuming and laborious, which is the main reason for the continued lack of new antibiotics. Advances in nanotechnology have spawned the development of many promising antibacterial nanomaterials.[98,99] Among them, CDs show great advantages due to their small particle size, fluorescence stability, and excellent biocompatibility, which contribute to a wide range of clinical applications. CDs synthesized from therapeutic drugs usually possess more abundant functional groups and new activities compared to the original reagents, holding broad promise for improving the treatment efficiency of bacterial infectious diseases.[3,100] To date, several mechanisms have been proposed to explain the antimicrobial effects of CDs through disrupting bacterial structures and substances, including physical/mechanical disruption, inhibition of bacterial metabolism, triggering oxidative stress, and photocatalytic effects.[60,101] The most common antibacterial mechanisms of CDs are cationic adsorption and oxidative stress induced by reactive oxygen species (ROS). The former can damage the cell wall by electrostatic attraction of the negatively charged surface of bacteria, while the latter produces ROS (singlet oxygen, superoxide anion free radicals, *etc.*) with a short life cycle, which can only cause irreversible damage to the substances contained in the bacteria in a short period of time, without harming normal cells and tissues.[100,102] These two factors improve the selectivity of raw antibiotics for bacteria, which is the reason why CDs generally have better biocompatibility and a lower risk of drug resistance.

Ciprofloxacin (CI) is a synthetic third-generation quinolone antimicrobial agent with broad-spectrum and good antibacterial activity and is reported to be 2–4 times more potent than norfloxacin and enoxacin.[103] Ciprofloxacin also has excellent pharmacokinetic properties with few side effects. However, in recent years, the widespread increase of drug-resistant pathogens has made ciprofloxacin increasingly ineffective; so it is imperative to develop new antibiotics with high antibacterial activity and low drug resistance.[104–106] In 2017, Huang *et al.* prepared fluorescent CDs (g-CDs, em = 432 nm) using a hydro-

thermal method with ciprofloxacin hydrochloride as the sole precursor.[65] Since the synthesis temperature was lower than the decomposition temperature of the functional groups of ciprofloxacin, g-CDs inherited and retained the functional structure of ciprofloxacin (as shown in Fig. 2a) as well as its bactericidal ability. It still has antimicrobial activity against *Staphylococcus aureus* (Gram-positive bacteria) and *Escherichia coli* (Gram-negative bacteria). In addition, the incomplete polymerization and carbonization of ciprofloxacin molecules preserve their pH sensitivity, effectively transforming the irregular pH-induced fluorescence intensity changes of the raw materials into refined and consistent variations of the fluorescence intensity of g-CDs at different pH values. Compared with the antibiotic molecule itself, g-CDs are endowed with fluorescence properties. As shown in Fig. 2b, fluorescence intensity is a simple and intuitive method for sensing pH and Al^{3+} concentration, which is another advantage of CDs. This work demonstrated the feasibility of preparing antibiotic-derived CDs by low-temperature carbonization to retain the bactericidal function of precursors. In 2023, Li *et al.* also prepared CCDs and copper-doped Cu-CCDs by a hydrothermal method using ciprofloxacin as the raw material.[66] Compared with ciprofloxacin, the obtained CDs have better water solubility, and Cu-CCDs have better synergistic antibacterial effects. As shown in Fig. 2c, CCDs have a positive surface charge and bind to the negatively charged surfaces of *Staphylococcus aureus* and *Escherichia coli* by electrostatic attraction, destroying the bacterial structure, which is a new antibacterial mechanism belonging to carbon dots. Whereas conventional antibiotics are easily excreted by bacteria, leading to drug resistance, CCDs remain attached to bacteria through electrostatic interactions, avoiding drug resistance and overcoming the limitations of conventional antibiotic treatments.

Levofloxacin is one of the most widely used representative quinolone antibiotics with a trace positive charge (zeta potential = +1.32 mV). The hydroxyl group and quinoline structure of levofloxacin are the active sites responsible for its bactericidal function, killing bacteria by binding to bacterial DNA-binding proteins or an efflux pump mechanism, resulting in a broad spectrum of antibacterial effects.[107] However, levofloxacin generates antibiotic resistance (2 weeks or less after administration) and has poor solubility in the physiological environment, posing some challenges for its clinical application.[108,109] The excellent water solubility, biocompatibility and synergistic bactericidal mechanism of CDs can help address the limitations of levofloxacin. In 2021, Zhang *et al.* prepared F-CDs by the hydrothermal method using levofloxacin hydrochloride as the only raw material.[67] As shown in Fig. 3a, F-CDs have good water solubility, bright blue fluorescence emission at 428 nm, and excellent bactericidal effect against both Gram-positive and Gram-negative bacteria. The antibacterial mechanism of F-CDs involves three key actions: they wrap around the cell surface, leading to indirect toxicity and restraining proliferation; they adhere to bacteria and break down their membranes; and upon internalization into bacteria, F-CDs generate a large amount of ROS even under dark conditions, inducing bacterial oxidative stress and disrupting homeostasis to achieve a bactericidal effect. F-CDs also have very low cytotoxicity, making them a new antibacterial agent with few side effects, good water solubility and improved performance. In the same year, Liu *et al.* synthesized LCDs by a one-step hydrothermal method using levofloxacin as the precursor.[68] As shown in Fig. 3b, levofloxacin was slightly soluble in water, while LCDs were soluble in water to form a pale yellow solution and retained the antibacterial effect. The zeta potential of LCDs (+28.00 ± 0.50 mV) was 21 times higher than that of levofloxacin (+1.32 ± 0.28 mV). UV-vis and fluorescence spectra

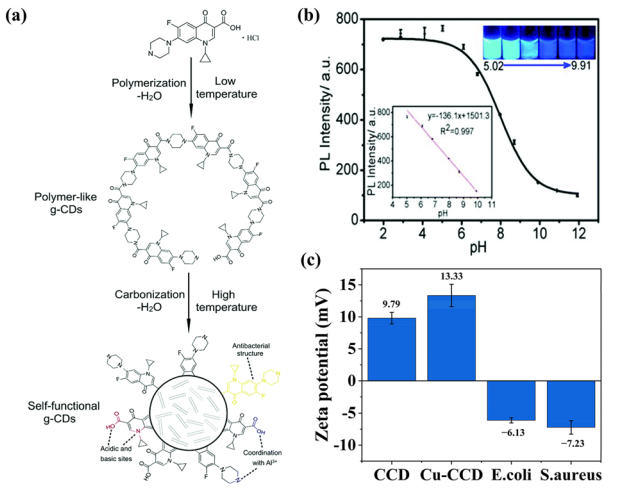

Fig. 2 (a) Schematic of the synthesis process of g-CDs based on the active structure preservation (ASP) method. Reproduced with permission from ref. 65. Copyright 2017 Royal Society of Chemistry. (b) pH-Sensitive response of g-CDs, and (c) zeta potential of bacterial and synthetic CDs. Reproduced with permission from ref. 64. Copyright 2023 MDPI.

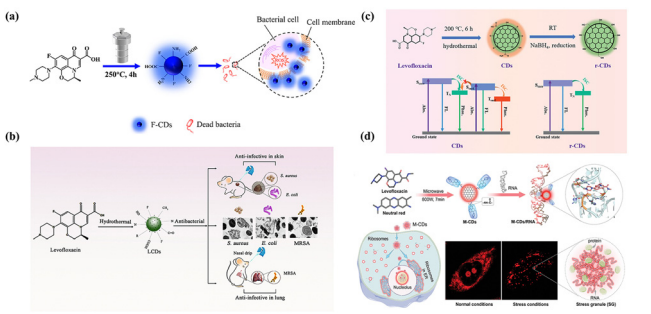

Fig. 3 (a) Schematic diagram of the synthetic route and bactericidal mechanism of F-CDs. Reproduced with permission from ref. 67. Copyright 2021 ACS Publications. (b) Schematic illustration for the synthesis and antibacterial properties of LCDs. Reproduced with permission from ref. 68. Copyright 2022 Elsevier. (c) Schematic of the preparation procedure and the possible phosphorescence emission processes for CDs and r-CDs. Reproduced with permission from ref. 70. Copyright 2021 Wiley Online Library. (d) Schematic representation of the synthesis, structure, RNA binding behaviors, and cellular RNA imaging of M-CDs. Reproduced with permission from ref. 71. Copyright 2023 Wiley Online Library.

