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Advances in the delivery systems for oral antibiotics

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ABSTRACT

Oral antibiotics have served as a primary strategy for bacterial infection. However, the increasingly prominent issues including antibiotics resistance and intestinal dysbiosis sounded the alarm to this traditional administration strategy. Herein, we summarize the state-of-the-art advances in the delivery of oral antibiotics. In this review, the emergency of bacterial infection and the effect of excessive antibiotics are discussed at first. Then, current attempts to prevent microflorae from resistance and dysbiosis are briefly enumerated, including oral co-administration systems (like protectors, adsorbents, activity enhancers, etc.) and nanoparticle-based delivery systems. Moreover, we also briefly introduce the development of mimetic antibiotics based on metal particles and highlight a novel micelle nanoparticle system, which possesses a positive charge and glucosylated surface to achieve targeted treatment. We strongly believe such an ingenious design could be applied in more scenarios for oral antibiotics delivery. Ultimately, we also put forward a concise summary and perspective of this field.

1. Introduction

Bacterial infection is a pathological change caused by invading bacteria, which can lead to fever, local abscess, inflammation, and other symptoms [1–4]. If left untreated, bacterial infection can cause sepsis, septic shock, and even death. Thus, bacterial infection is still an urgent issue in the biomedical and clinical field [5–7]. To treat bacterial infection, several antibacterial drugs have been proposed, such as phage, engineered strains, antimicrobial peptides, and antibodies [8–10]. Among them, antibiotics, which are especially worked by oral administration, have always been considered as a primary stratagem for anti-bacterial treatment [11–15]. However, more and more disadvantages are exposed with the deepening of research. It has been demonstrated that oral antibiotics may influence the type and number of intestinal microflorae [16–18]. Thus, they can severely disrupt the homeostasis of the gastrointestinal tract and increase the risk of gastrointestinal diseases [19–22]. Meanwhile, the overuse of antibiotics promotes the emergence of resistant strains [23–25], which has brought great challenges to modern medicine. Hence, it is still highly anticipated to optimize the delivery systems of orally administrated antibiotics to avoid injury to intestinal microflorae and the formation of drug-resistant bacteria. Herein, the delivery systems of oral antibiotics, which have come to the forefront as promising stratagems in biomedical fields, are briefly reviewed. Finally, challenges and prospects of these novel systems are proposed based on existing research.

2. Oral co-administration systems

To avoid the above-mentioned problems, current delivery attempts tend to promote the adsorption of exaggerated antibiotics or build more accurate and targeted drug delivery strategies [26,27]. As early as the last century, scientists applied beta-lactamase to protect the intestinal microflorae against the negative effect of repeated antibiotic stimulation [28]. In this preliminary research, it was demonstrated that by feeding mice a combination of four beta-lactamase-producing anaerobic strains, ceftriaxone could be prevented from affecting gut microbial environment and colonization resistance. Except for ceftriaxone, additional works have shown that the resistance of ampicillin and piperacillin can be avoided by oral administration of beta-lactamase [29,30]. Thus, this co-administration delivery mixed with protectors has been considered useful to reduce the side effects of some antibiotics. However, this "stop-loss" approach cannot fundamentally deal with the loopholes caused by excess antibiotics exposure [31,32].

Apart from that, non-specific adsorbents such as carbon-based materials have been applied to absorb excess antibiotics, as shown in Fig. 1a [16,33,35–40]. This work not only explored the adsorption of activated *prosopis juliflora* carbon on multiple antibiotics like sulfadiazine and tetracycline in multi-composition systems, but also analyzed the

