

# Quinolone Antibiotics: Resistance and Therapy

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**Abstract:** The clinical application of quinolone antibiotics is particularly extensive. In addition to their high efficiency in infectious diseases, the treatment process brings multiple hidden dangers or side effects. In this regard, drug resistance becomes a major challenge and is almost unavoidable in the clinical application of quinolones. Both genetic and phenotypic variations contribute to bacterial survival resistance under antibiotic therapy. This review is focusing on the drug discovery history, compound structure, and bactericidal mechanism of quinolone antibiotics. Recent studies bring a more in-depth insight into the research progress of quinolone antibiotics in the causes of death, drug resistance formation, and closely related SOS response after disease treatment at this stage. Combined with the latest clinical studies, we summarize the clinical application of quinolone antibiotics and further lay a theoretical foundation for the mechanism study of resistant or sensitive bacteria in response to quinolone treatment.

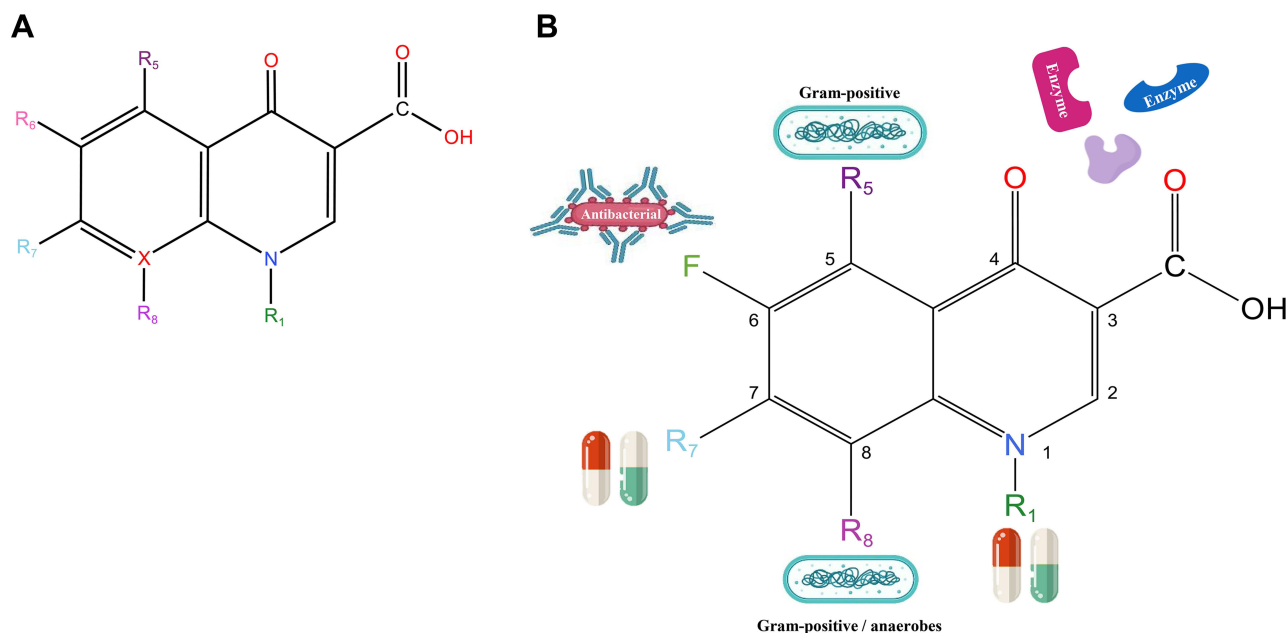
**Keywords:** quinolone antibiotics, disease treatment, SOS response, lethality, bacteria

## Introduction

The earliest quinolone antibiotics were discovered in the 1960s.<sup>1</sup> Their basic structures consist of bicyclic skeletons, carboxylic acids, and keto groups at positions 3 and 4, respectively, which are necessary for their pharmacological activity<sup>2,3</sup> (Figure 1). To obtain broad-spectrum antibiotics, the so-called fluoroquinolones (FQs) can be synthesized by introducing fluorine atoms into the chemical structure of quinolone. For instance, norfloxacin was discovered in 1979, followed by a series of fluorine-containing new quinolones that emerged as FQs. And FQs are one of the most widely prescribed broad-spectrum antibiotics and show sufficient antibacterial activity against both Gram-negative and Gram-positive bacteria.<sup>4</sup>

