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Carbon dots as nano-pioneers: A critical review on advances in fabrication and antibacterial mechanism

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ABSTRACT

The global rise in antibiotic resistance advocates the urgent need for exploring novel antibacterial therapies, including both innovative antibiotics and non-antibiotic therapy. This review outlines a roadmap for advancing nanotechnology-based ultra-small antibacterial agents like carbon dots (CDs) to combat multidrug-resistant pathogens.

CDs, zero-dimensional carbon nanomaterials measuring under 10 nm in size, are gaining attention for their potential applications across various fields, including energy storage, electronics, chemistry, and biomedicine. With properties like tunable photoluminescence (PL), customizable surface functionalities, and efficient photo-electron transport, CDs can achieve potent antibacterial effects through mechanisms such as reactive oxygen species (ROS) generation, membrane disruption, and intracellular interactions. This review presents a critical analysis of the overview of CDs, including the various processes involved in their fabrication, the antibacterial action and mechanism of CDs, factors impacting CDs antibacterial activity, current challenges, research gaps, and potential future directions for the long-term sustainable development and implementation of CDs in antimicrobial innovations. Current challenges, including scalability, biocompatibility, sustainability, and regulatory concerns, are reviewed, along with insights on how addressing these gaps could position CDs as sustainable alternatives to antibiotics in antimicrobial technology.

1. Introduction

The emergence of antimicrobial-resistant diseases is considered a major concern to humanity's health [1]. This challenge is largely driven by the recurring usage and exploitation of antibiotics, both in therapeutic and agricultural settings [2]. At the location of the bacterial spread and infections, bacterium releases substantial quantities of extracellular polymeric substances (EPS), facilitating the formation of biofilms-complex protective structures that can protect the bacterial communities and prevent the entry of antibacterial medications such as antibiotics [3]. Notably, 80 % of human bacterial illnesses are thought to be entangled with biofilms [4]. The process of biofilm formation is highly intricate and tightly controlled, involving the phenomena of quorum sensing (QS). A cell-density-dependent communication mechanism mediated by pheromones and biochemical compounds secreted by each species of bacteria function as autoinducers.

Furthermore, the increased proximity and limited transport of drug molecules inside the EPS matrix promotes biofilm-dependent diseases and, as a result, the formation of multidrug-resistant (MDR) species because biofilms shield microorganisms from therapeutics, antibiotics, and sanitizing agents. Consequently, antibiotics are ineffective in treating biofilm-related illnesses due to the inherent antibiotic resistance

Abbreviations: **MDR**, Multi-drug resistant; **QDs**, Quantum dots; **CDs**, Carbon dots; **PL**, Photoluminescence; **ROS**, Reactive oxygen species; **GQDs**, Graphene quantum dots; **QY**, Quantum yield; ***S. aureus***, *Staphylococcus aureus*; ***S. epidermidis***, *Staphylococcus epidermidis*; ***E. coli***, *Escherichia coli*; ***P. aeruginosa***, *Pseudomonas aeruginosa*; ***B. subtilis***, *Bacillus subtilis*; **MIC**, Minimum inhibitory concentrations; **NIR**, Near infrared; **MRSA**, Methicillin-resistant *S. aureus*.

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of biofilm-embedded bacterial pathogens[5]. It also leads to the development of various challenges in formulating antibacterial medication and mitigating antimicrobial resistance [6]. Biofilm-associated diseases mostly result in extended illnesses, leading to prolonged treatment durations, increased healthcare costs, or even greater fatalities with recurrent bacterial diseases [7]. The ongoing outbreaks of bacterial infections emphasize the urgent need to investigate potential and inventive therapeutic strategies.

According to a World Health Organization (WHO) estimate, drug-resistant diseases could result in the deaths of 10 million people yearly globally by 2050 and affect up to 24 million people into severe impoverishment by 2030 due to antibiotic resistance [8]. These days, the severe acute respiratory syndrome (SARS-CoV-2) caused coronavirus disease 2019 (COVID-19) poses a serious and persistent risk to the health of humans. Among the most fatal epidemics in the recorded history of humanity is the COVID-19 pandemic [9]. Nanoscale materials with distinctive physical and chemical characteristics have been extensively employed to diagnose illnesses caused by viruses with antibacterial functionalities [10].

In nanotechnology, quantum dots (QDs) have become popular as potential innovators, intriguing for transforming the development of nanotherapeutics [11]. The most commonly employed QDs are "Carbon Dots (CDs)," which include various nanoparticles with different chemical and optical characteristics. CDs offer distinctive electronic and photoelectric capabilities acquired from their inherent band gap, exceptional grafting capabilities, inexpensive synthesis expenses, and dispersion characteristics in several solvents [12]. Introducing heteroatoms like S and N into the system modified CD's electric conductivity and optical characteristics.CDs are quasi-spheroidal, carbon-based fluorescent nanomaterials that are typically 10 nm or smaller. They are divided into four types: carbon quantum dots (CQDs), graphene quantum dots (GQDs), polymer dots (PDs), and carbonized polymer dots (CPDs), as illustrated in Fig. 1.

CQDs have crystalline carbon cores with intense PL and can produce ROS under light, which harms bacterial cells [14]. GQDs are tiny graphene fragments that damage bacterial membranes and cause oxidative stress. PDs and CPDs produced from polymer precursors provide flexible surface chemistry for functionalization, which improves bacterial targeting and antibacterial efficacy. CDs have multiple antibacterial activities, involving membrane rupture, ROS formation, interfering with DNA and protein synthesis, and biofilm suppression, all while being low toxicity to human cells [15]. CDs surfaces can be customized with biocompatible polymers to increase safety and medication delivery. Notably, many CDs create ROS when activated by light, making them excellent agents for photodynamic antibacterial therapy. CDs assist in overcoming bacterial resistance and offer promising platforms for administering antimicrobial medications, resulting in better treatment outcomes with fewer side effects [16].

CDs are widely used in biochemical sensors [17], cell-based and biological imaging [18], drug administration [19], energy storage [20], sensing [21] and antimicrobial treatments [22] because of their chemically stable nature good optical characteristics, high quantum yields (QYs), significant water dissolution, exceptional bio-compatibility, antimicrobial capabilities and lower toxicities [23,24]. Furthermore, CDs can disrupt bacterial DNA and enzymatic functions, adding to their broad antibacterial effectiveness.

Furthermore, the surface charge of CDs enables electrostatic interactions with negatively charged bacterial membranes, resulting in membrane breakdown. CDs may be readily tailored utilizing several active groups, comprising amino ($-NH_2$), carboxyl (–COOH), epoxy, and hydroxyl (–OH) groups, independent of their variations in core architectures [25,26]. CDs have effectively deactivated multiple microbial species, with benefits such as minimum invasion, low undesirable effects, ease of bioimaging, and consistent applicability [27]. These characteristics, combined with their simple synthesis from various carbon-rich precursors, place CDs as an adaptable and efficient substitute to traditional antibiotics, especially for focusing on antimicrobial resistance and allowing cutting-edge applications such as antimicrobial coatings, wound dressings, and targeted systems for drug delivery. This review will cover an overview of CDs and the different processes involved in their synthesis of CDs, the antibacterial activity and mechanism of CDs, factors influencing the antibacterial activity of CDs, as well as current challenges, research gaps, and future potential for the long-term sustainable development and application of CDs in antimicrobial technologies.