showed that the core of LCDs formed a graphitic carbon structure, and the fluorescence emission peak shifted from a blue waveband to a green waveband. It has been proposed that levofloxacin kills bacteria by binding its –COOH and C=O groups to DNA helicase and topoisomerase IV. In addition, the presence of F atoms increases the affinity of levofloxacin to bacterial DNA gyrase and enhances penetration into the bacterial cell wall, resulting in a synergistic antibacterial effect. IR and XPS characterization showed that LCDs have similar surface functional groups and chemical bonds to levofloxacin, with the C–F bond still present, indicating that LCDs inherited the active groups. LCDs have antibacterial effects on both Gram-positive and Gram-negative bacteria, and the bactericidal effect of LCDs is greater than that of the levofloxacin hydrochloride molecule itself. Moreover, the minimum inhibitory concentration of LCDs remains unchanged even after prolonged bacterial passage, indicating that the antibiotic resistance of LCDs is also significantly lower than that of antibiotics themselves. By studying the antibacterial mechanism of LCDs, it was found that the improvement of drug resistance was mainly due to the stronger adhesion caused by the electrostatic attraction between positively charged LCDs and the bacterial cell membrane, while the improvement of the bactericidal effect was mainly due to the production of a large amount of ROS inside the cell, which damaged not only the cell wall but also the cell membrane. However, levofloxacin hydrochloride can directly penetrate the bacterial cell wall and cell membrane without completely destroying them. This was further confirmed using a bacterial infection model and a methicillin-resistant *Staphylococcus aureus* infection *in vivo* model of pneumonia in which the infected wound area after LCD treatment was reduced more significantly than that in the control group, and there was no ulcer or hypertrophic scar around the wound of the mouse. Compared with antibiotics alone, LCDs were more effective in killing bacteria and had a shorter healing time at infected tissues in both animal models. In addition, the cytotoxicity of LCDs was evaluated. The results showed that at bactericidal concentrations, LCDs did not cause any damage to animal cells and tissues, reflecting the excellent biocompatibility of levofloxacin hydrochloride after being made into CDs. This is one of the most complete studies to date to analyze and compare the antibacterial effects, side effects, water solubility, antibacterial mechanisms and application potential of the antibiotic itself and its derived CDs in a live infection model. It demonstrated that levofloxacin-derived CDs significantly enhanced the antibacterial activity and water solubility, and also conferred resistance to drug-resistant bacteria, overcoming the limitations of antibiotics in treatment. Similarly, Jiang *et al.* synthesized cobalt-doped levofloxacin-based CDs (Co-Lvx-CDs) by a simple hydrothermal method using levofloxacin and vitamin B12, which contains Co element with oxidase activity and no transition metal toxicity, as carbon sources.[69] Co-Lvx-CDs retained the quinoline and carboxyl groups and the excellent antibacterial activity of levofloxacin. Co doping endowed the material with OXD and POD dual enzyme activities. Co-Lvx-CDs can rapidly produce large amounts of ROS, whose oxidase activity is much better than those of most existing nanoenzymes, which not only enhances the killing ability of levofloxacin molecules against Gram-negative bacteria, but also overcomes the limitation of raw material molecules to kill most Gram-positive bacteria. Interestingly, Co-Lvx-CDs also exhibit bright blue-green fluorescence with an absolute quantum yield of 21.8%, which reflects their potential application in fluorescence anti-counterfeiting and information encryption.

In addition to their antibacterial and anti-infection applications, carbonization of levofloxacin into CDs also endows them with photoluminescence properties, enabling their applications in cell imaging and optical information encryption. In 2021, Qu *et al.* developed a novel type of CDs with time-dependent phosphorescence color properties using a one-pot hydrothermal method with levofloxacin, focusing on the development and exploration of the phosphorescence properties of antibiotic-derived CDs and their potential for advanced dynamic information encryption.[42] Levofloxacin exhibits green phosphorescence due to the presence of an azacyclic structure. As shown in Fig. 3c, the extended conjugate structure of the nitrogen heterocycle is formed in the carbon core of CDs during carbonization, which is responsible for the N-related triplet state of CDs with green phosphorescence emission. The phosphorescence of CDs can change from orange to green in a very short time (1 s), enabling the development of a multi-level dynamic phosphorescence colored 3D code. In 2023, Bi *et al.* prepared novel RNA-targeting red emitting CDs (M-CDs) using a microwave method with neutral red and levofloxacin as precursors.[71] Neutral red promotes the graphitization process and the formation of the carbon core of M-CDs. Levofloxacin has a nitride-containing hetero-ring, has specific binding affinity for RNA, and has a carboxyl group, which can be attached to the surface of the M-CD mother core formed by neutral red through an amidation reaction, shaping the surface structure of M-CDs. The fluorescence quantum yield of M-CDs is as high as 22.83%, and the red fluorescence intensity at 642 nm increased after binding to RNA. As shown in Fig. 3d, M-CDs with RNA targeting properties can be rapidly internalized into cells within 5 seconds, allowing real-time imaging of the dynamic process of intracellular stress granules in response to oxidative stress, revealing some features not identified by previously reported RNA and protein biomarkers. All the above works demonstrate the potential application of levofloxacin-derived CDs in photoluminescence and imaging.

Amoxicillin is one of the most important semisynthetic penicillin broad-spectrum β-lactam antibiotics, belonging to the aminopenicillin family and is used to treat infections caused by susceptible Gram-positive and Gram-negative bacteria. In 2023, Zhou *et al.* synthesized antibiotic-derived CDs by the hydrothermal method using amoxicillin and sodium carbonate (a salt) as precursors.[72] As shown in Fig. 4a, these CDs exhibit fluorescence properties with a maximum emission wavelength at 303 nm, with no excitation dependence and strong fluorescence stability. CDs exhibit good selectivity and sensitivity to benzidine and can be used as an effective fluo-

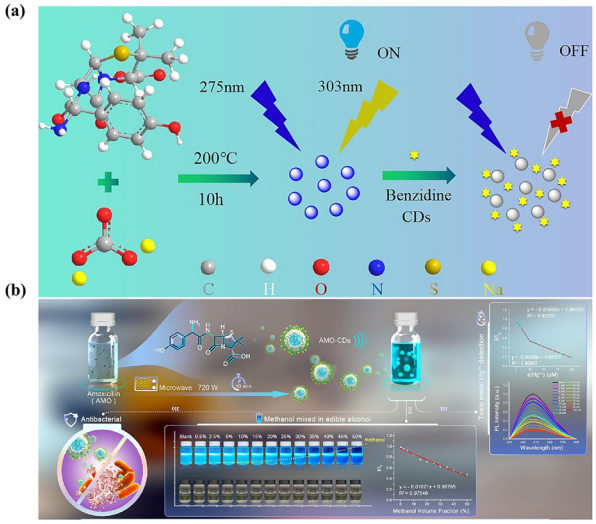

Fig. 4 (a) Schematic diagram of the preparation process of CDs and quenching effects. Reproduced with permission from ref. 72 Copyright 2023 Elsevier. (b) The schematic synthesis and multi-application of AMO-CDs. Reproduced with permission from ref. 74. Copyright 2024 Elsevier.

rescent probe to monitor benzidine. The linear detection ranges of CDs are 0.2–2 μM and 2–16 μM, with a detection limit as low as 0.08 μM. CDs as a fluorescent probe have the advantages of simple and rapid operation, low cost, short analysis time, high selectivity and sensitivity, and good stability. This work demonstrates the application potential of amoxicillin-derived CDs for the sensing and analysis of specific substances through fluorescence properties. In 2024, Xu *et al.* synthesized three metal-doped CDs (Me-CDs) using expired amoxicillin and three nitrates as precursors.[73] Among them, iron-doped Fe-CDs have high peroxidase activity and can efficiently catalyze H_2O_2 to produce free radicals that oxidize TMB. The degree of delayed oxidation of TMB under antioxidant conditions can be used to indirectly measure the total antioxidant capacity in human serum. This is an effective way to deal with expired antibiotics, which can avoid drug abuse and environmental pollution. Moreover, the obtained Me-CDs are more water soluble than amoxicillin itself, thanks to the formation of hydrophilic groups on the surface of CDs during the carbonization process. Similarly, Jiang *et al.* used amoxicillin as the sole precursor to rapidly synthesize CDs (AMO-CDs) by a one-step microwave method.[74] As shown in Fig. 4b, AMO-CDs retained parts of the amoxicillin structure and chemical bonds, thereby preserving its antimicrobial activity. Compared with the raw material, the antibacterial properties of AMO-CDs are significantly improved, which is attributed to their improved water solubility, which allows for a higher effective concentration of the antibacterial agent. At the same time, AMO-CDs exhibit excitation wavelength-dependent fluorescence characteristics, and display "on–off" fluorescence sensing behavior for Hg^{2+}, while demonstrating "off–on" behavior for fatty alcohol. AMO-CDs can be used to detect the concentration of Hg^{2+} and the volume fraction of fatty alcohol in mixed solvents. In summary, AMO-CDs exhibit low cytotoxicity, improved water solubility and antibacterial activity, and application potential for analytical detection, demonstrating the versatility of drug-derived CDs.

In conclusion, antibiotic-derived CDs mostly retain the antibacterial structural features of their raw materials, while improving their antibacterial properties through multiple mechanisms. These enhancements include improved water solubility, which increases the effective concentration of the antibacterial agent, enhanced adhesion between CDs and bacterial surface *via* increased surface charge, and improved ROS production efficiency, addressing the inherent limitations of antibiotics such as poor water solubility, limited effectiveness against Gram-positive bacteria and a single antibacterial mechanism, highlighting the importance of the preparation of antibiotic-derived CDs. In addition, antibiotic-derived CDs exhibit unique fluorescence properties that enable their use in fluorescence sensing and biological imaging, and those exhibiting phosphorescence emission can also be used for dynamic information encryption, showing the versatility of these materials after the polymerization and carbonization of antibiotic molecules.

2.2 CDs synthesized from anti-inflammatory drugs

Anti-inflammatory drugs are different from antibiotics, which target inflammation only caused by bacterial infection. Inflammation may occur whether or not there is a bacterial infection, such as in the case of rheumatoid arthritis. Inflammation is a pathological process that consists of a series of protective responses when tissues are damaged. If the inflammatory response is excessive, it will cause body damage, typically characterized by redness, swelling, heat, pain and dysfunction.[110,111] Drugs that affect the body's inflammatory response mechanisms are called anti-inflammatory drugs (true "anti-inflammatory drugs"). These drugs are divided into non-steroidal drugs, such as antipyretic analgesics (such as aspirin and paracetamol), and steroidal anti-inflammatory drugs (such as dexamethasone).[112,113] CDs derived from anti-inflammatory drugs have been reported for a long time, often inheriting the anti-inflammatory effects of their raw materials.