## Mechanism of Quinolone Action

The term quinolone is often used in a general sense to categorize a class of compounds including quinolones, nalidixones, quinazolines, isothiazoquinolones, etc. Mechanistically, quinolones can target two basic bacterial enzymes, DNA helicase (topoisomerase II)<sup>5</sup> and DNA topoisomerase IV,<sup>6</sup> both of which contain four subunits (2 GyrA or ParC and 2 GyrB or ParE). The enzymes can transfer one region of double-stranded DNA to another, thereby forming the enzyme-quinolones-DNA complexes.<sup>7-11</sup> Quinolones mainly target helicases and topoisomerases that are critical for regulating the superhelix of genomic DNA in the process of replication and transcription in bacteria.<sup>12,13</sup> These complexes prevent the movement of replication forks and transcriptional complexes in vitro, thereby inhibiting bacterial growth.<sup>14-16</sup> Quinolones capture DNA helicase and DNA topoisomerase IV on DNA in the form of complexes, therefore leading to DNA break. However, their effects can be limited by proteins such as drug-enzyme-DNA complexes that reversibly inhibit DNA replication or fragment bacterial chromosomes. In one pathway, chromosome fragmentation stimulates excessive accumulation of highly toxic reactive oxygen species (ROS)-related compounds that are the main causes of cell death.<sup>17</sup> DNA double-strand break (DSB) is a potentially fatal DNA damage, while FQs contribute to DSB by binding to the active site of type II topoisomerase after DNA cleavage to form a quinolone-enzyme complex that disrupts the reconnection of lysed DNA.<sup>18</sup>



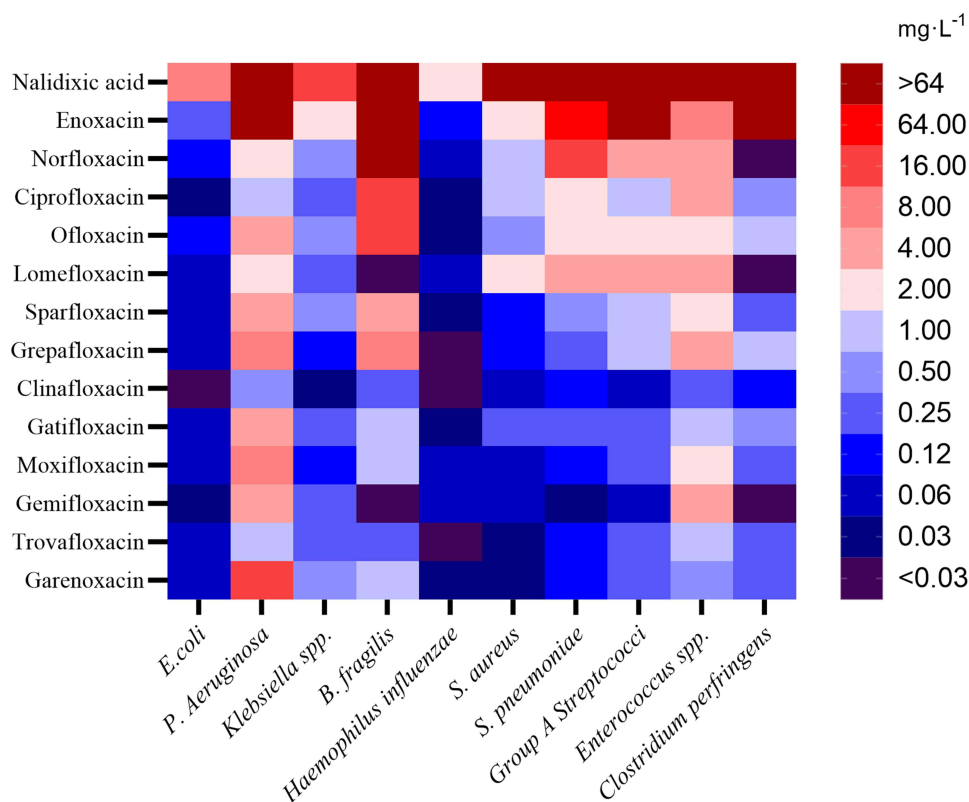
**Figure 1** Core structure of quinolone antibiotics. **(A)** Six important modification positions include R<sub>1</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, and X for improving the drug activity. X=C defines quinolones and X=N defines naphthenes. **(B)** Each modification position has different effects such as antibacterial, affecting pharmacokinetics, enhancing activity and enzymatic binding.

Quinolones are divided into first, second, third, and fourth generations according to their discovery history and their antibacterial properties. At present, third-generation antibiotics are most commonly used in clinical practice. The types, structural changes, and characteristics of each generation of antibiotics are shown in Figure 2. In general, the further optimization or refinement of the synthesis approaches of drugs can enhance their bactericidal effects, but drug resistance may also occur after the structural modifications, which should be further investigated in the future study.

Recently, the discovery of various new antibiotics has been seriously hindered by the occurrence of drug-induced resistance. The challenge of drug resistance caused by quinolone antibiotics needs to be addressed urgently. This review focuses on the formation mechanism of quinolone antibiotic-resistant bacteria, summarizes the research progress in this field, and provides a more in-depth understanding of the research progress of quinolone antibiotics in infectious disease therapy.