2. Fabrication of CDs

There are two basic techniques for fabricating CDs: (i) top-down and (ii) bottom-up methodologies. "Top-down" procedures encompass arc discharge, ablation by laser, electrochemical exfoliation, chemical oxidation, and ultrasonic passivation, whereas "bottom-up" approaches

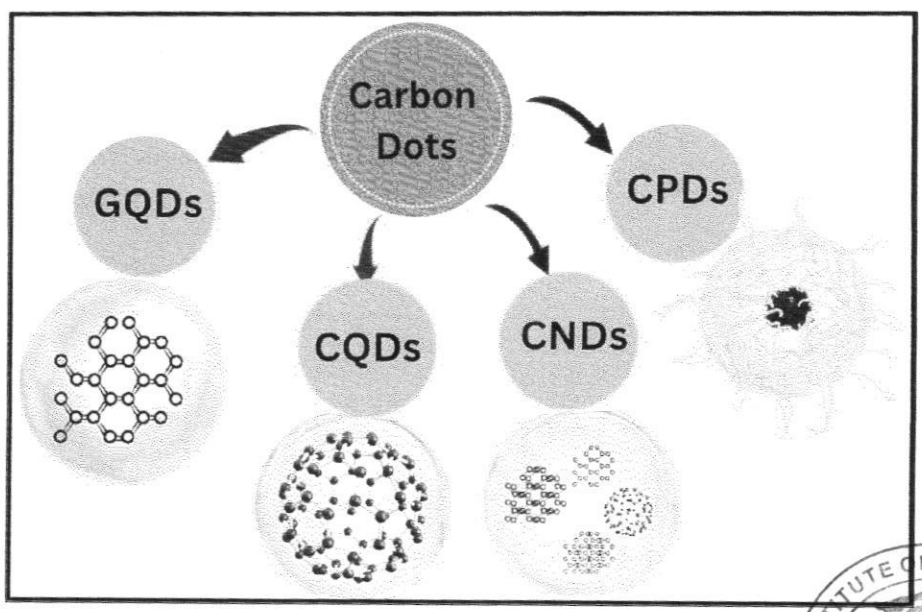

Fig. 1. Classification of CDs and their architectural representation (Copyright © Elsevier 2024. All rights reserved, reprinted with permission) [13].

comprise combustion/thermal processes, microwave pyrolysis, template process and solvothermal/hydrothermal synthesis [28] as shown in Fig. 2. Every technique has benefits and drawbacks.

2.1. Top-down techniques

Top-down synthesis strategies are critical for developing carbon dots (CDs) with specific characteristics for antibacterial applications. Among these, the arc discharge approach stands out for producing high-quality CDs with tunable properties that have shown tremendous potential in treating microbial infections, despite the fact that the process requires a lot of energy and limited yields [30–32].

Laser ablation, which employs a high-energy laser to break down carbon targets in liquid media, allows for the development of CDs with functional surfaces that improve optical and antibacterial properties, making them ideal for application as antimicrobial coatings and wound dressings, in spite of the size and quantum yield challenges [33,34]. Electrochemical exfoliation distinguishes itself by generating CDs richer with oxygen-containing functional groups that promote solubility and biocompatibility, necessary for applications such as wound healing, sterilization, and antibacterial surfaces [35]. Similarly, chemical oxidation produces CDs with hydrophilic surfaces by using powerful oxidizing chemicals, which improves their association with biological systems [36]. This approach is useful for large-scale antibacterial CD manufacture, but it demands meticulous purification to ensure safety [37,38]. Finally, ultrasonic passivation employs high-frequency vibrations to produce stable, functionalized CDs with long-lasting antibacterial activity. This technology enables scalable production and surface modification, allowing for the creation of CDs that are useful in disinfection, the production of antibacterial coatings for healthcare equipment and wound treatment [39,40].

2.2. Bottom-up techniques

Bottom-up techniques for CDs synthesis rely on the construction of carbon nanostructures from molecular precursors, which provide variable surface characteristics and functional groups critical for antibacterial effectiveness. Amongst these, the combustion/thermal process requires the high-temperature deterioration of biological precursors in the presence of oxygen, resulting in CDs with high luminescence and surface moieties that promote microbial contact. Despite the need for high temperatures, this approach produces biologically active CDs that are both cost-effective and scalable for antibacterial use [41,42]. Microwave pyrolysis rapidly heats and carbonizes natural precursors, producing CDs with high QY, well-defined surface functions, and good fluorescence. Its low consumption of energy and compatibility with green solvents make it suitable for biological applications.

The high QY and surface control acquired through microwave synthesis immediately improve the antibacterial properties of the resultant CDs [43,44]. In the template-assisted process, CDs are produced within organized frameworks, which allows for greater control over their size and shape. After carbonization, template removal produces homogenous CDs with optimum surface properties that allow for contact with bacterial membranes and encourage the generation of ROS, which contributes to effective antibacterial action. However, this method's scalability is limited by its level of complexity and cost, as well as its low yield and laborious purification process [45–47].

The solvothermal/hydrothermal approach is especially promising for antibacterial applications because it can retain bioactive functional groups (such as oxygen and N-containing moieties) from plant-based or biomass-derived precursors [48]. These CDs have high biological compatibility, water-soluble nature, and low toxicity, as well as potent antibacterial and antifungal properties resulting from ROS production and membrane rupture [49]. The hydrothermal method, in particular, is environmentally safe, inexpensive, and capable of making highly luminous, monodisperse CDs appropriate for antibacterial therapies, coatings, and drug administration [12,50–52]. Overall, CDs antibacterial activity is closely related to their production method. Techniques like microwave pyrolysis and hydrothermal processing not only provide environmental and economic benefits but also produce CDs with improved surface reactivity, structural homogeneity, and functional versatility, all of which are necessary for effective antibacterial action.

3. Physical-chemical properties of CDs

CDs have a unique set of physicochemical features that not only determine their structural and functional activity but also support their antibacterial potential. CDs are nanomaterials less than 10 nm in size, composed of sp^2/sp^3 hybrid carbon scaffolds and loaded with surface functional groups such as –OH, –COOH, and $–NH_2$ that increase their solubility, reactivity, and contact with microbial membranes as illustrated in Fig. 3 [53,54]. Their architectural classification into graphene-based and amorphous CDs enables customized optical and chemical functions, which are further strengthened by elemental doping (e.g., N,

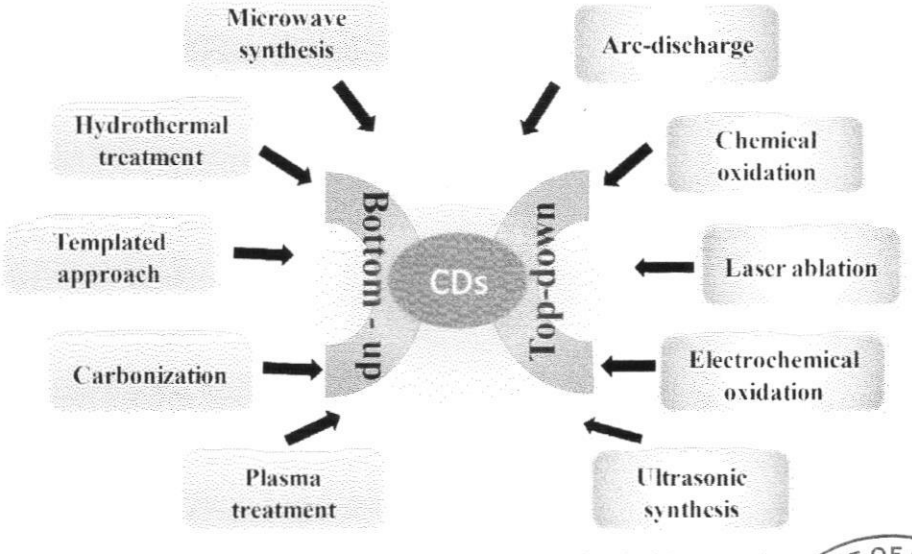

Fig. 2. Diagrammatic representation of various top-down and bottom-up processes employed for the fabrication of CDs (Copyright © Elsevier 2021. All rights reserved, reprinted with permission)[29].