Aspirin, also known as acetylsalicylic acid, is mainly used to relieve mild to moderate pain, for the antipyretic treatment of fever caused by flu, and for the treatment of rheumatic pain. Recently, some studies have also suggested that aspirin may reduce the risk of cancer and heart disease.[114,115] However, aspirin has some side effects, including the potential to cause gastric injury and liver injury at high doses, and it has poor solubility in a physiological environment similar to water.[116] Developing aspirin-derived CDs to address its disadvantages is a feasible strategy. In 2016, Yang *et al.* synthesized carbon nanodots (FACDs) through a microwave method using aspirin and hydrazine as precursors.[75] FACDs exhibit bright blue fluorescence at 432 nm, which the raw material does not have, and have good dispersibility in water. The fluorescence of FACDs remains stable in complex environments, with good resistance to photobleaching and low cytotoxicity. FACDs are excellent

reagents for *in vitro* cell imaging and *in vivo* animal imaging. FACDs retain the acetyl group of aspirin while having a greater number of amide groups, which accounts for their more potent anti-inflammatory effects compared to the aspirin molecule, both *in vivo* and *in vitro*. This work successfully improved the water solubility and anti-inflammatory activity of aspirin through the preparation of CDs, while also enabling new properties and applications. In 2019, Liu *et al.* used adenosine, which has osteogenic properties, and aspirin, which can prevent bone loss, to prepare blue fluorescent CDs (AACDs) with an optimal emission wavelength of 410 nm using a one-step hydrothermal method.[76] AACDs exhibit long-term cell imaging capability. Moreover, they not only enhance and guide the osteogenic differentiation of rat bone marrow mesenchymal stem cells (rBMSCs), but also demonstrate more effective osteogenic differentiation behavior compared to the mixture of adenosine and aspirin, which may benefit from the higher cell retention rate of AACDs compared with their homologous precursors. In 2022, Deng *et al.* used the hydrothermal method with aspirin as a precursor to prepare fluorescent carbon dots (aspCDs) under alkaline conditions, which combined the blood–brain barrier penetration ability and the anti-inflammatory effects of aspirin with the fluorescence and drug-loading properties of CDs.[77] AspCDs retain the anti-inflammatory active site of the acetyl group and possess a negative surface charge, enabling stable circulation in the blood stream due to electrostatic repulsion from negatively charged cell membranes. AspCDs emit blue fluorescence at 400 nm, have the ability to image *in vitro* and *in vivo*, and can penetrate the blood–brain barrier, distributing throughout the brain. AspCDs can have a stronger anti-inflammatory effect than aspirin in brain inflammation, likely due to the increased solubility of CDs compared to aspirin itself. In addition, aspCDs can be used as functional carriers to load drugs of specific polarity for broader and deeper biomedical applications, which is another advantage of drug-derived CDs.

Dexamethasone (Dex), a highly stable corticosteroid, has been widely used as a potent anti-inflammatory agent to regulate the expression of inflammatory factors in clinical practice.[117] Dexamethasone is also a widely used osteogenic drug, which stimulates the up-regulation of bone-related genes such as alkaline phosphatase and osteocalcin during bone regeneration in order to promote the differentiation of stem cells into osteoblasts.[118] In 2022, Yu *et al.* developed a new type of blue fluorescent CDs (DCDs) using citric acid, ammonium fluoride and trace amounts of dexamethasone through a simple hydrothermal method.[78] These DCDs retain the anti-inflammatory activity of dexamethasone and are rich in reducing groups, featuring an even higher concentration of reducing groups on their surface compared to dexamethasone. Therefore, DCDs have a better ROS scavenging ability than dexamethasone, demonstrate significant anti-inflammatory effect *in vitro* and *in vivo*, and can promote the osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs) under both normal and inflammatory conditions. In addition, DCDs can also promote the phenotypic transformation of macrophages in the inflammatory environment to achieve continuous immune regulation for bone regeneration. DCDs combine the anti-inflammatory activity of dexamethasone with the rich surface functional groups and fluorescence performance of CDs, improving the treatment effect and enabling cell imaging. The abundant hydroxyl group on the surface of dexamethasone can promote its own polymerization to form carbon nanodots. Liu *et al.* took advantage of this feature to synthesize CDs with red and blue double fluorescence peaks from dexamethasone and 1,2,4,5-tetraaminobenzene (TAB) through a hydrothermal method.[79] The *ortho*-diamino residues on the surface of these CDs have highly sensitive formaldehyde sensing abilities. With the increase of formaldehyde concentration, the red fluorescence intensity of the CDs gradually decreased while the blue fluorescence gradually increased, such that the blue/red fluorescence intensity ratio significantly increased. Moreover, these CDs have intracellular lysosomal targeting ability and can image the intracellular formaldehyde concentration *via* a fluorescence dual-channel ratio. Although this report primarily takes advantage of the feature that dexamethasone is prone to condensation to form carbon cores, it also demonstrates that this drug is a highly suitable precursor for CDs.

Not only dexamethasone and aspirin, drugs with benzene rings and phenolic hydroxyl groups also have the potential to synthesize CDs. Acetaminophen, also known as paracetamol, is a very common analgesic used for colds and fever, joint pain, cancer pain, and pain after surgery.[119] In 2024, Qi *et al.* prepared green fluorescent N-doped CDs (G-CDs) by a hydrothermal method with acetaminophen and ethylenediamine; the resultant CDs exhibited a fluorescence quantum yield of 21.94% and could be dispersed in the medium as a solid-state luminescent material.[80] G-CDs showed excellent fluorescence stability at a pH range of 6–12; however the fluorescence was almost completely quenched outside this range of pH values. G-CDs can be used as fluorescent ink for anti-counterfeiting with dual encryption capabilities by taking advantage of their sensitivity toward strong acids and strong bases. The above results indicate that drug molecular precursors are promising for the synthesis of CDs with excellent luminescence and great application potential in the field of optics (Fig. 5).

2.3 CDs synthesized from guanidines

Guanidine is a basic chemical group that can be easily hydrolyzed, with the chemical formula -CN_3H_4, in which the C atom is connected to three N atoms, one *via* a double bond and the remaining two *via* single bonds. Compounds that contain guanidine structures are called guanidine compounds.[81,120] Guanidine compounds are ubiquitous in nature and can be found in the amino acid arginine and the neurotransmitter agmatine, as well as in many natural alkaloids, such as tetrodotoxin and clam toxin.[121] In the past few decades, people's interest in functional molecules and drugs with guanidine structures has increased exponentially. Thus, nowadays guanidine compounds have been widely used in pharmaceutical chemistry.[122,123] Guanidine compounds are able to bind

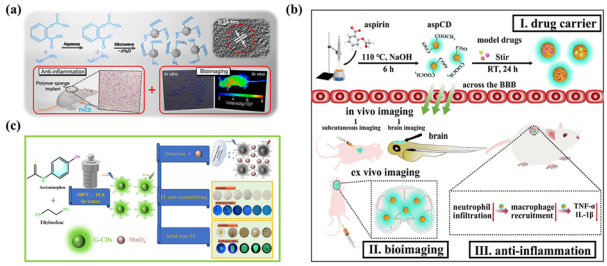

Fig. 5 (a) Schematic illustration of microwaved FACDs *via* the "one-step" method and the application of anti-inflammation and bioimaging. Reproduced with permission from ref. 75. Copyright 2016 ACS Publications. (b) Schematic representation of the synthesis and application of aspCDs. Reproduced with permission from ref. 77. Copyright 2022 Elsevier. (c) Schematic diagram of the preparation and potential applications of G-CDs. Reproduced with permission from ref. 80. Copyright 2024 Elsevier.