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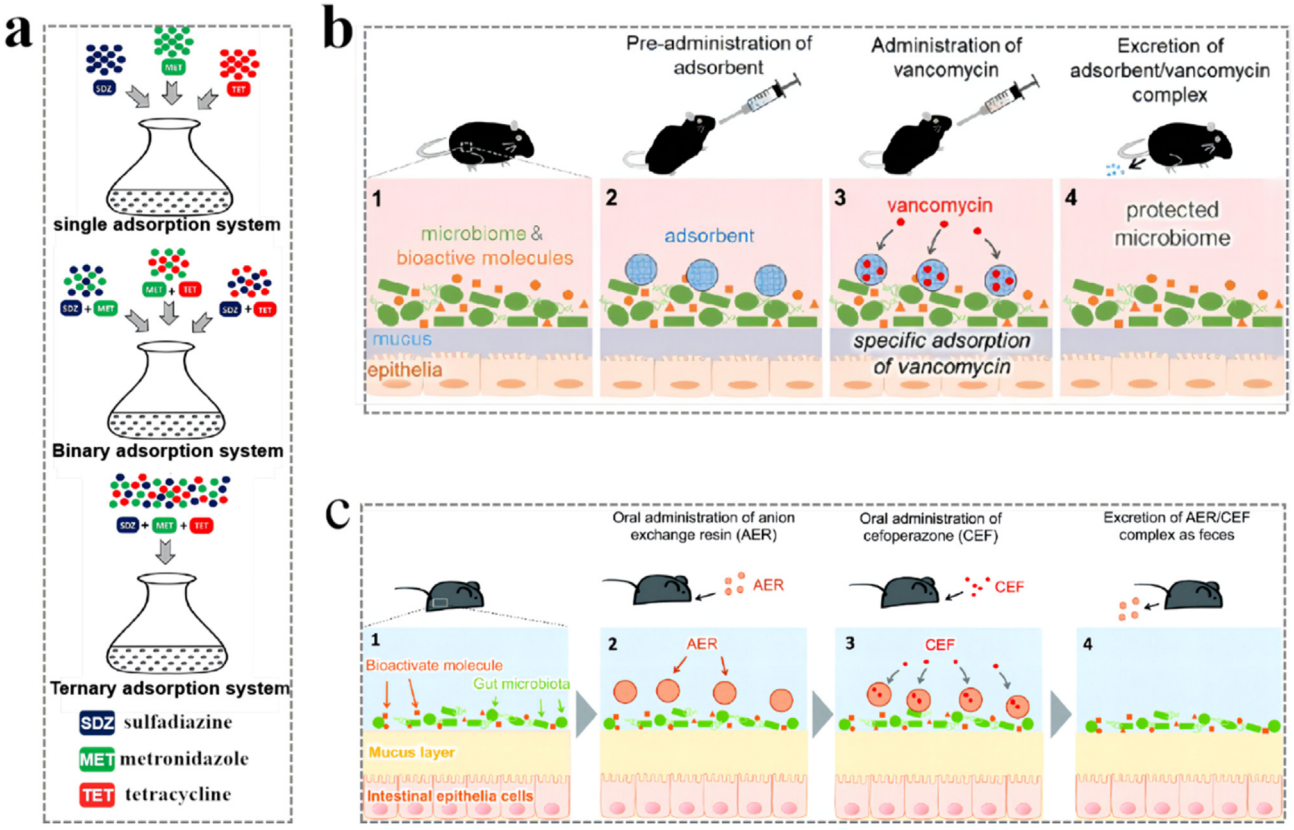

Fig. 1. (a) Scheme of antibiotic adsorption by activated carbon in the aquatic solution of multiple components [33]. (b) Scheme of ion exchanges resin specific-adsorbs vancomycin in the intestine [16]. (c) Scheme of antibiotics adsorption by anion exchange resin in the gut [34].

synergistic and antagonistic adsorption discipline in this removal progress [33]. Meanwhile, Andremont and his group effectively reduced the effects of antibiotic exposure on gut microbiota by utilizing an oral charcoal-based adsorbent [35]. However, while causing nonspecific adsorption of excess antibiotics, these materials may also adsorb biological compounds in the intestine, such as bile acid and nutrients. Thus, these process causes unknown risks. Despite the above obstacles, these nonspecific adsorbents have given new thoughts on how to directly avoid exposure to unwanted antibiotics, which also inspired the development of specific adsorbents like anion exchange resin (Fig. 1b and c) [16,34]. Unlike non-specific carbon-based absorbents, these resins achieve specific adsorption of antibiotics through tailored ligands or electrostatic effects. Such resins increased the adsorption rate of antibiotics while having minimal effect on other biological components.

Finally, the combination of antibiotics with other activity enhancers provides an alternative method to solve the increasing emergence of antibiotic-tolerant strains [41–45], and these combinations can be categorized as shown in Fig. 2a. Such combination therapy is thought to be effective in suppressing the development of resistance, improving antibacterial efficacy, and decreasing toxicity to the microflorae. To develop this strategy, numerous works have been proposed to discover the relationship between antibiotic uptakes, resistance, and gut coordination [46–48]. Among them, antibiotic-antibiotic combinations are the most common strategy. For example, colistin combined with rifampicin can be more effective than single one in treating the infection caused by pseudomonas aeruginosa, thus avoiding excessive antibiotics [49]. Besides, the candidate drugs and ratio must be optimized to get the best therapeutic effect based on the absorption and metabolism features of each component. Hence, although such strategy has been widely accepted, there are still many barriers needed to be overcome in clinical precision treatment [50,51].