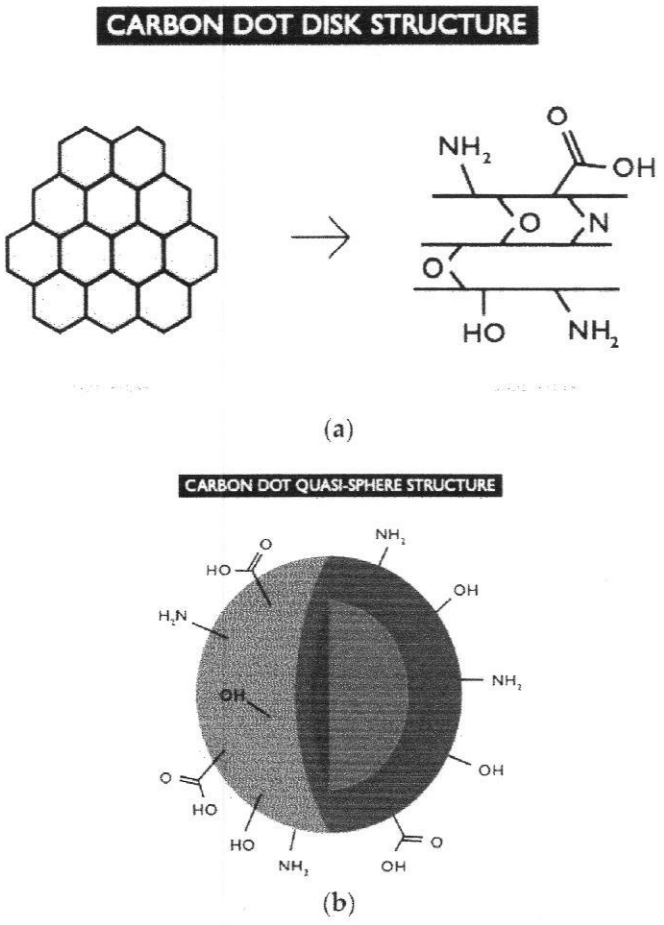

Fig. 3. CDs architecture with various surface-active groups (Copyright © MDPI 2021. All rights reserved, reprinted with permission [57].

S, P) to alter electronic characteristics. CDs absorb UV–Vis owing to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ electronic transitions [55]. This allows for the formation of ROS during light irradiation, which is an important antibacterial mechanism. Their PL properties, which include high QY, adaptable emission, and photostability, aid in the real-time imaging and monitoring of bacterial activities.

High QY and surface passivation increase fluorescence efficacy, facilitating identification and observation in microbiological experiments [56]. Furthermore, CDs work as effective nanocarriers for antibiotics or metal ions, enhancing medication stability, bioavailability, and combinatorial bactericidal action. The utilization of several precursors, including amine-rich compounds, biomass, and antibiotic drugs, allows for the production of CDs with customized antibacterial characteristics, broad-spectrum efficacy, and low cytotoxicity. Their photothermal conversion capacity under near-infrared light enables targeted bacterial elimination [3].

Moreover, the intrinsic biocompatibility of CDs, especially those made from biological waste, ensures low cytotoxicity while allowing for biofilm penetrating and intracellular activities. CDs size-dependent features, such as increased cellular absorption contact with bacterial membranes and along with their chemical and thermal stability, make them ideal for drug administration, photodynamic treatment, and antimicrobial coatings [58]. These associated physical and chemical characteristics are critical to CDs performance as multifaceted nanomaterials in fighting bacterial infections, particularly in photo-assisted or environment-responsive antibacterial techniques.

4. Antibacterial activity and mechanism of CDs

The developing risks associated with antibiotic resistance, caused by bacteria's increased capacity to resist vital drugs, pose a significant global health concern, transforming many diseases uncontrollably [59]. The increase of MDR pathogens, along with the delayed advancement and discovery of innovative medicines, exacerbates the problem. Current forecasts suggest that by 2050, antibiotic resistance might cause a further 300 million fatalities and incur a cost burden of $100 trillion [60]. Thus highlights the pressing requirement for novel solutions to tackle MDR bacteria. The bacterial cell wall, a vital functional as well as structural barrier, is a significant focus for innovative antibacterial strategies, such as advancing the creation of new medicines and delivery methods [61–63]. Sun et al. [64] investigated the biological compatibility and cytotoxic effects of surface-passivated CDs and less reactive chemicals, being the initial study to test the cytotoxicity of PEG1500N-passivated CDs. The outcomes demonstrated relatively low effects on human tumor cell lines (MCF-7, HT-29), equivalent to PEG1500N itself. While CDs have minimal intrinsic toxicity, they can be reduced even more by modifying their surface with bio-compatible polymers such as polyethylene glycol or amino acids.

4.1. Mechanisms of antibacterial action

In spite of being relatively harmless to mammalian cells, CDs exhibit a variety of antimicrobial actions, including membrane rupture, intracellular ROS production, interference with electron transfer, intracellular penetrating that affects DNA and protein synthesis, and suppression of biofilm growth [65]. Furthermore, CDs are efficient drug delivery transport, having the ability to encapsulate drugs and increase the effectiveness of therapy while preserving their chemical properties and biological compatibility, which makes them intriguing options for specialized antibacterial therapeutics [66]. Antimicrobial medications include quinolones, sulfonamides, antibiotics, and chemical pharmaceuticals. These medications are taken for extended periods, which increases bacterial resistance to antibiotics and has a negative impact on health. As a result, there is a critical need to discover alternative, effective antibacterial agents. Thus, with the progress of nanotechnology, CDs are produced [67]. The weak antibacterial action inhibits development and multiplication, allowing the host's innate defenses to cope with infected microorganisms. The major antibacterial function of carbon quantum dots is to destroy bacteria, resulting in their elimination [68–70].

4.2. ROS generation and oxidative stress

Cellular damage impedes cell development and destroys cells. CDs have been shown to be nontoxic in both in vitro and in vivo settings. They exhibit a wide spectrum of UV to near-IR luminescence light, demonstrating a significant photodynamic impact. Photo-excited CDs produce ROS, which kill or inhibit microbes. CDs destroy bacteria due to oxidative damage caused by ROS. In low concentrations, ROS functions as a messenger molecule inside the cell. It has been observed that CDs are connected with ROS production, which inhibits the microbes represented in Fig. 4 [71]. Oxidative stresses occur when the degree of ROS formation surpasses the bacterium's inherent antioxidant defense. It causes oxidative harm to the nucleosides, lipids, and proteins, resulting in cell destruction and bacterial death rates.

Heteroatoms in CDs increase ROS production due to increased free electron inclusion in CDs. The inclusion of N heteroatoms in CDs produces a positively charged group and improves their electrostatic double-layer adhesion to the negatively charged bacterial surface, causing ROS production near the desired pathogen [72]. The method of action encompasses CDs adherence to the bacterial surface, which leads to photo-triggered ROS production, disrupting and penetrating the bacterial cell wall.