## Lethality of Quinolone Antibiotics

The use of antimicrobial agents requires the rapid killing of pathogens, avoiding the induction of drug resistance, and improving the resolution of infectious diseases. Antimicrobial management also includes limiting the lethal effect, especially the protection of beneficial intestinal microbiota during therapy. Therefore, a better understanding of the process of cell death helps the manipulation of the bacterial flora.<sup>19</sup> The earlier dogma that cell death was directly caused by specific types of stressors has been challenged, while a growing body of literature demonstrated that these lesions can stimulate the cellular accumulation of toxic substances, such as ROS under aerobic conditions and reactive nitrogen under anaerobic conditions. The first-generation compounds exerted a lethal effect via the accumulation of ROS. In the second-generation compounds, the effect of ROS is strongly dependent on the ROS concentration. For instance, the killing action of norfloxacin is related to the ROS at low/moderate concentrations but does not lead to cell death at high ROS concentrations. However, the effect of the third-generation compounds such as ciprofloxacin is not as lethal as that of previous generations, which may be due to the increased ability of chromosome fragments. The addition of Cmur8 methoxy in the drug structure can enhance the lethality of the fourth-generation compounds.<sup>20</sup> The detection of various quinolone derivatives showed two killing modes including the accumulation of toxic ROS and the lethal DNA breaks. ROS could be easily detected and play a dominant role in the quinolone-mediated killing. In contrast, the quinolone-mediated DNA breakage may exert a significant effect due to deficiency in ROS detoxification or reducing ROS levels.<sup>21</sup>

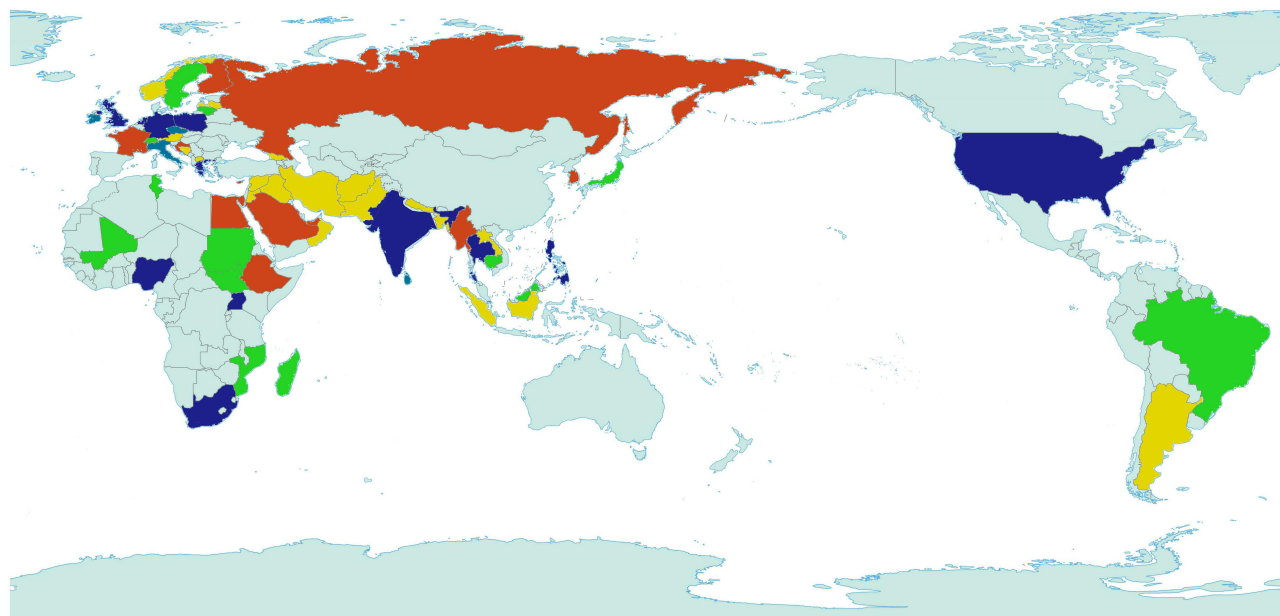


**Figure 2** Classification and features of quinolone antibiotics. Quinolone antibiotics are developed from generations to generations, and a wider spectrum of activity is obtained by adding different substituents at different positions in the core structure. Substituent positions and groups are outlined in red.