3. Nanoparticle-based delivery systems

Initially, delivery of antibiotics with nanoparticles was believed to be a promising strategy, which raised much interest in keeping the balance of microflorae and conquering strain resistance [52]. The common nanoparticle vehicles for antibiotic delivery are mainly divided into several types: lipid or liposome, mesoporous silica nanoparticles, metal-based nanoparticles, carbon nano-material, and polymer networks, respectively [53–62]. In contrast to the direct delivery mode, these vehicles can greatly contribute to the targeted delivery of antibiotics, the enhanced penetration of cellular barriers, and improved stability. It is of great interest that some antibiotic delivery systems show great advantages. For example, Li et al. developed an intelligently responsive delivery system based on vancomycin-linked micelle microcarriers, which remarkably reduced antibiotic toxicity and resistance (Fig. 2b) [52]. Interestingly, such system extends the antibacterial spectrum of vancomycin to a broader range. Vancomycin only eliminates Gram-positive bacteria, but with the carrier, it also eliminates Gram-negative bacteria. However, although delivery of antibiotics with nanoparticles has shown supremacy function over direct delivery, the selection of vehicle materials and the design of targeted functions are still the bottleneck restricting the rapid development of this stratagem.

Mesoporous silica nanoparticles (MSNs) and metal-organic-frameworks (MOF) materials possess great potential in drug encapsulation and release, due to their porous structure and large specific surface area [63–68]. Different from the formation mechanism of micelles, metal ions and organic antibiotics can build tight connections with each other through coordination bonds [69–74]. However, such connections are not irreversible. Most MOF materials will degrade due to their pH-sensitivity, to achieve effective drug delivery. Zhang et al. have proposed a novel stratagem for blocking antibiotics in MSNs via MOF materials (Fig. 3a)