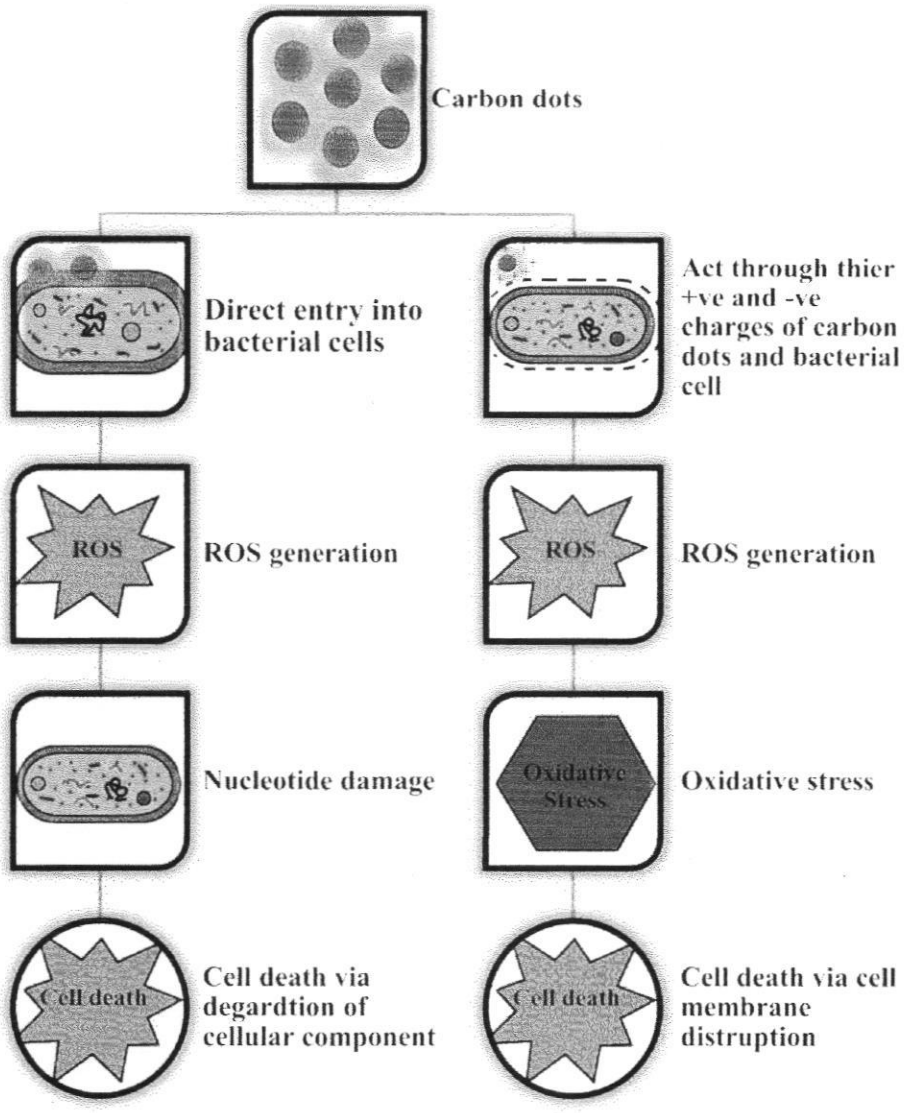

Fig. 4. Antibacterial process of CDs (Copyright © Elsevier 2024. All rights reserved, reprinted with permission) [74].

ROS formation creates oxidative stress with the disrupting DNA/RNA and induces the modification in essential gene expression in addition to oxidative harm toward biomolecules [74]. When CDs come into proximity to a bacterial cell within visible or ambient light, they produce ROS by activation of the O_2 in water or air, resulting in the formation of individual O_2 or OH free radicals, which destroy essential biomolecules and cause cell death [75]. ROS is claimed to induce mitochondrial malfunction, lipid peroxidation, intracellular protein deactivation, and cell membrane breakdown, subsequently causing apoptosis or necrosis, which eventually leads to cellular death [76].

Elham and colleagues successfully synthesized CDs from walnut oil using a hydrothermal process. The produced CDs are 12 nm in dimension and have a high QY of around 54 %. It has pH and photostability with cytotoxicity and apoptosis characteristics of CDs. It displayed exceptional cytotoxic against MCF-7 and PC-3 in comparison to HT-29 human cancer cell lines, which were assessed using the MTT test. Their cell mortality process is controlled by the initiation of caspases 3 and 9, as well as the mitochondrial membrane potential (MMP). Their cellular uptake is assessed using fluorescence microscopy. CDs have a major influence on caspase-3, no effect on caspase-9, and their MMP does not significantly change [72].

4.3. Antibacterial potential of CDs

Shahshahanipour et al. [77] revealed the formation of CDs from the henna plant (*Lawsonia inermis*) employing a hydrothermal technique that required no extra reagents. The CDs, with a quasi-spheroidal framework and dimensions ranging from 3-7 nm, demonstrated great solubility in ethanol and water owing to their active groups, such as OH, COOH, NH_2, and carbonyl group (C=O). They displayed a zeta potential of −39 mV, suggesting superior dispersion and endurance in aqueous fluids. These CDs serve as bio-compatible fluorescent sensors for methotrexate detection while also exhibiting antimicrobial characteristics.

The antibacterial capacity was evaluated towards *Staphylococcus aureus* (Gram-positive) and *Escherichia coli* (Gram-negative), with stronger efficiency towards gram-negative bacteria at greater levels, possibly owing to variations in cell wall architecture and permeability. Arumugam et al. [78] hydrothermally fabricated CDs from turmeric leaves (*Curcuma longa*) and investigated their antibacterial effectiveness towards Gram-negative *E. coli* and *Klebsiella*, as well as Gram-positive *S. aureus* and *Staphylococcus epidermidis*. The CDs, which had a mean size of 2.6 nm and blue fluorescence in aqueous solution, demonstrated high photostability across a variety of ambient settings involving pH, salt, and ultraviolet radiation.

Bactericidal activities were found at a dosage of 0.25 mg/mL for

E. coli and *S. aureus* after 8 h. *Klebsiella pneumoniae* and *S. epidermidis* demanded 1 mg/mL for the entire elimination 24 h later. The postulated process includes the formation of ROS as a result of CDs-free electrons interacting with dissolved O_2. The CDs negative zeta potential (−7 mV) is attributable to the existence of COOH and C=O groups. It performs an important role in electrostatic associations that assist in killing bacteria, dipole–dipole associations, London dispersion forces and Van der Waals forces. The study demonstrated the effectiveness of turmeric-derived CDs as antibacterial agents.

4.4. Influence of positively charged surfaces or electrostatic interaction

Positively charged CDs successfully attack negatively charged bacteria, causing membrane disruption and cytoplasmic leaks, which results in the mortality of bacteria [79]. Investigators employed biogenic polyamines to create extremely positively charged CDs [80]. Bing et al. [81] constructed negative, positive, and neutral CDs. They discovered that positively and negatively charged CDs caused 90 % *E. coli* mortality at 500 μg/ml, whereas neutral CDs had no impact. Positively charged CDs, such as those generated from spermidine and loaded with N and P (N, P-CDs), impair bacterial membranes and mitochondrial activity [82].

Negatively charged CDs inhibit the growth of bacteria by interfering with *E. coli* multiplication and QS in *S. aureus* [83]. Resveratrol-derived CDs also inhibit mitochondrial activity in cancerous cells. While enhancing the positive charge of CDs improves their antibacterial properties, it also diminishes biocompatibility, which poses a difficulty [84].