DNA replication can be blocked within minutes after the addition of quinolones in bacterial cultures. The effect of cleaved complex correlates with the inhibition of DNA synthesis,<sup>22</sup> while the concentration of quinolones that prevent DNA replication correlates with the bacteriostatic parameter MIC.<sup>23</sup> DNA synthesis can be recovered after drug removal,<sup>24,25</sup> and inhibition of DNA synthesis does not rapidly kill cells.<sup>25,26</sup> Therefore, the cleaved complex is bacteriostatic rather than lethally damaging. Several species of bacteria are expressed two types of DNA topoisomerases including DNA helicases and DNA topoisomerase IV, while some bacteria such as *Mycobacterium tuberculosis* are only expressed helicases. These enzymes can change the DNA topology by introducing DSBs, traversing the other duplex (or another region of the same duplex), and then repairing the break. Quinolones can bind with helicase or topoisomerase IV and disrupt the DNA structure, allowing each 5' end to be covalently bound to GyrA (helicase) or ParC (topoisomerase IV). When the cell metabolism is slowed during starvation or plateaus, compounds such as ciprofloxacin are lethal to large numbers of bacteria through inducing chromosome fragmentation.<sup>27</sup> The addition of nutrients can stimulate the lethal activity of quinolones during the plateau phase.<sup>28</sup> The presence of multiple lethal patterns suggests that drug concentration and latency are important factors and should be considered in data interpretation.<sup>29,30</sup>

## Development of Resistance to Quinolone Antibiotics

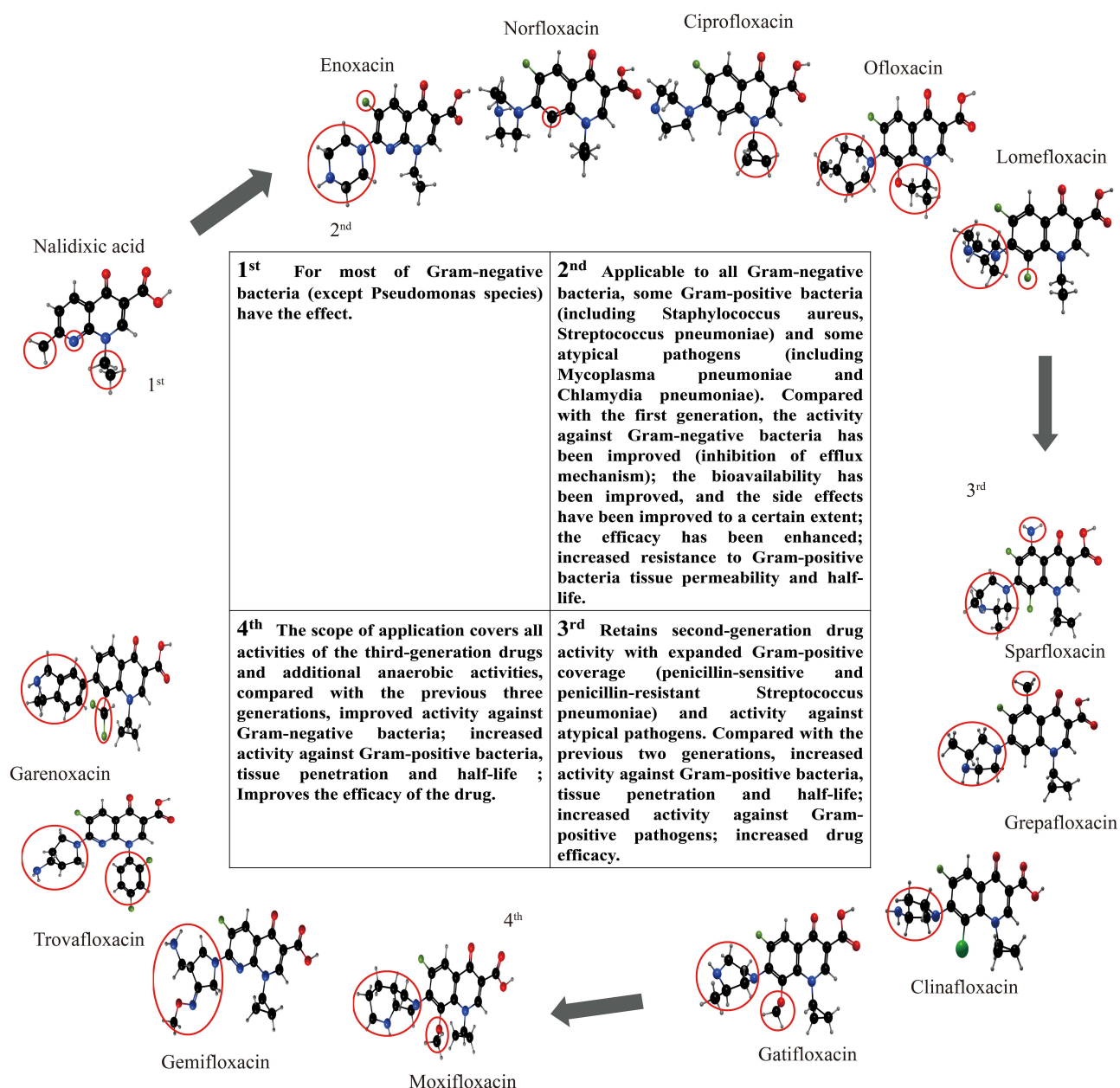
Currently, the formation of bacterial resistance caused by the abuse of antibiotics leads to significant problems in public health. As a class of broad-spectrum antibiotics, quinolone antibiotics have a wide range of applications in the clinic due to their effective bactericidal functions, whereas their accompanying problems of drug resistance become a great challenge. According to the World Health Organization's Global Antimicrobial Resistance and Use Surveillance System (GLASS) report, the main antibiotic-resistant bacteria in the world are *Escherichia coli*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Neisseria Gonorrhoeae* (Figure 3).<sup>31</sup> FQs have a very low minimum inhibitory concentration (MIC) for many bacterial strains. Therefore, most flora dies quickly due to the FQ treatment, whereas a small population of flora still survives (Figure 4). Before exposure to antibiotics, resting cells may



