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An Overview of Fluoroquinolones

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Authors' contributions

This work was carried out between all authors. Author SS gave idea, designed the work and performed the analyses of the work. Author KM collected the literature and wrote the first draft. All the authors read and approved the final manuscript.

Review Article

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ABSTRACT

The fluoroquinolones are broad-spectrum bactericidal agents inhibiting DNA synthesis. They are active against gram positive and gram negative organisms like *P. aeruginosa, Mycoplasma, Chlamydia, Staphylococci* and a few of the *Streptococci*. They are useful in the treatment of pneumonia, urinary tract infections, bacterial diarrhea, and skin and soft tissue infections. The use of quinolones began with its first generation that consisted of nalidixic acid. From that time, a large number of newer fluoroquinolones having a variety of structures and a broader spectrum of activity have been developed forming the five generations. The more number of fluoroquinolones developed and its widespread usage is attributed to its high bioavailability and tissue penetration. Moreover, the development of resistance to the most commonly used antibiotics has led to the need for alternatives. The various derivatives of fluoroquinolone have varying levels of activity depending on the various groups attached at different positions. Generating a derivative with increased activity will help to reduce the Minimum Inhibitory Concentration (MIC), thereby reducing the possibility of developing resistance to it. This paper gives an overview of fluoroquinolones, their mechanism of action, their uses, resistance development and their adverse effects.

Keywords: Fluoroquinolone activity; fluoroquinolone generations; fluoroquinolone resistance.

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1. INTRODUCTION

Antimicrobials are substances that are used to kill or inhibit the growth of bacteria, fungi and protozoa. These compounds were initially discovered when certain microorganisms had the ability to kill or inhibit the growth of other microorganisms by releasing some compounds into the growing medium and now these microorganisms are grown in a large scale and the antibiotics are purified from the medium. Penicillin is an antibiotic exuded from *Penicillium notatum* in the presence of appropriate substrate and is used for large scale production. In order to achieve potential broad spectrum activity of these compounds, they could be modified by chemical methods or mutagenesis. The antimicrobial compounds can also be synthesized chemically like the quinolones, sulphonamides and trimethoprin. Their mechanism of action involves targeting one of the following activities that are required for cell survival. They are cell wall synthesis, DNA synthesis, RNA synthesis, protein synthesis and intermediary metabolism.

The β-lactam antibiotics target cell wall biosynthesis [1]. Linezoid, tetracylines, aminoglycosides, chloramphenicol, macrolides and streptogramins inhibit protein synthesis during initiation, elongation and termination. A different class of drugs includes rifampins that prevent DNA transcription. Metabolic pathways are blocked by compounds called antimetabolites like sulfonamides, flucytosine and trimethoprim. Quinolone derivatives of nalidixic acid that disrupt DNA synthesis form another class of drugs. Viral replication can be inhibited by drugs like ancyclovir and ganciclovir.

In the early 1940s, before the discovery of penicillin and tetracycline, there was no cure for microbial infections like gonorrhoea, pharyngitis, pneumonia, etc. After the discovery of antimicrobials, such diseases could be easily cured and has lead to the betterment of health. This has lead to the increased use of these drugs. The indiscriminate use of these antibiotics leads to the development of resistance. They do so via spontaneous mutation or by DNA transfer. This process enables some bacteria to resist the activity of certain antibiotics, rendering the antibiotics ineffective [2]. When such organisms develop resistance to distinct drugs of different structure and function, they are said to be Multi-drug resistant (MDR). The spread of MDR strains has led to the emergence of Extensive Drug Resistance (XDR) due to improper treatment. Hence there is a continuous requirement of drugs to which microorganisms haven't developed resistance and are effective against microorganisms. In this review the use of quinolones, a group of relatively new drugs that have a broad spectrum, are discussed which include a large number of infections associated with the urinary tract, gastrointestinal tract or the abdomen.