4.5. Influence of hydrophobic interaction

Yang et al. [85] found that introducing quaternary ammonium compounds with longer alkyl chains to CDs improves their antibacterial properties by enabling them to make contact with positively charged cells of bacteria via electrostatic and hydrophobic mechanisms. It causes damage to the surface and reduces Gram-positive bacterial survival to 20 % at 2.5 μg/mL. Sviridova et al. [84] improved CDs antibacterial capability by adding tetraalkylammonium groups, resulting in significant advantages for *S. aureus* (minimum inhibitory concentrations (MIC) 3.1 μg/ml) and *E. coli* (MIC 7.9 μg/ml). The equilibrium of positive charge and hydrophobic properties is critical; shortened or too-long alkyl chains diminish effectiveness. Because of their positive charge and hydrophobicity, alkyl-triphenylphosphonium (TPP)-amended CDs may permeate cell and mitochondrial membranes, boosting mitochondrial absorption by hundreds of times owing to the negative potential of the mitochondrial membrane. In general, altering CDs with hydrophobic alkyl chains increases membrane permeation, resulting in membrane rupture and increased antibacterial activity.

4.6. Influence of particle shape and size

Hui et al. [86] discovered that the size of CDs affects their antibacterial effectiveness. C60-CDs generated from breaking off the C_{60} cage had substantial antibacterial activity towards *S. aureus*, lowering the possibility of survival to 2.3–4.7 % at 200 μg/ml, comprising antibiotic-resistant strains. This action was ascribed to a curvature matching among C_{60}-CDs and bacterium surfaces, which disrupted the cell membrane. On the contrary, the graphene oxide equivalents had no antimicrobial activity.

C_{60}-CDs had no impact on *Bacillus subtilis*, *E. coli*, or *Pseudomonas aeruginosa*. CDs' tiny size enables them to pass through cell membranes and associate with DNA, which renders them ideal for introducing nucleic acids such as plasmids, longer dsRNA, and siRNA into the cells of animals. Amine-activated CDs attach to the negatively charged polyphosphate backbone of nucleic acids, shielding them from nucleases and increasing cellular absorption, resulting in altered gene expression [87].

C_{60}-CDs and graphene quantum dots (GQDs) are carbonaceous nanomaterials with different structural, optical, and functional features. C_{60}-CDs generated from fullerene (C60) have strong electron affinity, redox activity, and distinctive PL, which makes them appropriate for photocatalysis, bactericidal applications, and energy harvesting [88]. Conversely, GQDs made from graphene or graphene oxide have controllable fluorescence, significant quantum-confined effects, and great biological compatibility, rendering them suitable for bioimaging, drug administration, and optoelectronics applications [89]. While both materials show acceptable biocompatibility following functionalization, pristine fullerenes may exhibit cytotoxic effects, whereas GQDs are generally less toxic. C60-CDs perform in electron-driven applications, but GQDs are more adaptable for medical and optical applications [90].

4.7. Oxidative damage

Antimicrobial photodynamic inactivation (PDI) is an intriguing strategy that employs light to produce ROS and photosensitizers, resulting in oxidative harm to bacteria [91]. Current studies have investigated carbon-based nanomaterials, such as CDs, as replacement photosensitizers [92,93]. When exposed to visible or daylight, photoexcited CDs release ROS, which damage macromolecules and cause cell mortality [55,94–96]. Chong et al. [95] demonstrated that graphene CDs are phototoxic upon blue light, lowering the survival of cells by 20 % when subjected to a 405 nm laser.

Walia et al. [96] created CDs from carbohydrates and nitrogen-rich materials that specifically destroyed *E. coli* by producing oxidative stress, disrupting membranes, and destroying DNA. Meziani et al. [93] discovered that ethylene-dioxybisethylamine-activated CDs *suppressed E. coli* proliferation under visible light, with an 80 % suppression after 3 h of irradiation. Yu et al. [97] demonstrated that folic acid-derived CDs particularly attacked *S. aureus*, producing ROS that damaged bacterial superoxide dismutase, resulting in cellular death. CDs produced from arginine and lysine showed antibacterial activity towards both Gram-positive and Gram-negative bacteria (MIC 31–125 μg/ml), with increased effectiveness in acidic circumstances [98]. Furthermore, Zhang et al. [99] found that red-emitting CDs might cause cell death via mitochondrion-mediated apoptosis routes, indicating possibilities in bactericidal and cancer therapy.

4.8. Photothermal therapy

CDs play an important role in photothermal treatment by producing ROS and inducing the mechanical destruction of bacterial membranes [100]. Sattarahmady et al. [101] revealed that CDs made from ascorbic acid and copper acetate hydrate transform NIR (near-infrared) light into heat, causing the walls of bacteria cells to be damaged. It resulted in a substantial decline in colony-forming units of *S. aureus* and methicillin-resistant *S. aureus* (MRSA), with a three-fold drop when combined with radiation in comparison to CDs by itself. Despite their negative zeta potential, CDs bind to bacteria utilizing van der Waals forces, resulting in cell wall disintegration, enhanced permeation of the membrane, and oxidative damage. Lu et al. [102] created a CDs-doped chitosan/nano-hydroxyapatite scaffolding with potent antibacterial properties towards *S. aureus* and *E. coli*, which were further improved (75 % to 99 % inhibition) by NIR radiation. Despite introducing photocatalysts that can boost bactericidal functionality, CDs are also excellent photosensitizers, boosting localized temperature under NIR light and leading to improved antimicrobial capability [103,104].

4.9. Impacting the architecture and functioning of DNA/RNA carbon

CDs can pass through bacterial walls and membranes, adhere to DNA and RNA via noncovalent associations, and cause structural modifications that inhibit bacterial development. These associations modify DNA's secondary arrangement, separate the double helix and impact

RNA [103]. Li et al. [73] used an electrochemical approach to create low-toxicity, biodegradable CDs from vitamin C, which had good antimicrobial and antifungal properties. CDs at doses of 100 μg/ml and 300 μg/ml effectively suppressed the development of several strains by destroying bacterial walls and permeating cells. To investigate how CDs interact with bacterial DNA and RNA, investigators employed methods such as dynamic light scattering, circular dichroism spectroscopy, and GE. The studies revealed that CDs enhance the hydrodynamic diameter of DNA and change its architecture, eventually disintegrating bacterial and fungal genetic mechanisms, which in turn causes cellular death.

4.10. Inhibition of biofilm development

Antibacterial methods may not often entail direct cytotoxicity, as with bacterial biofilm development, in which microbes attach to surfaces and build defensive extracellular matrices that boost their immunity towards antibiotics and external stresses [106]. CDs, including those produced from *Lactobacillus plantarum* (CDs-LP), have been demonstrated to limit *E. coli* adherence and biofilm development without impacting the progression of bacteria, probably via cellular communication and sulfur metabolism. Other CDs, such as polyethyleneimine and citric acid-based forms, greatly inhibit biofilm development in both Gram-positive (*Bacillus cereus, S. aureus, S. epidermidis, Streptococcus pyogenes*) and Gram-negative bacteria (*E. coli, Proteus mirabilis, P. aeruginosa*), although planktonic growth is untouched [107].

Light-initiated EDA-CDs are efficient towards planktonic cells, but they have little effect on developed biofilms as long as they are coupled with chemicals such as EDTA that specifically target biofilm framework [106]. Copper-doped CDs (Cu-CDs) increase catalytic function and produce ROS, which inhibits the attachment of bacteria and eliminates biofilms [108]. Notwithstanding these encouraging results, problems persist, including unknown specificity for some bacterial strains, uncertainties regarding CDs retention and metabolism in mammals, and inadequate direct comparability to traditional antibiotics [109]. While CDs have enormous possibilities for controlling biofilm-associated illnesses, more study is required to enhance their use and overcome these constraints [110].