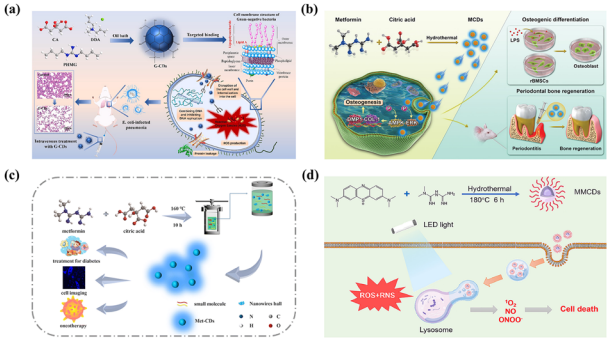

Fig. 6 (a) Schematic illustration of the synthesis of G-CDs, the antibacterial mechanism and the *in vivo* treatment of infected pneumonia. Reproduced with permission from ref. 81. Copyright 2023 Elsevier. (b) Schematic illustration of the synthetic procedure of MCDs and the working mechanism for promoting periodontal bone regeneration. Reproduced with permission from ref. 82. Copyright 2021 Wiley Online Library. (c) Flow chart of the preparation and applications of Met-CDs. Reproduced with permission from ref. 83. Copyright 2022 Royal Society of Chemistry. (d) Schematic illustration of the preparation of MMCDs and the underlying mechanism of tumor cell death induced by photodynamic lysosomal impairment. Reproduced with permission from ref. 84. Copyright 2024 Elsevier.

anions such as carboxylates, phosphates and sulfides through H bonds to form non-covalent interactions with proteins and molecular targets.[124] From a chemical perspective, guanidine can be described as a nitrogen-containing analogue of carbonic acid and a strong organic base with a pK_a value of 12–13, which has high stability after protonation under physiological conditions. Moreover, the alkalinity can be adjusted by adding appropriate electron-absorbing substituents to the nitrogen atom, so that the pK_a can be reduced to 7–8, which gives guanidine drugs a high degree of universality.[125,126] Guanidine drugs are widely used in the treatment of inflammatory conditions, cardiovascular disorders, diabetes and hypertension. In particular, many antimicrobial agents, for instance, the antibiotic streptomycin and the antimalarial drug proguanil, contain guanidine groups.[127,128]

In 2023, Zhang *et al.* used a bottom-up strategy with small molecules, employing citric acid as the carbon core source, and quaternary ammonium compounds (dimethyldienyl ammonium chloride, DDA) and guanidine compounds (polyhexamethylene guanidine, PHMG) as positively charged nitrogen sources, to prepare broad-spectrum antimicrobial guanidine CDs (G-CDs) *via* two-step thermal decomposition.[81] As shown in Fig. 6a, G-CDs exhibit excitation-dependent fluorescence emission spectra, with an optimal excitation wavelength of 310 nm and a maximum emission wavelength of 393 nm. Structural analysis showed that G-CDs retained the quaternary ammonium group and guanidine group of the raw materials. G-CDs show long-term and stable antibacterial activity against a variety of common clinical bacteria and drug-resistant bacteria, and exhibit excellent inhibitory ability against biofilm production, which is one of the critical factors leading to the development of bacterial drug resistance. CDs exhibit multiple complex bacteriostatic mechanisms, including depolarization of the potential difference between inside and outside the bacterial cell membrane, leading to the disruption of the cell wall and cell membrane and leakage of cytoplasmic components; in addition, CDs promote the generation of ROS in bacteria, and effectively bind to DNA and induce its conformational change that result in functional failure. G-CDs exhibit better antibacterial properties against Gram-negative bacteria. The bacterial efflux system is the main mechanism of bacterial drug resistance, and G-CDs reduce the activity of the internal efflux pump by promoting bacterial ATP efflux, which may be the critical factor due to which G-CDs do not induce bacterial drug resistance. The results of biosafety evaluation *in vivo* and *in vitro* as well as model experiments of pneumonia caused by intestinal *Escherichia coli* in mice showed that G-CDs had an excellent therapeutic effect and little side effect. This work highlights the application potential of guanidine-based CDs as new antibacterial agents and provides a clear pathway for the development of new carbon nano-material based antibacterial agents through appropriate selection of raw materials.

Biguanidine, a compound in which two guanidine groups fuse to form a highly conjugated system, is strongly alkaline and often exists in the form of salts (mainly hydrochloride). At present, biguanidine drugs have been found to have obvious therapeutic effects in the treatment of diabetes, malaria, influenza, ophthalmic infection, dental caries, dental plaque and so on.[129] Metformin, one of the most crucial biguanide drugs, is a mature first-line drug for the treatment of type 2 diabetes. It can reduce blood sugar without causing significant hypoglycemia or weight gain, offering a high safety profile.[130] Not only that, but recent studies have revealed that dimethyl biguanidine can also be used to treat various types of cancer, such as breast cancer, ovarian cancer, cervical cancer, lung cancer, and liver cancer.[131] Because metformin has the advantages of small molecular weight, well-defined structure, high nitrogen content, easy storage and low synthesis cost, it serves as an excellent precursor for the synthesis of CDs; metformin-

derived CDs have the potential to retain the therapeutic properties of the parent drug, enabling them to function effectively in disease treatment.[132–134]

In 2021, Ren *et al.* prepared metformin CDs (MCDs) with excellent biocompatibility by the hydrothermal method using metformin hydrochloride and citric acid as raw materials.[82] The amino group of metformin and the hydroxyl/carboxyl group of citric acid facilitated successful dehydration, condensation and carbonization in the process of CD synthesis. Structural characterization shows that there are amino and hydroxyl groups on the surface of MCDs. MCDs have excitation-dependent blue fluorescence emission, demonstrate efficient cellular uptake and imaging capabilities in both cells and mice, and have a strong ability for metabolism *in vivo*, resulting in less burden on the liver and kidneys. As shown in Fig. 6b, under *in vitro* inflammatory and normal conditions, MCDs can effectively promote the osteogenesis of rat mesenchymal stem cells (rBMSCs), while metformin molecules cannot. It is speculated that the surface of MCDs contains not only amino groups, but also hydroxyl groups, both of which are functional groups with osteogenic ability. The potential mechanism was further explored and it was found that the ERK/AMPK pathway played a key role in MCD-induced osteogenesis. Moreover, in the body, MCDs can promote periodontal bone regeneration more effectively than the raw material. In 2022, as shown in Fig. 6c, Su *et al.* also prepared CDs derived from citric acid and metformin (Met-CDs) by the hydrothermal method.[83] Met-CDs have a stable blue fluorescence emission center, which does not change with the excitation wavelength, and demonstrate significant pH sensitivity in acidic environments, favorable pH stability and high temperature sensitivity in alkaline environments. In addition, the use of diabetic cell models demonstrated that Met-CDs inherited the functions of metformin in treating diabetes and reducing the production of reactive oxygen species in diseased cells. Studies have shown that metformin exhibits anticancer effects under low glucose conditions. The article highlights that the effect of Met-CDs on A549 cells can be controlled by regulating the content of glucose in the cellular environment. When A549 cells are exposed to normal glucose, Met-CDs can be used as fluorescence imaging agents to label A549 cells, while when A549 cells are in a low glucose environment, Met-CDs can be used as an anticancer drug to inhibit the growth of A549 cells. The exploration of the mechanism shows that the mechanism of inhibition of tumor cell growth by Met-CDs is similar to that of Met. This work verifies that Met-CDs inherit the therapeutic ability of their raw materials for diabetes management and have the potential to be used as fluorescent probes and anticancer agents, and offer the potential for integrated disease diagnosis and treatment.

Metformin-derived CDs not only inherit the original mechanism of raw material molecules to inhibit the growth of tumor cells, but also develop additional more complex anti-cancer mechanisms to achieve multi-faceted synergistic tumor suppression. As shown in Fig. 6d, Bi *et al.* synthesized metformin and methylene blue (MB) derived CDs (MMCDs) by a hydrothermal method.[84] Under the irradiation of a light-emitting diode (LED), MMCDs shows higher $^1O_2$ production efficiency and NO production efficiency. It is worth noting that $^1O_2$ can further oxidize NO into peroxynitrite anions ($ONOO^-$), which have higher cytotoxicity toward cancer cells. Cell experiments show that MMCDs can destroy the integrity of the lysosomal membrane and kill nearly 80% of HepG2 cells under light irradiation, while exhibiting minimal cytotoxicity in the dark. In addition, the tumor volume and weight of mice with liver cancer treated with MMCD-based photodynamic therapy decreased significantly. Compared with metformin, MMCDs show red fluorescence emission of 642 nm, and the ability of lysosome imaging, as well as a more efficient photodynamic effect. Yu *et al.* synthesized MFCDs with independent blue fluorescence emission at 465 nm using metformin and 2-dithiobenzoic acid (DTSA) as raw materials.[85] The experimental results indicate that a low dose of MFCDs is also effective in the treatment of colorectal cancer, overcoming the limitation that only ultrahigh doses of metformin have anticancer effects while also reducing the side effects of liver and kidney injury caused by a large number of drugs. It is supposed that, compared with the raw material molecules, the enhanced anti-tumor effect comes from the chelation of guanidine functional groups on the surface of MFCDs with excess Cu^{2+} in the serum of patients with colon cancer. As shown in Fig. 7a, on the one hand, the chelation of MFCDs with Cu^{2+} reduces the amount of copper and zinc superoxide dismutase (Cu/Zn-SOD) activation. On the other hand, MFCDs convert Cu^{2+} to Cu^+, promoting the conversion of glutathione (GSH) to oxidized glutathione disulfide (GSSG). The decrease of copper and zinc superoxide dismutase (Cu/Zn-SOD) and glutathione (GSH) levels led to a decrease in the antioxidant activity of carcinogenic cells and the scavenging ability of reactive oxygen species (ROS). The increase of ROS in cells leads to DNA damage and cell cycle arrest, and finally leads to tumor cell death. This work once again illustrates the necessity of synthesizing CDs from drug molecular materials to enhance their anticancer activity. MGA-CDs derived from gallic acid and dimethylbiguanide were prepared by Wu *et al.*; these can freely pass through the blood–brain barrier and target mitochondria.[86]

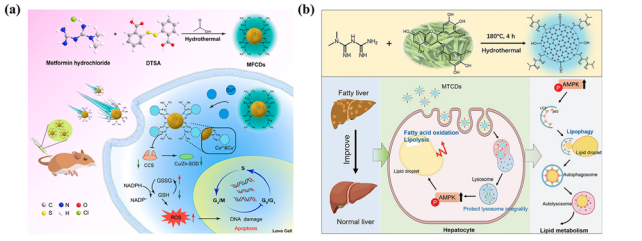

Fig. 7 (a) The synthesis of MFCDs and the process of inhibiting colorectal cancer. Reproduced with permission from ref. 85. Copyright 2023 Elsevier. (b) Schematic illustration of the preparation of MTCDs and the underlying mechanism of MTCDs for promoting lipid metabolism and improving MAFLD. Reproduced with permission from ref. 87. Copyright 2024 Wiley Online Library.