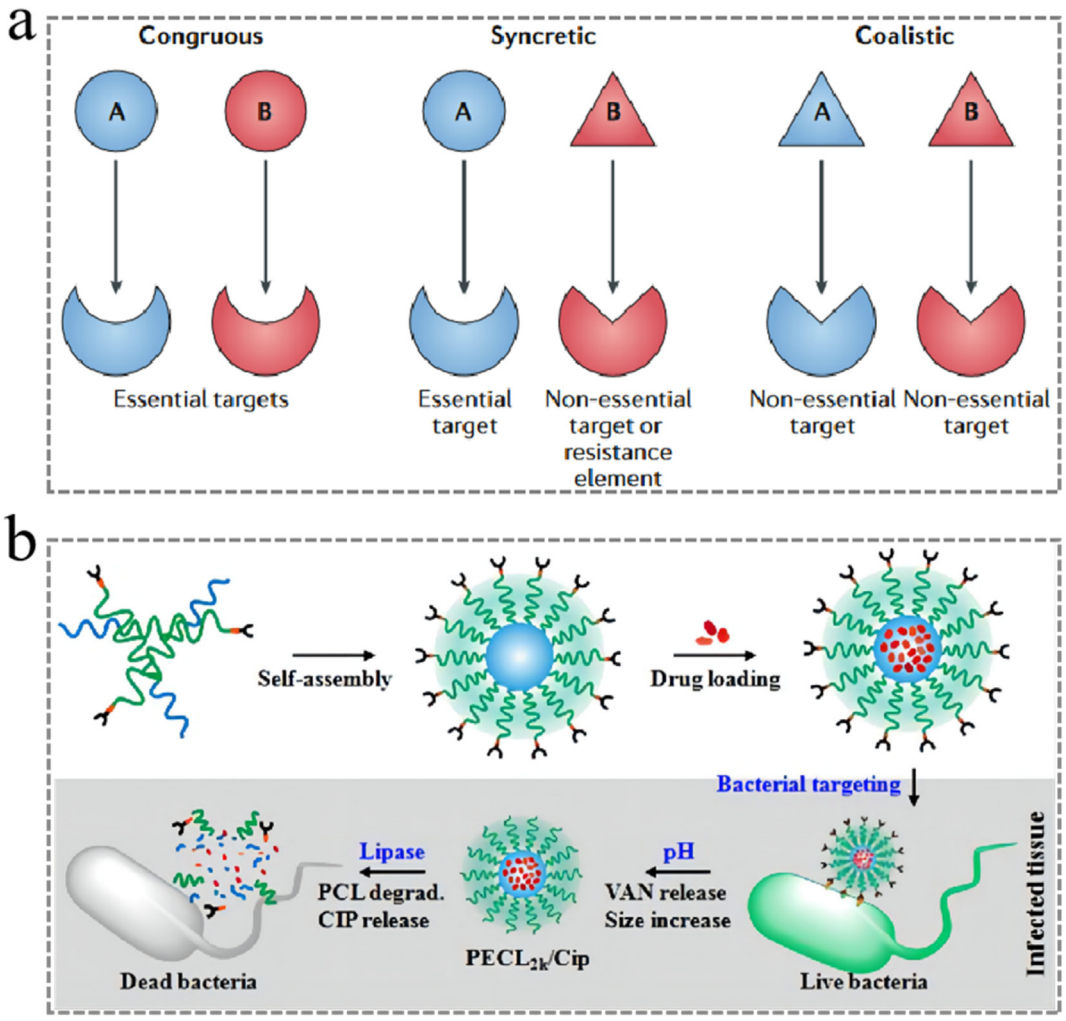

Fig. 2. (a) Categorization of combination therapy with antibiotics [42]. (b) Scheme of the formation of micelles nanoparticles-based antibiotics and their process of targeting and drug release [52].

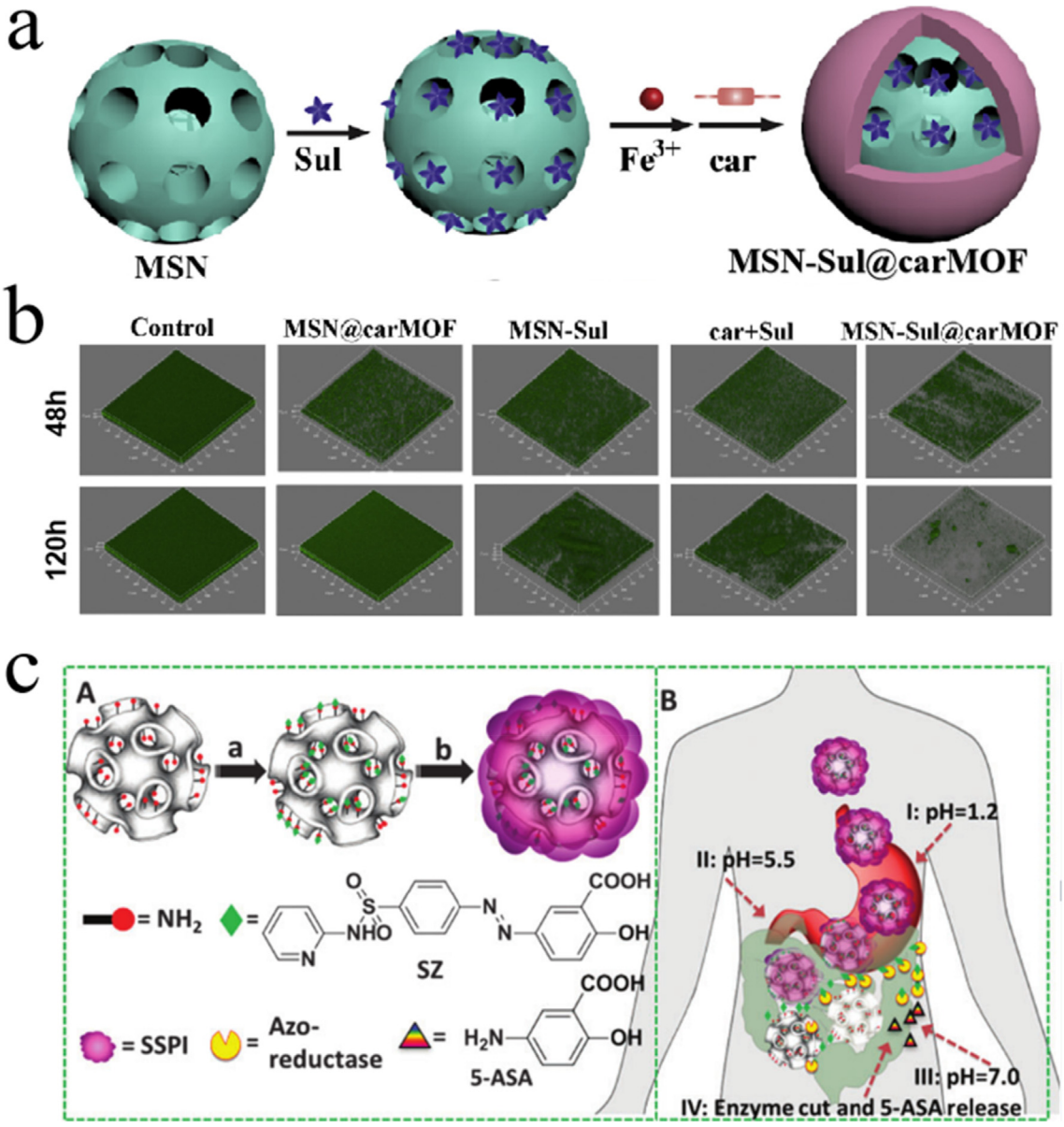

Fig. 3. (a) Scheme of the Fe^{3+}-based antibiotic delivery system. (b) Confocal laser scanning microscopy (CLSM) images of biofilms in different groups [55]. (c) Scheme of oral administration system based on responsive MSNs [62].