4.11. Type and degree of charge on CDs

Bacterial cell membranes engage with CDs based on the charge they carry and form. Bing et al. [82] discovered that bacterial cell wall associations change between the formation of positive, negative, and neutrally charged CDs derived from spermine, candle soot, and glucose. Positively charged CDs are shown to be antibacterial, while negatively charged and neutral CDs exhibit bacteriostatic properties. Nevertheless, they are seldom effective against *E. coli*. In addition, positively charged CDs generate more ROS than negatively charged CDs, but neutral CDs generate relatively little ROS. Nonetheless, no direct association between surface charge and ROS production has been identified.

4.12. Size and shape of CDs

Su et al. [111] demonstrated how the form and source of origin of CDs affect their antibacterial properties. They discovered that GQ-dots had size-dependent antibacterial activity toward *E. coli*.

Because of a small dimension of 15 nm, small-lateral-sized GQ-dots may easily permeate the plasma membrane, generating elevated levels of oxidative stress and ruptures in the membrane compared to large-lateral-sized GQ-dots of 50 nm. ROS generation caused by these GQ-dots has been associated with membrane disintegration and oxidative damage.

4.13. Functionalized groups on CDs

Functionalized CDs have shown great promise in use as antibacterial agents due to their capability to specifically target and distinguish between Gram-positive and Gram-negative bacteria via various surface changes. The functional groups of CDs have a considerable impact on their antibacterial activity [112]. Amine-activated CDs amended with lauryl betaine have multifunctional antibacterial characteristics, specifically labeling and eliminating *S. aureus* while coexistence with Gram-negative bacterium like *E. coli*. Quaternized CDs, with a positive charge and multicolored fluorescence, exhibit increased specificity and antibacterial activity versus Gram-positive bacteria, with a MIC of 8 mg/mL for *S. aureus*. Upon association, these CDs rupture the bacterial membrane, allowing flow out of contents within the cell [113]. Additional research has demonstrated the wide-spectrum antibacterial properties of CDs produced from diverse precursors. For example, Li et al. [73] employed vitamin C as a precursor to creating CDs that were effective towards *S. aureus*, *B. subtilis*, and ampicillin-resistant *E. coli*.

Hou et al. [114] employed ciprofloxacin hydrochloride to make CDs that had higher antibacterial activity towards Gram-negative *E. coli* than Gram-positive *S. aureus*. Likewise, penicillin-based CDs and F-CDs made from levofloxacin hydrochloride were discovered to be efficient towards both Gram-positive and Gram-negative bacteria. Microscopy indicates a crystalline lattice framework in F – CDs. Their tiny size (1.27 nm diameter) boosts their ability to fight bacteria by interacting with bacterial DNA and damaging cell membranes [115].

The study also found that smaller CDs have greater antibacterial capabilities due to improved cellular assimilation and membrane permeation. F – CDs exhibit promising antibacterial action by producing ROS that harms bacterial cells devoid of light exposure, transforming them into viable nano antibiotics [116]. Further investigation has looked at the photodynamic effects of citric-acid-based CDs in the treatment of *S. aureus*-infected lesions in mice, revealing considerable bacterial decrease. Supercationic CDs made from spermidine powder show strong antibacterial activity, especially against *S. aureus* (MRSA). P-doped CDs also showed considerable antibacterial activity, damaging bacterial cell membranes via electrical associations [117].

Ultimately, CDs derived from quaternary ammonium salt and ethylenediamine were discovered to possess wide-ranging antibacterial properties towards both Gram-positive and Gram-negative bacteria, with low cytotoxic and the possibility for biofilm visualization and elimination. These results highlight the intriguing possibility of CDs in generating novel antibacterial medicines, particularly for drug-resistant diseases [119]. Gram-positive and Gram-negative bacteria, in addition to MDR pathogens like MRSA, were all efficiently destroyed by the CDs, as shown in Fig. 5. The formation of CDs utilized a range of chemical precursors and methodologies, with an emphasis on their antibacterial effectiveness towards various microbial species. CDs are produced using a variety of procedures, including electrothermal, hydrothermal (200 °C and 250 °C), microwave, pyrolysis, and solvothermal approaches, each producing CDs with distinct bactericidal characteristics [120,121]. Ciprofloxacin and levofloxacin-based CDs had increased efficacy towards *E. coli*, with levofloxacin being efficacious towards *P. aeruginosa* and *B. subtilis*, demonstrating wide-ranging antibacterial properties. Vitamin C-derived CDs are effective towards *S. aureus*, *B. subtilis*, and *E. coli*, indicating their promise as a substitute for conventional antibiotics [122].

Citric acid, curcumin, and the quaternary ammonium salt of chitosan (used in combination with ethylenediamine) and spermidine were all employed to create CDs with action toward biofilms and antibiotic-resistant bacteria such as MRSA, which is especially useful in treating chronic infections [123]. The addition of functional precursors such as curcumin and 2,3-epoxypropyltrimethylammonium chloride improves the antibacterial properties range of CDs, notably towards *S. aureus* and *E. coli* [124]. In summary, the diagram underscores the adaptability of CDs derived from diverse chemical and pharmacological components,