The fluorescence properties of CDs give MGA-CDs the ability to image the mitochondria of glioblastoma cells. At the same time, the imaging will also cause mitochondrial membrane condensation and mitochondrial crest reduction, that is, the typical iron death-like morphological changes. The study of the mechanism shows that MGA-CDs may induce iron death by downregulating the expression of specific genes involved in the metabolic pathway of glycerol phospholipids. In short, MGA-CDs exhibit a significant anti-primary brain cancer effect and can be quickly cleared from the brain, making them a promising option for the treatment of intracranial tumors. This is a new attempt to explore metformin-derived CDs for the treatment of intracranial tumors and for developing new anti-cancer mechanisms.

In addition to their anti-tumor effect, metformin-derived CDs are also potential therapeutic agents for many other diseases. As shown in Fig. 7b, Bi *et al.* developed novel functional CDs, MTCDs, derived from metformin and tea polyphenols, incorporating several effective groups such as biguanidine and phenolic hydroxyl groups, which can reduce lipid deposition and oxidative stress in the liver and play a role in treating non-alcoholic fatty liver.[87] MTCDs can emit blue-green fluorescence, exhibit excellent lysosome targeting function, and selectively image lysosomes in cells, as well as display good biocompatibility and low biotoxicity. Mechanical studies have further shown that the excellent ROS scavenging and antioxidant ability of reductive groups such as guanidine and hydroxyl groups on the MTCD surface protect lysosomes from oxidative stress and activate AMP-activated protein kinase signal transduction in hepatocytes, initiating the process of fat phagocytosis to accelerate fat decomposition and lipid consumption.

Guanidine drugs are usually used as antimicrobials, and metformin is most commonly used in the treatment of diabetes. In recent years, it has also been found to have active effects and therapeutic potential in a variety of cancers, but large doses and high concentrations of drugs are needed. By preparing guanidine compounds as CDs, it is possible to not only retain the antibacterial and anti-tumor activity of the raw materials but also improve their efficacy and introduce new anti-tumor mechanisms, including targeting tumor overexpression markers, inducing iron death, and utilizing photodynamic therapy and so on. This approach forms a synergistic therapeutic effect with the original treatment mechanism, which can reduce the drug concentration and minimize metabolic toxicity of the liver and kidneys. Furthermore, the fluorescence properties of CDs can also lighten tumor sites and subcellular locations, realize treatment visualization, with the potential for integrating diagnosis and treatment.

2.4 CDs synthesized from other drugs

In addition, there are many other CDs derived from organic drug molecules that can retain specific functional groups and properties of their precursors, thereby enhancing their functionality. For instance, CDs synthesized from anticancer drugs like doxorubicin or paclitaxel can be engineered to specifically target cancer cells, potentially increasing the efficacy of cancer treatments and reducing side effects.[135,136] Similarly, CDs derived from antiviral drugs such as porphyrin can be utilized in antiviral therapies, improving the delivery and effectiveness of antiviral agents.[137] Finally, carbon dots derived from anti-osteoporosis drugs exhibit great application potential.

Osteoporosis (OP) is a serious metabolic bone disease caused by bone homeostasis imbalance, which is characterized by decreased bone mass, deterioration of bone microstructure and increased risk of brittle fractures. Osteoporotic fractures, especially hip and spinal fractures, can lead to severe pain, disability, and even death.[138,139] As society ages, the incidence of age-related osteoporotic fractures is increasing, arousing widespread concern. Osteoporosis results from the disruption of bone homeostasis, which is co-regulated by osteoclast bone resorption and osteoblast bone formation.[140] At present, the prevention of osteoporotic fractures is mainly through the use of drugs such as bisphosphonates, teriparatide, and raloxifene. Bisphosphonates (BPs) are one of the most powerful drugs for the treatment of bone and calcium metabolism-related diseases. Their activity is based on their unique chemical structure, called the P–C–P skeleton structure, which has a strong affinity for calcium ions in hydroxyapatite (HAP) on the bone surface.[141] Alendronate (ALEN) is one of the most effective and widely studied drugs among bisphosphonates. It works by inhibiting the formation of osteoclasts by blocking ATP synthesis. However, it has a long treatment cycle and slow metabolic process, which may lead to atypical long bone fractures and bisphosphonate-related jaw necrosis (BRONJ).[142] Because of the unique rich surface groups and excellent biocompatibility of CDs, the development of alendronate-derived CDs as a new drug for the treatment of osteoporosis may be an effective way to reduce side effects.

In 2023, Peng *et al.* synthesized highly efficient Alen-CDs with enhanced anti-osteoporosis properties *via* a one-step hydrothermal method using alendronate as the sole raw material.[88] As shown in Fig. 8a, the surface of Alen-CDs contains amino hydroxyl and phosphate groups inherited from alendronate, thereby retaining the inherent anti-osteoporosis properties of alendronate, and the richer hydroxyl and amino groups improve the problem of low bioavailability of prodrugs due to poor water

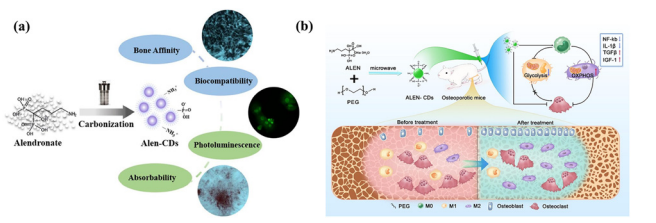

Fig. 8 (a) The synthesis process and multiple biomedical application of Alen-CDs. Reproduced with permission from ref. 88. Copyright 2023 Elsevier. (b) Schematic illustration of the synthesis and osteoporosis treatment using ALEN-CDs. Reproduced with permission from ref. 89. Copyright 2024 Elsevier.

solubility, resulting in better calcium deposition and bone regeneration efficacy compared to the precursors at the same concentration. Even at the same drug concentration, it has lower cytotoxicity than the raw material, indicating improved biocompatibility. Moreover, Alen-CDs emit bright blue fluorescence, and being endowed with fluorescence properties, they can address the limitation of tracking drug distribution in living bodies and selectively illuminate the nuclear region of cells. Under continuous exposure, they remain stable and do not cause cell morphological changes, which proves their application potential as a cell imaging reagents. Drug-derived Alen-CDs are excellent candidates for promoting osteoblast differentiation and can monitor the fluorescence of drug distribution during the period of treatment of osteoporosis. While Peng's work explored the potency of alendronate-derived CDs in enhancing efficacy, Xu's work focused on the efficacy of CDs in reducing the side effects of bisphosphonate-related jaw necrosis (BRONJ). As shown in Fig. 8b, Xu *et al.* synthesized ALEN-CDs from alendronate and PEG (as a passivator) *via* a microwave-assisted method, which shows bright blue fluorescence emission and cell imaging ability, but unlike the work of Peng, ALEN-CDs can selectively illuminate the cytoplasm rather than the nucleus.[89] Compared with ALEN alone, ALEN-CDs synthesized with alendronate and the PEG passivator reduced the time-dependent cumulative toxicity to cells, significantly reduced bone loss in ovariectomized mice (OVX), significantly alleviated the inflammatory reaction on the dental fossa bone surface in a mouse model after tooth extraction and promoted wound healing after tooth extraction in mice. This immunomodulatory mechanism is believed to induce a change in macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype by regulating mitochondrial oxidative phosphorylation. The synthesized ALEN-CDs not only retained the bone targeting and inhibitory effect on osteoclast formation, but also increased the postoperative immunomodulatory effect and effectively avoided bisphosphonate-associated jaw necrosis (BRONJ).

The above work shows that converting alendronate sodium, which is used to treat osteoporosis, to carbon nanodots by polymeric carbonization can not only preserve the ability of the drug itself to promote bone regeneration but also increase the water solubility of the drug and improve the absorption rate and utilization rate of the drug, ultimately boosting the therapeutic effect. Besides, CDs can also lower the side effects of alendronate and reduce the possibility of increased cell accumulation toxicity and related jaw necrosis over time. Owing to the unique advantages in clinical treatment brought about by a variety of performance improvements, we can also explore the utilization potentiality of the above CDs in the treatment of Paget's disease, osteolytic myeloma and malignant hypercalcemia, conditions where alendronate has a potential therapeutic effect.

3. Summary and discussion

CDs prepared through the bottom-up synthesis routes have a general character that the functional groups of precursors often remain on the surfaces of CDs. And thus, organic drug derived CDs usually inherit the therapeutic effects of the original drugs and even exhibit new functions. These drug-derived CDs always have the fluorescence properties of CDs, so the distribution of drugs in the body can be monitored by imaging during the treatment. Such drug-derived CDs can also enhance the directional release and targeting of drugs to the lesions, enhance the selectivity of diseased cells, reduce damage to normal cells and tissues, and reduce the side effects of drugs. Compared with the drug itself, the drug-derived CDs may introduce new therapeutic mechanisms, such as synergistic sterilization, binding by electrostatic gravity, breaking the bacterial cell membrane, multi-faceted anti-cancer action, iron death, photodynamically induced excessive ROS production and other ways to enhance the therapeutic efficacy of killing tumor cells. All these are new surprises brought by drug-derived CDs, which proves the unique potential of CDs as a new class of nanodrugs. What's more, the fluorescence imaging ability of drug-derived CDs is also helpful to understand the pathogenesis and treatment mechanism of specific diseases as well as the morphological changes of cells.