Quinolones are a group of synthetic broad spectrum antibacterial drugs that target DNA synthesis [3]. This class of antibiotics started with the discovery of nalidixic acid as early as 1962. These have been modified over the years to include new compounds that effectively act against a variety of gram positive and gram negative organisms. Fluoroquinolones are the derivatives of quinolones which are fluorinated at C-6 position of the quinolone ring. They act on two enzymes involved in DNA synthesis: DNA gyrase and topoisomerase IV and thereby block DNA replication and transcription, leading to cell death.

The different generations of quinolones have been classified based on their antibacterial activity on gram positive and gram negative organisms [4,5], with the first generation being the most narrow and the subsequent ones having an increase in spectrum of activity and on the novelty and complexity of the structures of quinolones. This classification has five generations as indicated in Table 1 [6].

Table 1. Classification of quinolones

Generation	Drug
First	Nalidixic acid
Second	Norfloxacin
	Ciprofloxacin
	Enoxacin
	Fleroxacin
	Lomefloxacin
	Ofloxacin
	Levofloxacin
	Rufloxacin
Third	SparFloxacin
	Tosufloxacin
	Gatifloxacin
	Gemifloxacin
	Temafloxacin
	Grepafloxacin
Fourth	Trovafloxacin
	Sitafloacin
	prulifloxacin
	Clinafloxacin
	Moxifloxacin
Fifth	Delafloxacin

2. STRUCTURE

All fluoroquinolones have a basic 4-quinolone structure, with a fluorine atom at C-6 position as stated below (Fig 1). Differences between the various fluoroquinolones are usually due to various groups that are attached at positions 1, 5, 7 and 8 [7].

The group attached to N-1 is responsible for the antibacterial property of the compound [8,9]. The most optimum group to be attached here has been found to be the cyclopropyl group, as seen in ciprofloxaxin, sparfloxacin and gatifloxacin [10]. It has been shown that a nitrogen group improves the pharmacokinetic properties, while on the other hand a sulphur atom increases the antibacterial properties of the fluoroquinolones at position 2, but is not commonly used. At position 3, a carboxylic group is essential to form a link with the ketone group present at position 4 [11]. This interaction is essential for binding to DNA gyrase, one of the enzymes targeted by fluoroquinolones, and then to bring about cell death. Replacement of the carboxylic acid group by a biosostere-fused isothiazolo ring helps to understand the structure-activity relationship among the quinolones. The nitrogen atom of the ring mimics the function of the carboxylic acid group [12,13]. The replacement of the ketone group at position 4 with other derivatives leads to inactive compounds and hence is not extensively studied. At position 5, substitutes of amino, nitro, halo or alkyl groups have been synthesised. An amino group at this position has found to increase absorption and tissue distribution in the body [14]. The substitution of H, F, Cl, Br, CH_3, SCH_3, $COCH_3$, CN and NO_2 groups have been studied at the C-6 position. Of all these substitutions, the fluorine atom substituent has been found to have increased activity by improving the binding ability and cell penetration of these fluoroquinolones [15]. Robinson et al has reported that the removal of the C-8 fluorine atom leads to the decrease in the ability to cause enzyme-

mediated DNA cleavage [15]. A piperazinyl group as in norfloxacin attached to C-7 position has been found to increase the antibacterial property, though other groups like 4-methylpiperzazin-1-yl substituent as in pefloxacin and ofloxacin, piperazin-1-yl substituent as in ciprofloxacin and enofloxacin and 3-methylpiperazine-1-yl substituent as in lomefloxacin and temafloxacin have also been synthesized [16]. In addition to the piperazinyl group, a methyl group attached to it at the C-4 position increases its activity towards gram positive micro-organisms. Substituent of halides or methoxy groups at position C-8 or the replacement of the C-8 carbon with nitrogen has been synthesized [17]. A fluorine or methoxy group attachment at position 8, as in gatifloxacin and moxifloxacin was proved to be more effective against resistant microorganisms than C-8 hydrogen (Fig 2).