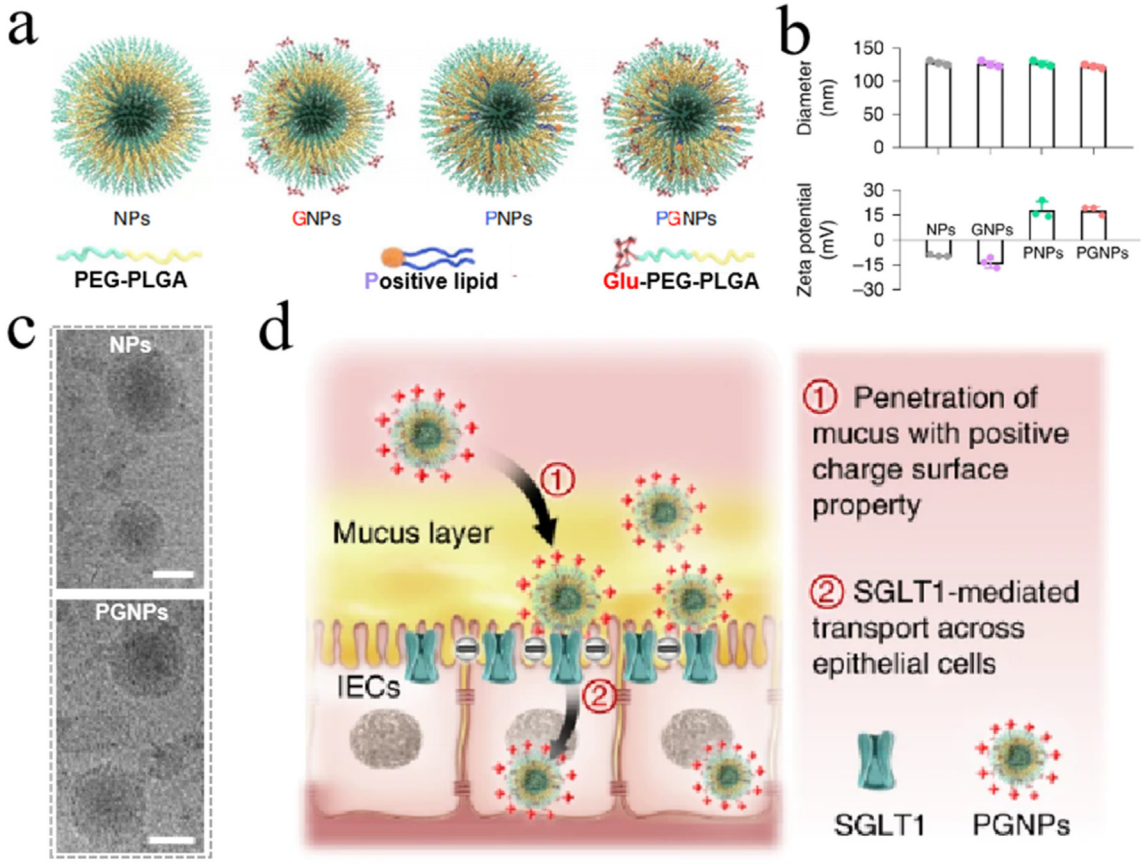

Fig. 4. (a) Formation mechanism of positive glucosylated nanoparticles for antibiotics delivery. (b) Dynamic light scattering analysis of formed micelle nanoparticles. The upper diagram represents the diameter of particles and the following diagram represents the zeta potential of different particles. (c) Transmission electron microscopy (TEM) images of positive glucosylated particles. Scale bars are 100 nm. (d) Scheme of up-taking of antibiotics-loaded nanoparticles and the effect on the intestinal microflorae *in vivo* [82].