**Figure 3** Global distribution of major quinolone resistant bacteria. Yellow represents *Escherichia coli*, green represents *Klebsiella pneumoniae*, red represents *Staphylococcus aureus*, blue represents *Streptococcus pneumoniae* and purple represents *Neisseria Gonorrhoeae*. Light green represents no data report.

randomly form during the culture process of bacteria.<sup>32–34</sup> If helicases and topoisomerases are not active due to cell dormancy, persistent bacteria may also survive after FQ treatment.<sup>35</sup> However, quinolone resistance also results from mutations that alter drug uptake, efflux, and structure.<sup>36–40</sup> Recent studies suggest that the mechanisms underlying quinolone resistance are primarily mediated by chromosomal mutations and/or uptake of plasmid genes that alter topoisomerase targets, modify quinolones, and/or reduce uptake or increase efflux of accumulated drugs.<sup>3,41</sup> Therefore, a single amino acid mutation in either of the two targeted enzymes of the quinolone (DNA helicase and topoisomerase IV) would impair their interactions with the quinolones, thereby reducing the response to the quinolone drug-like susceptibility. However, these mutations have been reported to be predominantly located in the amino-terminal regions of GyrA or ParC of these enzymes, and the most commonly mutant amino acids are serine residues and acidic residues (glutamic or aspartic acid).<sup>42</sup> Ser83 and Asp87 mutations are the most common mutations associated with drug resistance of *Escherichia coli* gyrA, and there are similar mutations at the same positions in other species.<sup>43</sup> This domain of these enzymes is responsible for anchoring the water-metal ion bridge, known as the quinolone resistance determining region (QRDR). Mutation of this QRDR disrupts the water-metal ion bridge, thereby reducing the drug affinity of the enzyme-DNA complex.<sup>44</sup> Mutations of serines account for more than 90% of the mutation pool, followed by mutations of acidic residues.<sup>45</sup> Single target mutations in DNA helicase and topoisomerase IV lead to increased extents of resistance.<sup>46</sup>

Since DNA helicases and topoisomerases are cytoplasmic enzymes, quinolones must pass through the bacterial envelope to exert killing effects. Therefore, the activity of quinolones is also influenced by their ability to penetrate cellular barriers and the effectiveness of efflux pumps to clear antibiotics from the cytoplasm. Currently, it is known that quinolones enter bacterial cells through porin and lipid pathways. Subsequently, drug resistance can be reduced not only by mutations of quinolone drug targets, but also by downregulation of porins, overexpression of efflux pumps, or changes in lipopolysaccharide (LPS) structure. Many quinolone-resistant bacterial strains have no mutation in the enzyme target QRDR<sup>47</sup> and are less sensitive to independent compounds such as cyclohexane, salicylate, and tetracycline, indicating that drug resistance is related to the broad-spectrum efflux activity.<sup>48</sup> It is known that the multiple antibiotic resistance (Mar) gene leads to resistance to many antibiotic compounds.<sup>49</sup> The mutation of this gene leads to the overexpression of acrAB efflux pump and the decrease of OmpF (outer membrane protein F) porin expression. MarA is a positive regulator of acrAB transcription, which can be induced by MPPA gene mutation or exposure to salicylate and tetracycline. Therefore, salicylates and tetracyclines may stimulate resistance to quinolones. In addition, MarA can block the



**Figure 4** MIC comparison of quinolones. The potency of each drug presented in the MIC<sub>90</sub> (mg L<sup>-1</sup>) of different Gram-negative and Gram-positive strains.

translation of *OmpF* gene and down-regulate *OmpX* expression due to porin expression, thus reducing the expression of many types of porins.<sup>50</sup> Another gene, *nfxB*, can cause resistance to quinolones and other antimicrobials and change the functional expression of *OmpF* on the cell surface, thereby reducing the entry of quinolones.<sup>51</sup> Quinolone resistance manners associated with efflux pumps include modification of the main promoter superfamily (MFS) or drug-resistant nodular division (RND) family of Gram-positive bacteria and multiple antibiotics and toxin excretion (Mate) and ATP binding cassette (ABC) of Gram-negative bacteria.<sup>50</sup>