However, the structures of many drug-derived CDs are unclear at present, and the exploration of their new properties are insufficient by far. To establish a clear structure–activity relationship, many positive contrast experiments between the drug precursors and the CDs should be carried out using the same disease model both *in vivo* and *in vitro*, and the therapeutic mechanisms of CDs should be studied in depth. In comparison with the CDs derived from traditional Chinese medicine, CDs made from organic drug molecules have more easily traceable structural sources and therapeutic mechanisms because the active components and the therapeutic sites of these drugs have been established before. The shortcomings of these traditional drugs, such as poor water solubility and toxic side effects, can be overcome by CDs. Furthermore, the luminescent drug-derived CDs can illuminate cells, tissues, lesions and tumors, which help monitor the therapeutic processes and disclose disease development. These special merits are enough to drive researchers to prepare more and more drug-derived CDs and investigate their applications in the future.

Author contributions

Z. W. designed the structure and content, assembled the literature and wrote this review. X. L., X. S., B. W., H. S. and Z. S. provided suggestions and revised this review. Y. M. and H. X. supervised the article writing.

Data availability

This is a review article, which has no data available. The figures cited from references are used with permissions obtained from the corresponding publishers.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was financially supported by the Shanghai Municipal Commission of Health and Family Planning (2022JC031) and the Science and Technology Commission of Shanghai Municipality (2024ZDSYS02).

References

1 B. Wang, G. I. N. Waterhouse and S. Lu, *Trends Chem.*, 2022, **5**, 76–87.
2 L. Đorđević, F. Arcudi, M. Cacioppo and M. Prato, *Nat. Nanotechnol.*, 2022, **17**, 112–130.
3 B. Wang, H. Song, X. Qu, J. Chang, B. Yang and S. Lu, *Coord. Chem. Rev.*, 2021, **442**, 214010.
4 B. Wang, H. Cai, G. I. N. Waterhouse, X. Qu, B. Yang and S. Lu, *Small Sci.*, 2022, **2**, 2200012.
5 B. Wang and S. Lu, *Matter*, 2022, **5**, 110–149.
6 M. K. Barman and A. Patra, *J. Photochem. Photobiol., C*, 2018, **37**, 1–22.
7 S. Xue, P. Li, L. Sun, L. An, D. Qu, X. Wang and Z. Sun, *Small*, 2023, **19**, 2206180.
8 Y. Liu, L. Zhang, H. Cai, X. Qu, J. Chang, G. I. N. Waterhouse and S. Lu, *Sci. Bull.*, 2024, **69**, 3127–3149.
9 N. Tejwan, A. K. Saini, A. Sharma, T. A. Singh, N. Kumar and J. Das, *J. Controlled Release*, 2021, **330**, 132–150.
10 A. Sharma and J. Das, *J. Nanobiotechnol.*, 2019, **17**, 92.
11 H. Wang, W. Su and M. Tan, *The Innovation*, 2020, **1**, 100009.
12 J. Li and X. Gong, *Small*, 2022, **18**, 2205099.
13 Z. He, Y. Sun, C. Zhang, J. Zhang, S. Liu, K. Zhang and M. Lan, *Carbon*, 2023, **204**, 76–93.
14 C. Xia, S. Zhu, T. Feng, M. Yang and B. Yang, *Adv. Sci.*, 2019, **6**, 1901316.
15 Y. Xiong, J. Schneider, E. V. Ushakova and A. L. Rogach, *Nano Today*, 2018, **23**, 124–139.
16 Y. Hu, O. Seivert, Y. Tang, H. E. Karahan and A. Bianco, *Angew. Chem., Int. Ed.*, 2024, **63**, e202412341.
17 S. Liu, Y. Xu, X. Wang, H. Zhou and T. Zhang, *Chem. Eng. J.*, 2024, **496**, 153914.
18 Y. Huo, S. Xiu, L.-Y. Meng and B. Quan, *Chem. Eng. J.*, 2023, **451**, 138572.
19 L. Rao, B. Sun, Y. Liu, Q. Zhang, G. Zhong, M. Wen, J. Zhang, T. Fu and X. Niu, *Ultrason. Sonochem.*, 2023, **101**, 106674.
20 Z. Peng, X. Han, S. Li, A. O. Al-Youbi, A. S. Bashammakh, M. S. El-Shahawi and R. M. Leblanc, *Coord. Chem. Rev.*, 2017, **343**, 256–277.
21 C.-L. Shen, H.-R. Liu, Q. Lou, F. Wang, K.-K. Liu, L. Dong and C.-X. Shan, *Theranostics*, 2022, **12**, 2860–2893.
22 J. Wang, Y. Fu, Z. Gu, H. Pan, P. Zhou, Q. Gan, Y. Yuan and C. Liu, *Small*, 2024, **20**, 2303773.
23 Y. Ma, L. Wu, X. Ren, Y. Zhang and S. Lu, *Adv. Funct. Mater.*, 2023, **33**, 2305867.
24 L. Chen, C.-F. Wang, C. Liu and S. Chen, *Small*, 2023, **19**, 2206671.
25 L. Li, Y. Li, Y. Ye, R. Guo, A. Wang, G. Zou, H. Hou and X. Ji, *ACS Nano*, 2021, **15**, 6872–6885.
26 Z. Zhu, R. Cheng, L. Ling, Q. Li and S. Chen, *Angew. Chem., Int. Ed.*, 2020, **59**, 3099.
27 W.-J. Zheng, Z.-N. Sun, Y.-M. Wang and H.-M. Xiong, *Nano Res.*, 2024, **17**, 8495–8503.
28 X. Niu, W. Zheng, T. Song, Z. Huang, C. Yang, L. Zhang, W. Li and H. Xiong, *Chin. Chem. Lett.*, 2023, **34**, 107560.
29 X. Niu, T. Song and H. Xiong, *Chin. Chem. Lett.*, 2021, **32**, 1953–1956.
30 H. Ding, R. Zhao, Z.-H. Zhang, J.-J. Yang, Z. Wang, L.-L. Xiao, X.-H. Li, X.-J. He and H.-M. Xiong, *Chem. Eng. J.*, 2023, **476**, 146405.
31 Y. Li, C. Liu, H. Sun, M. Chen, D. Hou, Y. Zheng, H. Xie, B. Zhou and X. Lin, *Adv. Sci.*, 2023, **10**, 2300543.
32 Y. Zhang and S. Lu, *Chem*, 2024, **10**, 134–171.
33 B. Wang, G. I. N. Waterhouse, B. Yang and S. Lu, *Acc. Chem. Res.*, 2024, **57**, 2928–2939.
34 S. J. Park, H. K. Yang and B. K. Moon, *Nano Energy*, 2019, **60**, 87–94.
35 Y. Han, Y. Wang, B. Zhao, Y. Bai, S. Han, Y. Zhang, S. Li, Z. Chen, C. Si, H. Yu, C. Zhang and W. Yu, *Adv. Compos. Hybrid Mater.*, 2023, **6**, 39.
36 B. Guo, G. Liu, W. Ye, Z. Xu, W. Li, J. Zhuang, X. Zhang, L. Wang, B. Lei, C. Hu, Y. Liu and H. Dong, *Food Hydrocolloids*, 2024, **147**, 109327.
37 J. Zhao, M. Zhang, S. Wang, Z. Cui, Z. Dai, H. He, S. Qin, S. Mei, W. Zhang and R. Guo, *Adv. Funct. Mater.*, 2024, **34**, 2401067.
38 J. Xu, Q. Liang, Z. Li, V. Y. Osipov, Y. Lin, B. Ge, Q. Xu, J. Zhu and H. Bi, *Adv. Mater.*, 2022, **34**, 2200011.
39 B. Zhao, H. Ma, H. Jia, M. Zheng, K. Xu, R. Yu, S. Qu and Z. Tan, *Angew. Chem., Int. Ed.*, 2023, **62**, e202301651.
40 C. Ji, W. Xu, Q. Han, T. Zhao, J. Deng and Z. Peng, *Nano Energy*, 2023, **114**, 108623.
41 X. Miao, D. Qu, D. Yang, B. Nie, Y. Zhao, H. Fan and Z. Sun, *Adv. Mater.*, 2018, **30**, 1704740.
42 Y. Liu, D. Cheng, B. Wang, J. Yang, Y. Hao, J. Tan, Q. Li and S. Qu, *Adv. Mater.*, 2024, **36**, 2403775.
43 H. Li, C. Sun, M. Zhang, W. Yan and Z. Kang, *Adv. Funct. Mater.*, 2024, **34**, 2405669.
44 M. Kuligowska and S. Neffe, *TrAC, Trends Anal. Chem.*, 2024, **176**, 117767.
45 A. M. P. Ajith, S. Pardhiya and P. Rajamani, *Small*, 2022, **18**, 2105579.
46 T. Li, N. Zhang, S. Zhao, M. Liu, K. Zhang, C. Zhang, J. Shu and T.-F. Yi, *Coord. Chem. Rev.*, 2024, **516**, 215987.