[55]. Of note, such nanoantibiotics could maintain their morphology under neutral conditions. Then, when exposed to an acid environment, the coordination bonds are progressively broken and the antibiotics are released from these nanoparticles. Meanwhile, the Confocal laser scanning microscopy (CLSM) images show that there has been an apparent antibacterial property in the group treated with fabricated nanoantibiotics, which demonstrated such nanoparticles as an effective antibiotic delivery system (Fig. 3b). Besides iron ions, other metal elements are often used to construct MOF structures such as copper and zinc [75–81]. In addition to packing with MOF materials, Yu et al. proposed a modified MSNs drug delivery system, which was with multiple biomarkers responsiveness (Fig. 3c) [62]. Because of the difference in biocomponents of the digestive tract environment, such programmable particles achieve the precise release of encapsulated drugs.

In recent, Zhu and his colleagues suggested an outstanding oral antibiotics delivery system based on positive glucosylated nanoparticles [82], as shown in Fig. 4a. Specifically, micelle nanoparticles loaded with antibiotics were constructed by the introduction of amphiphilic polymer chains and positive lipids. These fabricated nanoparticles were monodispersed and their size was concentrated at 100 nm (Fig. 4b and c). Because of a higher expression of sodium-dependent glucose transporter 1 (SGLT1) and glucose transporter type 2 (GLUT2) in the small intestine than that in other sites (Fig. 4d), such nanoparticles could be anchored in the proximal small intestine through glucosylated surface and glucose transporters binding. In addition, the positive lipid in nanoparticles helps such delivery systems penetrate the mucus layer covering the inner surface of the small intestine.

According to these features, it ensured the absorption of antibiotics in the proximal small intestine and avoid frequent stimulation to microflora from free drugs, as shown in Fig. 5a and b. Meanwhile, the *in vivo* imaging system (IVIS) imaging system and CLSM were utilized to determine the residual and uptake of fluorescent dye-loaded nanoparticles (Fig. 5c and d). The corresponding data analysis demonstrated that the glucosylated nanoparticles not only improve intestinal absorption, but also minimize the antibiotic residues at other sites (Fig. 5e and f). Hence, this strategy was significantly reducing the disease risk caused by antibiotics-related gut dysbiosis, such as intestinal opportunistic pathogens infection and metabolic disease obesity. To sum up, this work creatively pointed out an innovative nanoparticle system with a positive charge and glucosylated surface. We can foresee their great potential in other corresponding oral drug deliveries, which are not restricted to antibiotics.

4. Mimetic antibiotics

Recently, many strategies have been developed to alter the function of antibiotics [83–85]. Among them, metal-based nanomaterials have played a vital role in fighting bacterial infections because of their outstanding *trans*-membrane property and modifiability, especially gold nanoparticles (Au NPs) and silver nanoparticles (Ag NPs) [86–89]. Fig. 6 has shown several gold-based NPs or nanorods and their corresponding antibacterial properties. As shown in Fig. 6a and b, it has been demonstrated that pure Au NPs were unable to kill *E. coli*, and TEM images show that the morphology of the bacteria strain treated with Au NPs remained unchanged. Then, through scientific surface modification and doping with other elements such as Ag, Ru, and Pt, Au NPs were able to obtain a certain degree of antibacterial ability. Meanwhile, the ratio of two mentals elements (like Au and Pt) also affects the bacterial performances. Jiang and his colleague explored the ratio of Au and Pt elements to