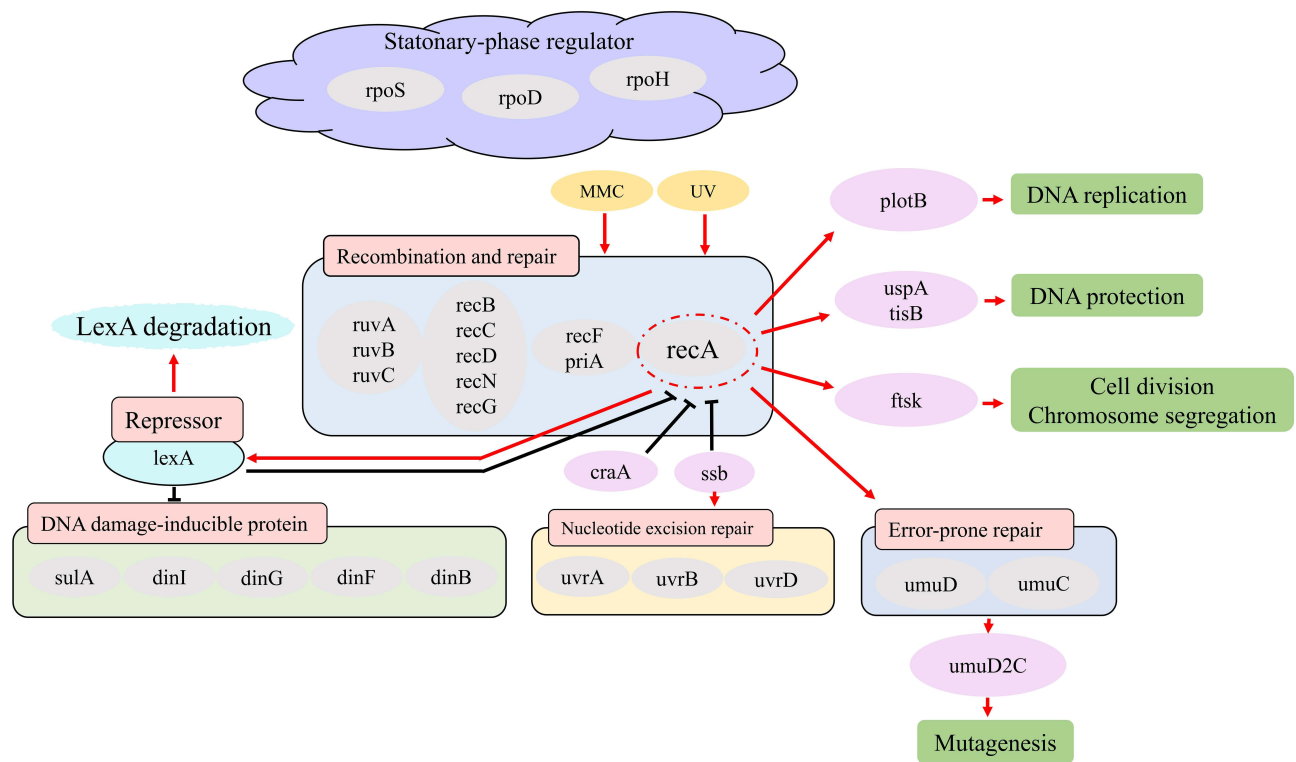
In addition to the bacterial genomic mutations, plasmid-mediated mechanisms play an important role in the generation of quinolone resistance. Plasmids carrying quinolone resistance genes can cause serious clinical problems and reduce drug sensitivity by 10–250 times.<sup>52</sup> The first plasmid family encodes *Qnr*, a pentapeptide repeat family protein. It is also reported that the *qnr* gene originates from the chromosomes of many aquatic bacteria and can compete with other *qnr* proteins from other sources, which can inhibit the entry of quinolones into the cleavage complex, reduce double-strand

breaks on chromosomes, and reduce the chromosome toxicity of quinolones.<sup>53</sup> More than 100 variants have been found in clinical isolates and can be divided into six subfamilies (qnrA, qnrB, qnrC, qnrD, qnrS, and qnrVC). These proteins are folded into a right quadrilateral  $\beta$ -helix and dimers to form a rod-like structure, whose size, shape, and electrostatic surface mimic the  $\beta$ -form of DNA.<sup>54</sup> The second plasmid family coding the protein related to quinolone resistance is Aac (6')-Ib-cr, which is a derivative of aminoglycoside acetyltransferase with Trp102Arg and Asp179Tyr mutations. The enzyme acetylates the unsubstituted nitrogen on the R7 piperazine ring, thereby inhibiting the activity of quinolones. Both mutations are necessary for this particular enzyme action. Trp102Arg mutations at the Asp179Tyr tyrosine aromatic ring result in its interaction with quinolones and fix it in this position.<sup>55,56</sup> The third family associated with quinolone resistance is plasmid-mediated quinolone efflux pumps, including OqxAB and QepA. Their encoded genes do not directly lead to high levels of quinolone resistance but can promote topoisomerase mutations by the adaptation of bacteria to low concentrations of quinolones.<sup>57,58</sup>