47 Y. Zhang, M. Chen, T. Wu, C. Lin, L. Xie and Q. Chen, *TrAC, Trends Anal. Chem.*, 2024, **176**, 117737.
48 S. Wei, H. Zhang, C. Wang, X. Yin, K. Hu, M. Liu, C. Jiang and G. Sun, *Chem. Eng. J.*, 2023, **474**, 145614.
49 J. Feng, L. Shi, D. Chang, C. Dong and S. Shuang, *Chem. Eng. J.*, 2024, **490**, 151839.
50 J. Hu, Z. Zheng, Y. Yang, L. Chen and W. Kang, *Adv. Healthcare Mater.*, 2024, 2401513.
51 M. Yang, Y. Han, A. Bianco and D.-K. Ji, *ACS Nano*, 2024, **18**, 11560–11572.
52 J. Li, S. Yang, Z. Liu, G. Wang, P. He, W. Wei, M. Yang, Y. Deng, P. Gu, X. Xie, Z. Kang, G. Ding, H. Zhou and X. Fan, *Adv. Mater.*, 2021, **33**, 2005096.
53 Y. Guo, Y. Sun, X. Geng, J. Wang, J. Hu, R.-B. Song, R. Yang, L. Qu and Z. Li, *Adv. Funct. Mater.*, 2024, **34**, 2401744.
54 Q. Wang, T. Zhang, Q. Cheng, B. Wang, Y. Liu, G. Xing, Z. Tang and S. Qu, *Adv. Funct. Mater.*, 2024, **34**, 2402976.
55 Y. Jiang, T. Zhao, W. Xu and Z. Peng, *Carbon*, 2024, **219**, 118838.
56 T. Zhang, Q. Cheng, J. H. Lei, B. Wang, Y. Chang, Y. Liu, G. Xing, C. Deng, Z. Tang and S. Qu, *Adv. Mater.*, 2023, **35**, 2302705.
57 M. Yi, M. Jing, Y. Yang, Y. Huang, G. Zou, T. Wu, H. Hou and X. Ji, *Adv. Funct. Mater.*, 2024, **34**, 2400001.
58 Y. Li, Y. Mei, H. Liu, H. Ding, Y. Huang, X. Zhong, Z. Geng, Z. He, W. Deng, G. Zou, X. Ji and H. Hou, *Nano Energy*, 2024, **130**, 110107.
59 Y. Gong, J. Huang, X. Xing, H. Liu, Z. Zhou and H. Dong, *Chem. Eng. J.*, 2024, **481**, 148523.
60 W. Song, X. Wang, S. Nong, M. Wang, S. Kang, F. Wang and L. Xu, *Adv. Funct. Mater.*, 2024, **34**, 2402761.
61 Q. Cheng, T. Zhang, Q. Wang, X. Wu, L. Li, R. Lin, Y. Zhou and S. Qu, *Adv. Mater.*, 2024, **36**, 2408685.
62 A. Truskewycz, H. Yin, N. Halberg, D. T. H. Lai, A. S. Ball, V. K. Truong, A. M. Rybicka and I. Cole, *Small*, 2022, **18**, 2106342.
63 W.-K. Luo, L.-L. Zhang, Z.-Y. Yang, X.-H. Guo, Y. Wu, W. Zhang, J.-K. Luo, T. Tang and Y. Wang, *J. Nanobiotechnol.*, 2021, **19**, 320.
64 M. Zeng, Y. Wang, M. Liu, Y. Wei, J. Wen, Y. Zhang, T. Chen, N. He, P. Fan and X. Dai, *Int. J. Nanomed.*, 2023, **18**, 6503–6525.
65 P. Hou, T. Yang, H. Liu, Y. F. Li and C. Z. Huang, *Nanoscale*, 2017, **9**, 17334–17341.
66 H. Miao, P. Wang, Y. Cong, W. Dong and L. Li, *Int. J. Mol. Sci.*, 2023, **24**, 6814.
67 J. Liang, W. Li, J. Chen, X. Huang, Y. Liu, X. Zhang, W. Shu, B. Lei and H. Zhang, *ACS Appl. Bio Mater.*, 2021, **4**, 6937–6945.
68 L.-N. Wu, Y.-J. Yang, L.-X. Huang, Y. Zhong, Y. Chen, Y.-R. Gao, L.-Q. Lin, Y. Lei and A.-L. Liu, *Carbon*, 2022, **186**, 452–464.
69 G. Niu, F. Gao, C. Li, Y. Wang, H. Li and Y. Jiang, *J. Mater. Chem. B*, 2023, **11**, 8916–8925.
70 J. Tan, Q. Li, S. Meng, Y. Li, J. Yang, Y. Ye, Z. Tang, S. Qu and X. Ren, *Adv. Mater.*, 2021, **33**, 2006781.
71 L. Jiang, H. Cai, W. Zhou, Z. Li, L. Zhang and H. Bi, *Adv. Mater.*, 2023, **35**, 2210776.
72 M. Liu, S. Li, Z. Li, Y. Li, Y. Zhang, J. Niu, L. Nie, C. Chen and Q. Zhou, *Microchem. J.*, 2023, **193**, 109046.
73 G.-Q. Zhang, W. Liu, Y.-H. Shi, Y.-X. Zou, L.-Y. Xu, H.-L. Cheng, T. Wang, W.-B. Li, Y. Zhao and Z.-H. Xu, *Microchem. J.*, 2024, **197**, 109720.
74 H. Wang, X. Zhao, X. Zhou, X. He, L. Xiao, X. Zhang, Y. Zhang, S. Nie and Y. Jiang, *Microchem. J.*, 2024, **201**, 110509.
75 X. Xu, K. Zhang, L. Zhao, C. Li, W. Bu, Y. Shen, Z. Gu, B. Chang, C. Zheng, C. Lin, H. Sun and B. Yang, *ACS Appl. Mater. Interfaces*, 2016, **8**, 32706–32716.
76 Y. Han, F. Zhang, J. Zhang, D. Shao, Y. Wang, S. Li, S. Lv, G. Chi, M. Zhang, L. Chen and J. Liu, *Colloids Surf., B*, 2019, **179**, 1–8.
77 X. Zhang, Q. Yu, P. Zhou, S. Yang, J. Xia, T. Deng and C. Yu, *Biomater. Adv.*, 2022, **139**, 212995.
78 C. Wan, M. Hu, X. Peng, N. Lei, H. Ding, Y. Luo and X. Yu, *Biomater. Sci.*, 2022, **10**, 6291–6306.
79 H. Liu, Y. Sun, Z. Li, J. Yang, A. A. Aryee, L. Qu, D. Du and Y. Lin, *Nanoscale*, 2019, **11**, 8458–8463.
80 M. Ran, H. Qi, T. Jing, J. Li, W. Li, J. Zhang, C. Luo, X. Zhu and Y. Gao, *Spectrochim. Acta, Part A*, 2024, **323**, 124907.
81 X. Zhang, X. Bai, X. Deng, K. Peng, Z. Zheng, J. Xiao, R. Zhang, Z. Huang, J. Huang, M. Chen and S. Weng, *Carbon*, 2023, **213**, 118229.
82 C. Ren, X. Hao, L. Wang, Y. Hu, L. Meng, S. Zheng, F. Ren, W. Bu, H. Wang, D. Li, K. Zhang and H. Sun, *Adv. Healthcare Mater.*, 2021, **10**, 2100196.
83 J. Wan, S. Xu, J. Li, M. Yu, K. Zhang, G. Wei and Z. Su, *Nanoscale*, 2022, **14**, 11359–11368.
84 H. Cai, X. Wu, L. Jiang, F. Yu, Y. Yang, Y. Li, X. Zhang, J. Liu, Z. Li and H. Bi, *Chin. Chem. Lett.*, 2024, **35**, 108946.
85 L. Yu, Y. Wang, K. Li, X. Li, M. He, C. Chen, F. Li, B. Liang, L. Li, N. Gu, Z. Liu, B. Li, G. Wang and J. Fan, *Carbon*, 2023, **212**, 118095.
86 K. Deng, L. Zhang, W. Gao, X. Lin, X. Long, Y. Wang and M. Wu, *Chem. Eng. J.*, 2023, **475**, 146473.
87 H. Cai, Y. Li, X. Wu, Y. Yang, A. C. Tedesco, Z. Li and H. Bi, *Adv. Funct. Mater.*, 2024, **34**, 2406096.
88 J. Wu, S. Yuan, Y. Jiang, Y. Jia, C. Ji, Z. Tan, W. Shi and Z. Peng, *Diamond Relat. Mater.*, 2023, **140**, 110571.
89 W. Xu, Y. Zhang, X. Huang, J. Wang, W. Zhang, S. Zhang, J. Ren, L. Liu, Y. Zhan, B. Zhang, Y. Li and H. Jin, *Chem. Eng. J.*, 2024, **494**, 152209.
90 M. Abbas, M. Paul and A. Huttner, *Clin. Microbiol. Infect.*, 2017, **23**, 697–703.
91 M. Qiao, G.-G. Ying, A. C. Singer and Y.-G. Zhu, *Environ. Int.*, 2018, **110**, 160–172.
92 M. Zabiszak, J. Frymark, K. Ogawa, M. Skrobańska, M. Nowak, R. Jastrzab and M. T. Kaczmarek, *Coord. Chem. Rev.*, 2023, **493**, 215326.