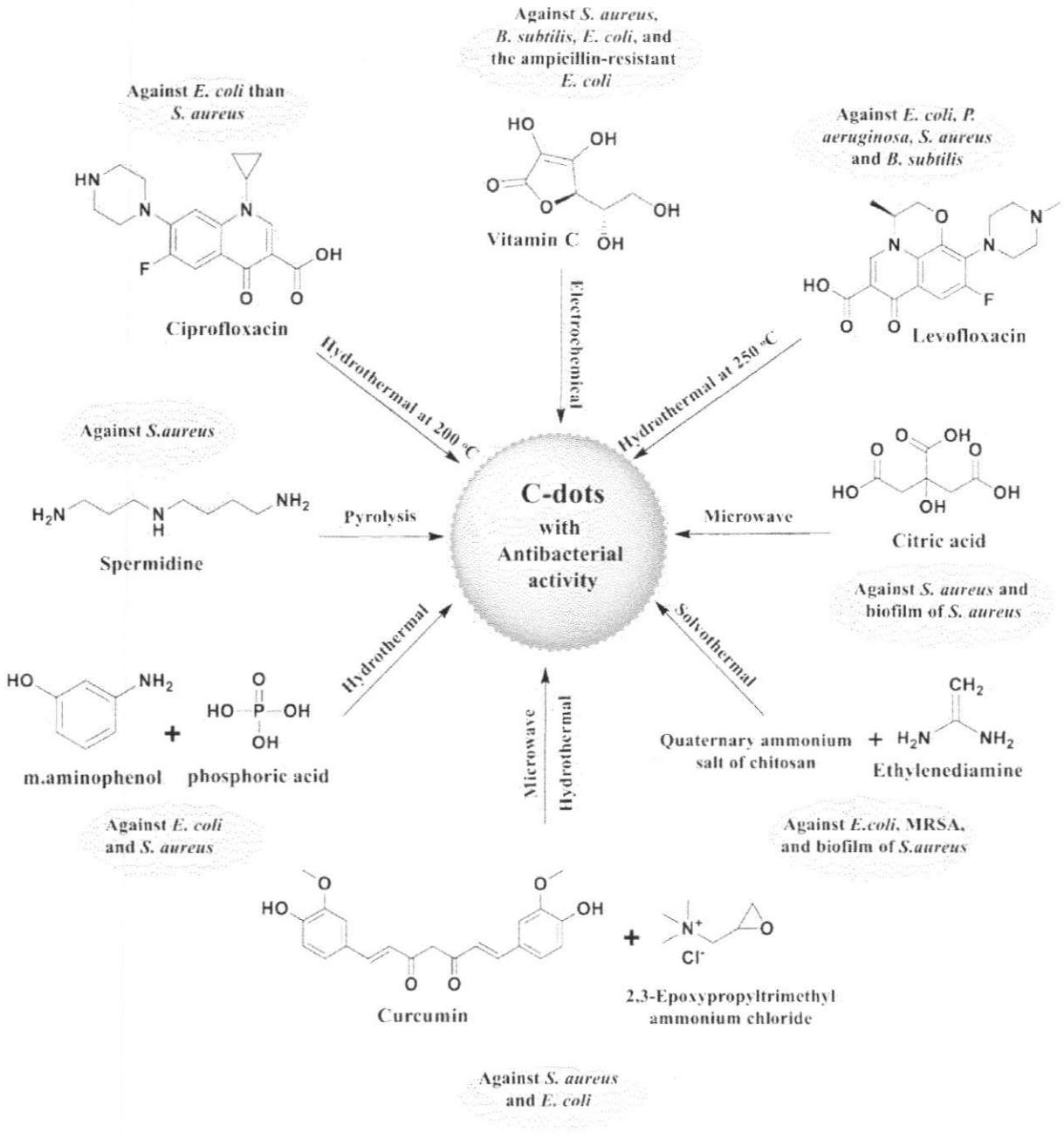

Fig. 5. Origin of CDs and wide-spectrum antibacterial action towards Gram-positive and Gram-negative bacterial species (Copyright © American Chemical Society (ACS) 2024. All rights reserved, reprinted with permission) [118].

making them interesting options for fighting bacterial illnesses, particularly those caused by resistant and biofilm-forming strains. Table 1 summarizes the various precursors utilized to synthesize antimicrobial CDs, their MIC values, and their associated applicability.

5. Biocompatibility and toxicological studies of CDs

CDs are being recognized as highly intriguing nanomaterials for antibacterial applications due to their high biological compatibility, adaptable surface characteristics, and low toxicity. Their carbon-based core composition and ability to passivate surfaces with biocompatible compounds (e.g., polyethylene glycol, amino acids) enable safe interactions with biological systems [23]. Several studies have indicated that CDs display low cytotoxicity in vitro, even at dosages effective towards bacteria, and good biocompatibility in in-vivo species, which include zebrafish embryos and mice [138]. Moreover, CDs PL nature enables tracking and controlled activation for photodynamic antibacterial therapy, where ROS can be generated in a targeted manner to kill bacteria while minimizing collateral damage to host tissues [139].

Furthermore, CDs PL nature enables monitoring and monitored activation for photodynamic antibacterial therapy, in which ROS can be produced in a targeted manner to eliminate bacteria while limiting collateral harm to host tissues [140]. Carbon dots offer a safer substitute with far fewer risks of systemic toxicity and long accumulation than other nanomaterials, such as silver nanoparticles (AgNPs), zinc oxide (ZnO) nanoparticles, and copper oxide (CuO) nanoparticles [141]. AgNPs and metal oxides are excellent antibacterial agents; however, they frequently exhibit dose-dependent cytotoxicity and possible genotoxic effects due to the unregulated release of metal ions and long-term oxidative stress.CDs break down more easily in biological contexts and

Table 1
Overview of the production, bactericidal characteristics, and applicability of antibacterial CDs.

Precursors	Synthesis approach	Bactericidal characteristics	Activity	Application	References
Glycerol (dimethyloctadecyl[3-(trimethoxysilyl) propy] ammoniumchloride	Hydrothermal	*S. aureus*: MIC – 4 μg/mL *B. subtilis*: MIC – 6 μg /mL	Electrostatic and hydrophobic associations.Photodynamic activity	Identify and selectively inactivate Gram-positive bacteria. Treating bacterial infections	[125]
Vitamin C	Electrochemical	Optimal antimicrobial concentration is 100 μg/mL toward *S. aureus* and *E. coli*	Modify DNA/RNA secondary frameworks and suppress key gene expressions.	Wide spectrum antibacterial	[126]
Carbon nanoparticles/ Polyethyleneimine (PEI)	Heating and stirring	At CDs of 1.9 mM, reduced levels of 6.0 logs for *Enterococcus faecalis* and 6.3 logs for *Enterococcus faecium* have been identified.	Photodynamic activity	Inactivating MDR bacteria	[127]
Cellulose nanocrystals/ Boric acid	Oil bath		Sequestrating iron ion	Bactericidal hydrogel	[128]
Citric acid 1,5-diaminonaphthalene	Hydrothermal	Deactivated *E. coli* and *P. aeruginosa* to the 6 log units	Photodynamic deactivation	Antibacterial nanofibers	[129]
Citric acid/ ethylenediamine $FeSO_4{\cdot}7H_2O$/Chitosan	Hydrothermal		Peroxidase-based catalytic function and electrostatic association	Bacterial biofilm eradication	[129]
Spermidine	Hydrothermal	*S. aureus*, *E. coli*, *P. aeruginosa*, (MIC 2–4 μg/ mL)	High positive charge; Disrupting bacterial membrane	Topical therapy for bacterial Keratitis.	[130]
p-Phenylenediamine	Hydrothermal	*S. aureus* (MIC – 2 μg/ mL) E. coli (MIC – 2 μg/ mL)	Disrupting bacterial membrane	Antimicrobial gauze	[131]
Polyamine Dopamine	Pyrolysis	*E. coli*, *P. aeruginosa*, *S. aureus*; (MIC 2–8 μg/mL)	Electrostatic associations lead to membrane lipid partitioning	Bactericidal coating inhibits biofilm growth.	[132]
Cigarette smoke	Combustion	Entirely suppress *E. coli* multiplication	The double helix framework of DNA is destroyed	Towards drug resistive bacteria	[133]
Perilla	Hydrothermal	*S. aureus*: 99.9 % inhibition rate CDs – 200 μg/mL	Photodynamic deactivation	Targeted deactivation of Gam-positive bacteria and healing of wounds	[134]
Artemisia argyi	Combustion	*P. aeruginosa*, *Proteus vulgaris*: 100 % inhibition rate CDs – 150 μg/mL	Inhibition of enzymatic action	Targeted deactivation of Gram-negative bacterium	[135]
Tea	Hydrothermal	*S. aureus*, MRSA and *S. epidermidis* (MIC – 64 μg/ mL)	Transmembrane associations and amino acid targets specifically	Eliminate catastrophic viral-bacterial pneumonia	[136]
Metronidazole	Hydrothermal	*Porphyromonas gingivalis*: 71 % inhibition rate CDs – 1.25 μg/mL	Nitro group	Targeted deactivation of *P. gingvivalis*	[137]

can be tailored to minimize ROS formation in non-target tissues. Experimental studies have shown that these CDs have effective bactericidal effects on both *S. aureus* and tetracycline-resistant *E. coli*, with significant decreases in colony-forming units following visible light exposure [142]. Mechanistic validation with scavengers such as potassium iodide confirmed the critical involvement of photogenerated holes and •OH radicals in the inactivation of microbial cells. The photocatalytic process of metal-free CDs under visible light radiation emphasizes their potential in antibacterial and tumor treatment applications, as illustrated in Fig. 6.

When exposed to visible light, surface functional groups on CDs, such as carbonyl and amide moieties, underwent a chemical change, leading to the production of ROS, specifically hydroxyl radicals (•OH). This process is triggered by the excited movement of electrons from the valence band (VB) to the conduction band (CB), resulting in electron-hole pairs. Photoexcited electrons and holes undergo redox reactions with molecular oxygen and water, resulting in different ROS. These ROS cause significant oxidative stress, which disrupts bacterial membranes, proteins, and nucleic acids, resulting in effective antibiotic activity. In tumor therapy, ROS cause oxidative damage to cancer cells, which promotes apoptosis and inhibits tumor development.