## Relationship Between Quinolone Antibiotics and SOS Response

Quinolones bind to the cleavage-junction active site of the DNA-cleavage complex. This binding produces cleavage complexes at a stable concentration and disrupts the replication process, leading to the stable cleavage complex colliding with the DNA replication system (replication fork, transcriptional complex, and targeting system). Therefore, the binding of quinolones results in chromosome breakage. In response to the effect of quinolones on DNA damage, SOS response and other DNA repair pathways are activated in bacteria. The downstream actions of SOS response include lengthening cell filaments by expressing LexA inhibitors and activating toxin-antitoxin modules to induce programmed cell death. *E. coli* efficiently repair DSBs through a series of enzymatic reactions related to homologous recombination and replication.<sup>59</sup> Treatment of double-strand breaks induces the SOS response, which is a complicated network of more than 40 genes.<sup>60,61</sup> Most of these genes are essential for the efficient repair of various DNA lesions, including DSBs.<sup>62,63</sup> It is known that SOS regulation is primarily controlled by the LexA and recA gene products in *E. coli*. Single-stranded DNA (ssDNA) regions are formed when DNA nucleotides are destroyed by genotoxins such as ultraviolet light and mitomycin. RecA wraps ssDNA and then triggers the SOS response. Additionally, the RecA/ssDNA interaction stimulates the degradation of LexA (an inhibitor of RecA during normal repair). Subsequently, the inactivation of LexA affects other genes (such as dinI) directly involved in the SOS response and downstream genes (such as rpoS) related to DNA replication, cell division, and mutation.<sup>64</sup> RecA and RecBC are essential for double-stranded repair in *Escherichia coli*. Based on the literature, Yamanaka et al summarized the gene network diagram of SOS response<sup>65</sup> (Figure 5), suggesting that the SOS response is intricate. Under the treatment of FQ antibiotics, the bacteria that can survive without developing genetic resistance are often referred to as “persistent bacteria”, and their survival is dependent upon the SOS gene network. Studies have verified mutations in all known SOS-regulated genes. To determine the functions necessary for tolerance in *E. coli*, studies found that cell survival was decreased after the loss of the dinG and UvrD helicases and the Holliday ligation processing enzymes (including ruvA and ruvB). And analysis of the corresponding mutants showed that bacterial tolerance can be induced not only by repairing double-strand breaks but also by the repair of collapsed replication forks and stalled transcriptional complexes. And mutations in the RecF gene lead to increased survival, suggesting that RecAF recombination is a poisoning mechanism that is not previously associated with FQ lethality. DinG plays a critical role in the upstream of SOS system to promote its induction, while RuvAB only participates in repair. UvrD directly promotes all repair processes initiated by FQ-induced damage and prevents RecF-dependent error repair, making it one of the key SOS functions required for tolerance.<sup>64,66,67</sup>

FQ ciprofloxacin causes phase transition of respiration and membrane potential of *Escherichia coli*, which is significantly related to its concentration. In the first stage, cells maintain their metabolic activity and membrane potential, accelerate  $K^+$  absorption, and produce low levels of superoxide and  $H_2O_2$ . However, the second stage is negatively correlated with the concentration of ciprofloxacin and depended on the SOS response. The second stage is also characterized by respiratory inhibition, membrane depolarization, leakage of  $K^+$  and glutathione, and cessation of glucose consumption, which can be considered cell death. Knockout of *atpA*, *gshA*, or *kefBkefC* gene disrupts the flux of proton and  $K^+$ , thereby changing the degree and duration of respiratory inhibition and potassium retention. The deletion of  $K^+$  outflow channels, KefB and KefC, increases the sensitivity of *Escherichia coli* to ciprofloxacin.<sup>68</sup>



**Figure 5** Schematic of a gene interaction network related to the SOS response in *E. coli* based on literature. The figure represents the inducible genes/proteins in the SOS response for repairing DNA damage. Black lines indicate pathways during normal repair and red lines indicate arrows activated/induced due to exposure to damaging substances. Recombination and repair, DNA damage-inducible protein, nucleotide excision repair, error-prone repair, and stationary-phase regulator have family molecules in each box.