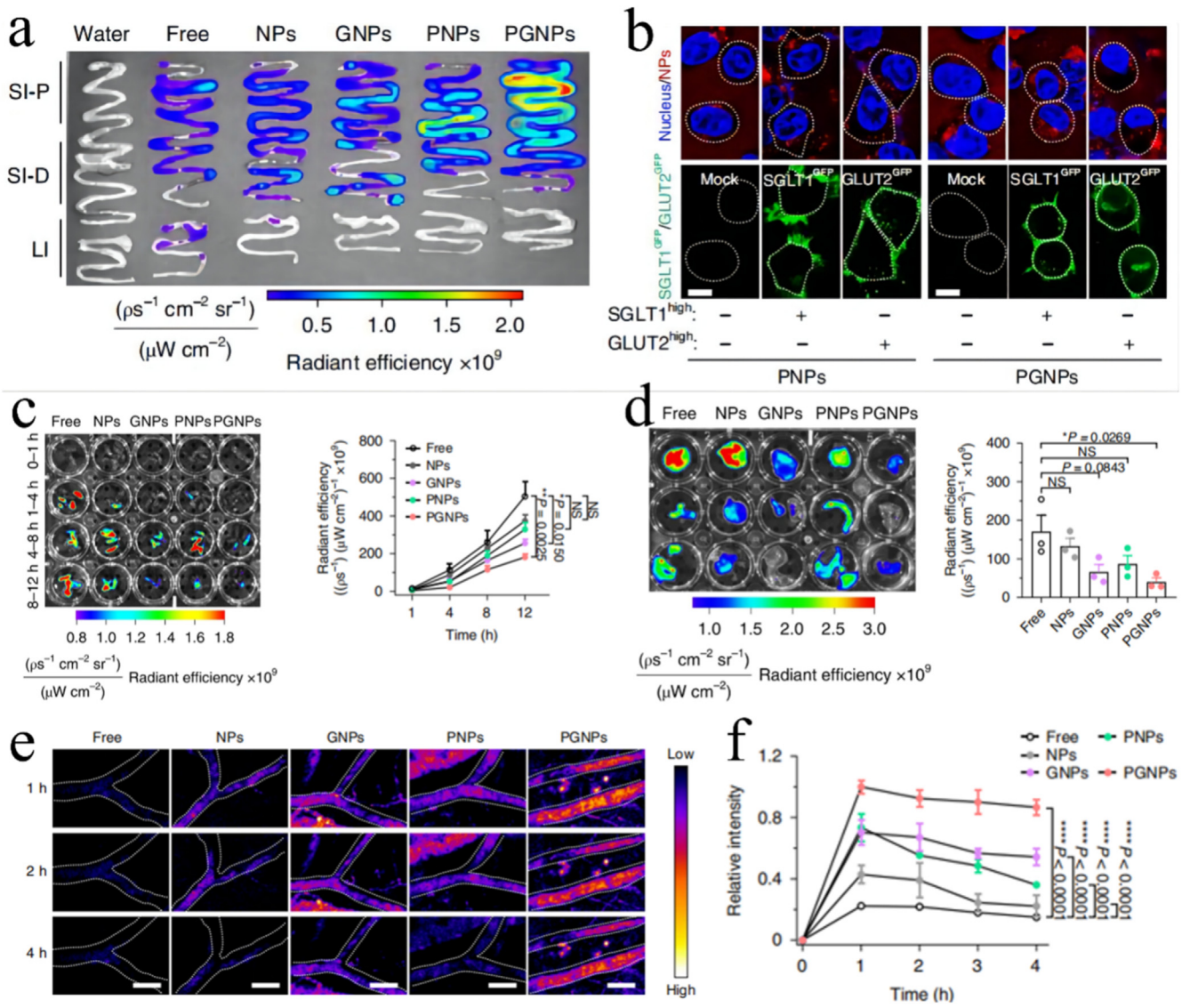

Fig. 5. (a) Images of the different distribution of the nanoparticles in the intestine. (b) Confocal images for uptaking of nanoparticles in cells with different receptors. Scale bars are 10 μm. (c–d) Confocal images and the corresponding analysis of nanoparticles remaining in fecal (c) and cecum (d). (e–f) Confocal fluorescent images and the corresponding analysis of such nanoparticles in ear vasculature, scale bars are 100 μm [82].

achieve the best catalyst chemical conversion through the best ratio (Fig. 6d). Such chemical formation endowed the complex nanoparticles excellent bacterial property. Although many advances have been achieved in mimetic antibiotics, most of them are delivered by intravenous injection or delivering patches, not oral administration. Meanwhile, their unknown biosafety and metabolic performances also commonly constrain their practical applications [90–93].

5. Conclusion and prospects

Today, orally administered antibiotics are still the first choice for clinic treatment of bacterial infections. This review concisely summarized the recent advances in the delivery system of oral antibiotics including oral co-administration systems (like protectors, adsorbents, activity enhancers, etc.), and nanoparticle-based delivery systems. We also briefly introduced mimetic antibiotics based on metal nanoparticles. All of these strategies aim to reduce the destruction of intestinal ecology and avoid the emergence of drug-resistant bacteria, while achieving ideal treatment purposes.

In addition to the stratagems mentioned in the article, we can also get novel ideas from other drug delivery systems. For example, bionic delivery systems, like bionic red blood cells [97], probiotic spore-based nanoparticles [98], and suction-cup-inspired micromotors [99], could be subtly utilized to deliver antibiotics into the gastrointestinal tract. Additionally, magnetically controllable vehicles like microneedles and particles could be anchored in the proximal small intestine through a simple magnetic field [100], and their submicron tips could achieve effective delivery of antibiotics by penetrating the mucus layer and internal epidermis. These hydrogel delivery systems could deliver antibiotics to the targeted area through the design of vehicles shape and physical-chemical properties, so as to effectively avoid exposure to the excess antibiotics. Despite numerous challenges, we believe that more effective delivery systems will be constructed to meet the precise delivery of various drugs in the context of multidisciplinary integration.