93 C. Chen, Y. Yin, P. Lu, T. Han, H. Wang and C. Li, *Angew. Chem., Int. Ed.*, 2024, e202415439.
94 B. M. Wei, L. P. Fox, B. H. Kaffenberger, A. M. Korman, R. G. Micheletti, A. Mostaghimi, M. H. Noe, M. Rosenbach, K. Shinkai, J. H. Kwah, E. J. Phillips, J. L. Bolognia, W. Damsky and C. A. Nelson, *J. Am. Acad. Dermatol.*, 2024, **90**, 885–908.
95 K. A. Gehrig and E. M. Warshaw, *J. Am. Acad. Dermatol.*, 2008, **58**, 1–21.
96 D. Panáček, J. Belza, L. Hochvaldová, Z. Baďura, G. Zoppellaro, M. Šrejber, T. Malina, V. Šedajová, M. Paloncýová, R. Langer, L. Zdražil, J. Zeng, L. Li, E. Zhao, Z. Chen, Z. Xiong, R. Li, A. Panáček, R. Večeřová, P. Kučová, M. Kolář, M. Otyepka, A. Bakandritsos and R. Zbořil, *Adv. Mater.*, 2024, 2410652.
97 X. Wang, S. Zhao, G. Fang, R. Wang, X. Lyu, X. Shao, P. Ling, C. Meng, J. Chen and Y. Mu, *Nanoscale*, 2024, **16**, 8597–8606.
98 M. Ge, F. Jiang and H. Lin, *Mater. Today Bio*, 2024, **29**, 101255.
99 Q. Bu, D. Jiang, Y. Yu, Y. Deng, T. Chen and L. Xu, *Drug Resist. Updates*, 2024, **76**, 101102.
100 W.-B. Zhao, K.-K. Liu, Y. Wang, F.-K. Li, R. Guo, S.-Y. Song and C.-X. Shan, *Adv. Healthcare Mater.*, 2023, **12**, 2300324.
101 B. Sun, F. Wu, Q. Zhang, X. Chu, Z. Wang, X. Huang, J. Li, C. Yao, N. Zhou and J. Shen, *J. Colloid Interface Sci.*, 2021, **584**, 505–519.
102 C. Gao, X. Qu, L. Fu, J. Chen, Y. Chu and H. Qiu, *Chem. Eng. J.*, 2024, **497**, 154717.
103 D. M. Campoli-Richards, J. P. Monk, A. Price, P. Benfield, P. A. Todd and A. Ward, *Drugs*, 1988, **35**, 373–447.
104 F. Liu, Y. Shen, Y. Hou, J. Wu, Y. Ting, C. Nie and M. Tong, *J. Hazard. Mater.*, 2024, **476**, 134982.
105 N. Kraupner, S. Ebmeyer, J. Bengtsson-Palme, J. Fick, E. Kristiansson, C.-F. Flach and D. G. J. Larsson, *Environ. Int.*, 2018, **116**, 255–268.
106 S. Kaushik, J. Thomas, V. Panwar, P. Murugesan, V. Chopra, N. Salaria, R. Singh, H. S. Roy, R. Kumar, V. Gautam and D. Ghosh, *Nanoscale*, 2022, **14**, 1713–1722.
107 R. Davis and H. M. Bryson, *Drugs*, 1994, **47**, 677–700.
108 V. R. Anderson and C. M. Perry, *Drugs*, 2008, **68**, 535–565.
109 M. Hurst, H. M. Lamb, L. J. Scott and D. P. Figgitt, *Drugs*, 2002, **62**, 2127–2167.
110 Y. Li, W. Liu, Y. Wang, T. Liu and Y. Feng, *Adv. Healthcare Mater.*, 2024, **13**, 2401384.
111 J. N. Fullerton and D. W. Gilroy, *Nat. Rev. Drug Discovery*, 2016, **15**, 551–567.
112 P. J. Barnes, I. Adcock, M. Spedding and P. M. Vanhoutte, *Trends Pharmacol. Sci.*, 1993, **14**, 436–441.
113 P. Dara, O. Talabi and M. Iderapalli, *Br. Med. J.*, 2021, **372**, n679.
114 P. Patrignani and C. Patrono, *J. Am. Coll. Cardiol.*, 2016, **68**, 967–976.
115 B. M. J. P. Group, *Br. Med. J.*, 2024, **385**, q780.
116 J. A. Sbarbaro and R. M. Bennett, *Ann. Intern. Med.*, 2008, **86**, 183–185.
117 N. Schiffmann, Y. Liang, C. E. Nemcovsky, M. Almogy, M. Halperin-Sternfeld, N. C. Gianneschi, L. Adler-Abramovich and E. Rosen, *Adv. Healthcare Mater.*, 2023, **12**, 2301053.
118 F. A. Formica, G. Barreto and M. Zenobi-Wong, *J. Controlled Release*, 2019, **295**, 118–129.
119 Z. Cao, K. Han, H. Lu, S. Illangamudalige, C. A. Shaheed, L. Chen, A. J. McLachlan, A. E. Patanwala, C. G. Maher, C.-W. C. Lin, L. March, M. L. Ferreira and S. Mathieson, *Drugs*, 2024, **84**, 953–967.
120 S.-H. Kim, D. Semenya and D. Castagnolo, *Eur. J. Med. Chem.*, 2021, **216**, 113293.
121 R. G. S. Berlinck, *Nat. Prod. Rep.*, 2002, **19**, 617–649.
122 R. G. S. Berlinck, A. E. Trindade-Silva and M. F. C. Santos, *Nat. Prod. Rep.*, 2012, **29**, 1382–1406.
123 R. G. S. Berlinck and S. Romminger, *Nat. Prod. Rep.*, 2016, **33**, 456–490.
124 F. Saczewski and Ł. Balewski, *Expert Opin. Ther. Pat.*, 2009, **19**, 1417–1448.
125 S. Zhang, R. Zhang, R. Li, Z. Zhang, Y. Li, H. Deng, J. Zhao, T. Gu, M. Long, X. Wang, S. Zhang and Z. Jiang, *J. Membr. Sci.*, 2022, **663**, 121063.
126 L. Heys, C. G. Moore and P. J. Murphy, *Chem. Soc. Rev.*, 2000, **29**, 57–67.
127 D. Kathuria, A. D. Raul, P. Wanjari and P. V. Bharatam, *Eur. J. Med. Chem.*, 2021, **219**, 113378.
128 H. Zhao, K. D. Swanson and B. Zheng, *Trends Cancer*, 2021, **7**, 714–730.
129 O. Grytsai, I. Myrgorodska, S. Rocchi, C. Ronco and R. Benhida, *Eur. J. Med. Chem.*, 2021, **224**, 113726.
130 C. R. Sirtori and C. Pasik, *Pharmacol. Res.*, 1994, **30**, 187–228.
131 L. O'Connor, M. Bailey-Whyte, M. Bhattacharya, G. Butera, K. N. L. Hardell, A. B. Seidenberg, P. E. Castle and H. A. Loomans-Kropp, *J. Natl. Cancer Inst.*, 2024, **116**, 518–529.
132 X. Du, M. Zhang, Y. Ma, Y. Zhang, W. Li, T. Hu, Y. Liu, H. Huang and Z. Kang, *J. Mater. Chem. B*, 2024, **12**, 2346–2353.
133 Z. Feng, J. Wang, X. Chen, J. Liu, Y. Zhu and X. Yang, *Colloids Surf., B*, 2022, **210**, 112236.
134 E. Kirbas Cilingir, E. S. Seven, Y. Zhou, B. M. Walters, K. J. Mintz, R. R. Pandey, A. H. Wikramanayake, C. C. Chusuei, S. Vanni, R. M. Graham and R. M. Leblanc, *J. Colloid Interface Sci.*, 2021, **592**, 485–497.
135 L. Yang, Z. Wang, J. Wang, W. Jiang, X. Jiang, Z. Bai, Y. He, J. Jiang, D. Wang and L. Yang, *Nanoscale*, 2016, **8**, 6801–6809.
136 Y. Yuan, B. Guo, L. Hao, N. Liu, Y. Lin, W. Guo, X. Li and B. Gu, *Colloids Surf., B*, 2017, **159**, 349–359.
137 A. Fibriani, A. A. P. Taharuddin, N. Yamahoki, R. Stephanie, J. Laurelia, D. F. Agustiyanti, P. H. Wisnuwardhani, M. Angelina, Y. Rubiyana, R. A. Ningrum, A. Wardiana, D. Desriani, F. Iskandar, F. A. Permatasari and E. A. Giri-Rachman, *J. Genet. Eng. Biotechnol.*, 2023, **21**, 93.

138 T. Vilaca, R. Eastell and M. Schini, *Lancet Diabetes Endocrinol.*, 2022, **10**, 273–283.
139 Y. Yao, X. Cai, Y. Chen, M. Zhang and C. Zheng, *Med. Res. Rev.*, 2024, 1–15.
140 W. Hu, S. Chen, X. Zou, Y. Chen, J. Luo, P. Zhong and D. Ma, *J. Adv. Res.*, 2024, DOI: **10.1016/j.jare.2024.08.019**.
141 E. Billington, F. Aghajafari, E. Skulsky and G. A. Kline, *Br. Med. J.*, 2024, **386**, e076898.
142 O. D. Fede, V. Fusco, D. Matranga, L. Solazzo, M. Gabriele, G. M. Gaeta, G. Favia, D. Sprini, F. Peluso, G. Colella, P. Vescovi and G. Campisi, *Eur. J. Intern. Med.*, 2013, **24**, 784–790.