## Clinical Application of Quinolone Antibiotics

Currently, quinolone is mainly used in the treatment of infectious diseases such as respiratory tract infection, gastrointestinal infection, gynecological infection, sexually transmitted diseases, urinary tract infection and prostatitis, bone and joint infection, skin and soft tissue infection, and other diseases. Oral or intravenous quinolones can successfully be used to treat a variety of infectious diseases. The clinical efficacy of quinolones has been verified in respiratory tract infections including acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia, hospital-acquired pneumonia, and bacterial sinusitis. Some quinolones are also useful in the treatment of immunocompromised patients with febrile neutropenia.<sup>69–71</sup> It should be noted that not all FQs are approved for the treatment of all these infections, but the exchange and use of all FQs are discouraged in the clinic.

At present, the most commonly used FQs in the United States are ciprofloxacin, levofloxacin, gatifloxacin, and moxifloxacin.<sup>72</sup> Ciprofloxacin has been approved for simple and complex urinary tract infections (including cystitis, pyelonephritis and chronic bacterial prostatitis, genitourinary and rectal gonorrhea without complications), skin and other soft tissue infections, bone and joint infections, infectious diarrhea and typhoid, intra-abdominal infections (when used with metronidazole), sinusitis and hospital-acquired pneumonia, etc. Ciprofloxacin is also approved for empirical treatment in patients with febrile neutropenia, prevention and treatment of anthrax, and lower respiratory tract infections (including acute bacterial deterioration of chronic bronchitis, pneumonia (except *pneumococcal pneumonia*), hospital-acquired pneumonia, etc). Levofloxacin is approved for the treatment of simple and complex urinary tract infections (including pyelonephritis and chronic bacterial prostatitis), skin and skin structure infections, acute maxillary sinusitis, acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia (including pneumonia caused by penicillin) drug-resistant *Streptococcus pneumoniae* and multidrug-resistant *Streptococcus pneumoniae* and hospital-acquired pneumonia.<sup>73</sup> Gatifloxacin is approved for the treatment of simple and complex urinary tract infections (including pyelonephritis), simple genitourinary gonorrhea, simple skin and skin structure infections, acute sinusitis,

chronic bronchitis, and acute bacterial exacerbation of community-acquired pneumonia.<sup>74</sup> Moxifloxacin is approved for the treatment of acute bacterial sinusitis, simple skin and skin structure infections, chronic bronchitis, and community-acquired pneumonia.<sup>75</sup> Gemifloxacin is approved for the treatment of acute bacterial exacerbation of chronic bronchitis and mild to moderate-severe community-acquired pneumonia.

The possible danger caused by the use of quinolones is mainly associated with unreasonable drug use. In view of the existing problems, the specific measures are as follows: 1) Strictly follow the doctor's instructions, formulate medication rules based on the pharmacological characteristics of quinolones and the actual application in the hospital, and strengthen the guidance on the scope of application, dosage, course of treatment, adverse reaction treatment, and combination medication of quinolones; 2) Provide health education for clinical medical staff, publicize the pharmacological characteristics, usage and matters needing attention of quinolones through lectures, guide rational drug use, and open a consultation hotline in the pharmacy department, and promptly answer the questions of patients, their families and clinical medical staff in the process of disease treatment; 3) Dynamically understand the medication situation of clinicians, especially the unreasonable situation in the selection process of quinolones, and judge whether the condition analysis in the prescription meets the applicable standards of quinolones. At the same time, the problems (whether the dosage is appropriate, the frequency is reasonable, or the combination drug is correct) should be addressed.

## Conclusions and Future Perspectives

By reviewing the association of quinolones with drug resistance and SOS response, we found that the current research on quinolones mainly focuses on two aspects including direct targeting action leading to lesions and indirect accumulation of poisons and cell death. Regarding the formation of drug resistance, the methods mainly focus on three aspects including mutations targeting enzyme site, antibiotic efflux, or the carrying plasmid. Studies have shown that quinolone antibiotics are closely related to the SOS response, and multiple genes are involved in the regulation of this process. Although our understanding of quinolone antibiotics is gradually becoming clearer, some issues are still existed and deserved our consideration. For instance, the binding of quinolone antibiotics to the target is a reversible reaction, so does it necessarily mean that its sterilization depends primarily on the accumulation of toxins after treatment, and there is a possibility of other sites of action. On the other hand, the ROS generation contributes to the quinolone-related toxin. However, the unanswered questions remain whether other important toxins are involved, how the repair-related protein recF regulates and kills bacteria through the cytotoxic mechanism, and how the toxin expression is balanced in the body. Furthermore, quinolones have a significant bactericidal effect and are widely used in infectious disease treatment. The precautions for their use are needed to reduce the risk of drug abuse.

## Abbreviations

FQ, fluoroquinolones; ROS, reactive oxygen species; DSB, double-strand break; MIC, minimum inhibitory concentration; QRDR, quinolone resistance determining region.

## Disclosure

The authors report no conflicts of interest in this work.

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