Declaration of competing interest

The authors declare no competing financial interests.

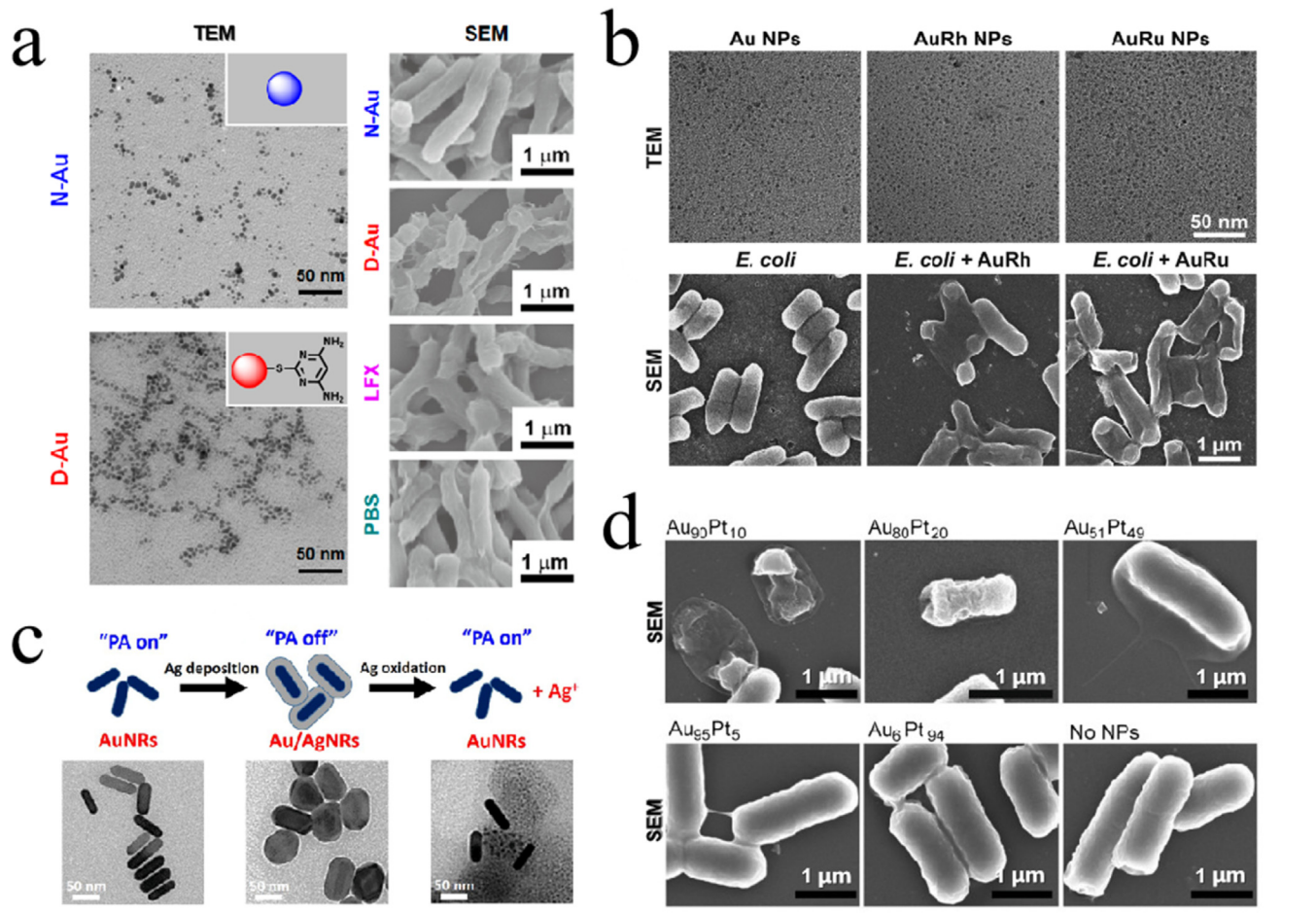

Fig. 6. (a) TEM images of metal-gold-based antibiotics and SEM images of *E. coli* in the corresponding groups [83]. (b) TEM images of Au and Rh bimetallic nanoparticles and SEM images of *E. coli* treated with different strategies [94]. (c) Scheme of bimetallic nanoparticles composed of Au and Ag elements [95]. (d) SEM images of *E. coli* treated with nanoparticles composed of different proportions of Au and Pt [96].

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