Furthermore, the CDs display good biocompatibility, showing low cytotoxicity against mammalian cells in the absence of light, emphasizing their potential for therapeutic usage [142].CDs reduced inherent toxicity and increased biodegradability make them ideal for biomedical applications such as wound dressings, administration of drugs, and antibacterial coatings, all of which require long-term biocompatibility.

6. Conclusion

CDs constitute a potential family of nanomaterials with strong antibacterial properties, providing a variety of strategies for combating microbial threats while being generally nontoxic to mammalian cells. Their multifunctional features include mechanical rupture of bacterial membranes, intracellular creation of ROS, interference with electron transport, suppression of protein and DNA synthesis, and biofilm formation prevention. These mechanisms combine to create CDs strong and adaptable antibacterial agents with great potential in biomedical applications like biosensing, biological imaging, drug delivery, and photocatalysis[143].

CDs have several advantages, including inexpensive production costs, ease of synthesis, scaling, minimal cytotoxicity, and surface customization. Their chemical stability and biological compliance make them ideal as nanocarriers for targeted drug administration, where they

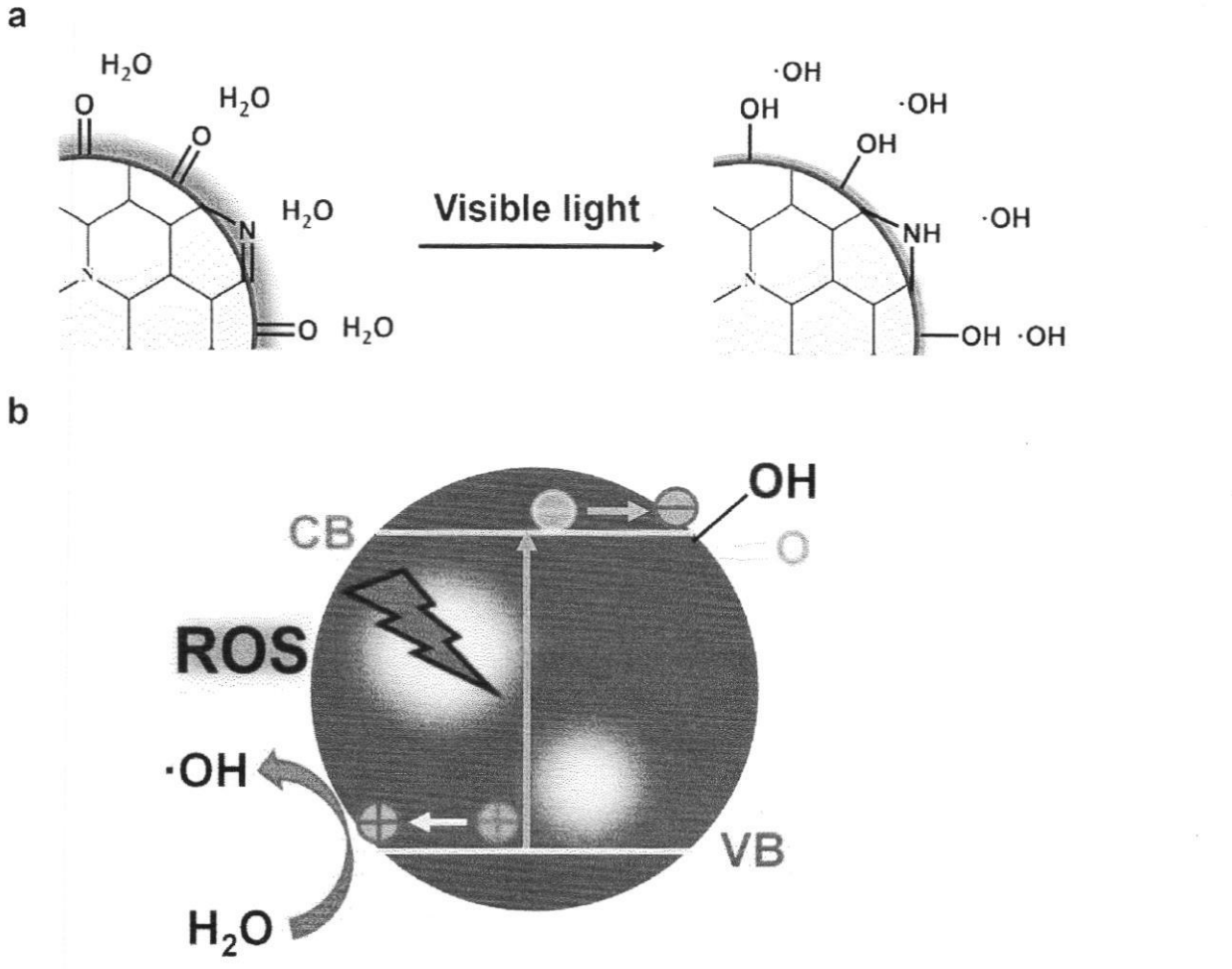

Fig. 6. Schematic representation of structural alterations of CDs upon visible light radiation and photocatalytic mechanism of CDs in aqueous solutions (Copyright © Elsevier 2023. All rights reserved, reprinted with permission) [142].

improve drug loading and distribution while maintaining therapeutic efficacy. Positive surface charges and hydrophobic changes, such as alkyl chains, improve their antibacterial activity by allowing electrostatic interactions with negatively charged bacterial membranes and promoting membrane penetration [144]. Despite these promising characteristics, various hurdles and research gaps must be solved prior to CDs reaching their full therapeutic and economic potential. A key shortcoming is an insufficient understanding of their antibacterial processes, notably strain-specific selection among bacteria with identical Gram classifications.

There is also an inadequate understanding of CD retention, metabolism, and excretion in mammalian systems, raising concerns about their long-term biocompatibility and systemic toxicity. In addition, while some studies have reported enzymatic destruction of CDs in vivo, the particular biochemical processes responsible for carbon core disintegration are inadequately unexplored [145]. Another significant challenge is the lack of defined synthesis and characterization techniques, which results in diversity in CD size, shape, surface chemistry, and optical properties. These variations make it difficult to reproduce and compare results across investigations. Furthermore, few studies have carefully compared CDs antibacterial potency to conventional antibiotics under standardized conditions, limiting a reliable assessment of their relative performance [146].

Technical hurdles remain in controlling particle shape and obtaining uniform heteroatom doping, such as nitrogen inclusion, which is critical for enhancing CD functional characteristics. Furthermore, transforming environmentally friendly synthesis processes from laboratory to industrial scale remains challenging, necessitating rigorous reaction condition optimization and stringent quality control measures. Environmental considerations, such as waste creation and byproduct management, emphasize the importance of long-term solutions for valorizing or safely disposing of synthesis residues [147]. Future research should focus on developing economically viable and scalable production methods, improving control over physicochemical qualities, and comprehensively examining CDs safety, biocompatibility, and pharmacokinetics in vivo. Addressing these shortcomings will be critical to harnessing the full potential of CDs as next-generation antibacterial agents and nanocarriers in antibacterial applications [148].

CRediT authorship contribution statement

Kayeen Vadakkan: Writing – original draft, Investigation, Conceptualization. **Gajanan Sampatrao Ghodake:** Writing – review & editing, Validation, Supervision. **Suriyakala Gunasekaran:** Writing – review & editing, Conceptualization. **Chin Wei Lai:** Writing – review & editing, Validation, Supervision. **Nelson Pynadathu Rumjit:** Writing – review & editing, Supervision, Investigation.

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

Data will be made available on request.

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