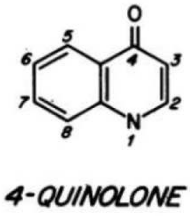

Fig. 1. Structure of basic Quinolone

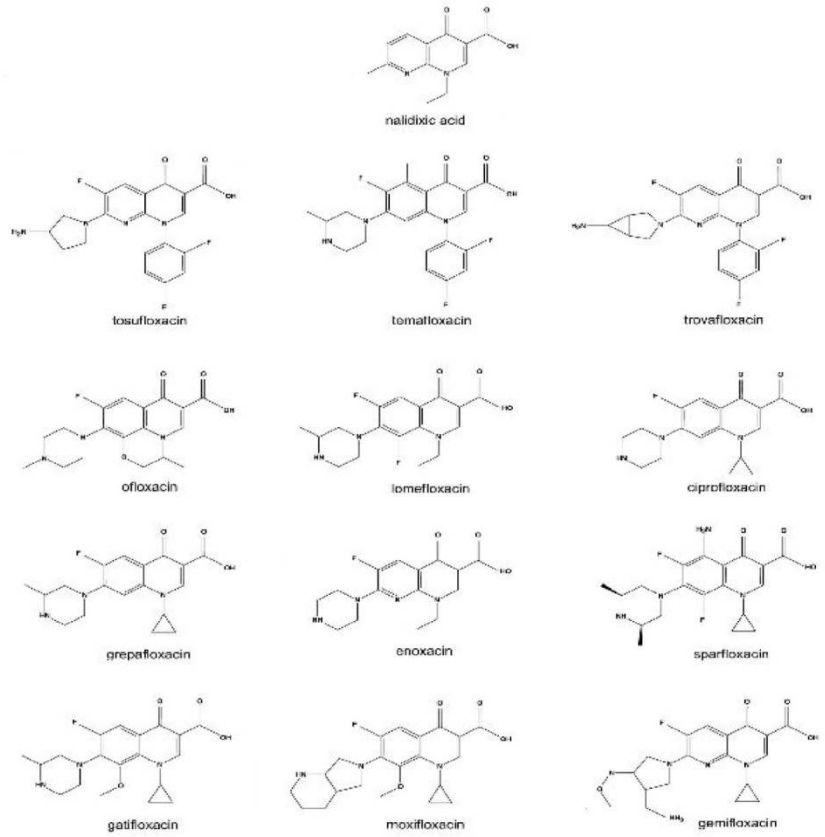

Fig. 2. The structures of different fluoroquinolones

2.1 Role of C-8 substituent on fluoroquinolone potential against *Mycobacterium spp.*

The replacement of the C-8 hydrogen by fluorine, chlorine or methyl groups alters the oral pharmacokinetics and broadens the spectrum of activity. It also reduces the selection of mutants [18,19]. Alkylation at C-8 leads to an increase in the lipophilicity of the drug and hence increases half life and tissue penetration of the drug and also its activity against gram positive microorganisms [20]. A methoxy group has been shown to increase the activity against clinical isolates of *M. tuberculosis* [21]. Drug activity of different fluorquinolones including ciprofloxacin, moxifloxacin, sparfloxacin, PD129603, etc, were shown to have a multiple fold reduction in MIC_{99} in *Mycobacterium* mutants when compared to those compounds that do not have a fluorine or methoxy group at position 8 [22].

3. MECHANISM OF ACTION

Fluoroquinolones enter the cells by porins and target two enzymes: DNA gyrase and topoisomerase IV. DNA gyrase or topoisomerase II helps in producing negative superhelical twists. They remove the positive twists that occur during replication, when the replication fork unwinds the DNA [23]. The other enzyme, topoisomerase IV is involved in the decatenation of the linked daughter chromosomes to ultimately produce two distinct daughter cells [24]. DNA gyrase is made up of two each of the subunits encoded by *gyrA, gyrB* [25]. Similarly, topoisomerase IV is made up of two each of the subunits encoded by *parC* and *parE*. Homology studies have shown that there is a similarity between *parC* and *parE* and *gyrA* and *gyrB*. And hence, as expected, these enzymes bind at similar sites on the DNA. The active tyrosine residue in the enzymes: DNA gyrase and topoisomerase IV bind near α helices [26]. These enzymes being positively charged can easily bind to negatively charged DNA.

When fluoroquinolones bind to these enzymes, it blocks the activity of these enzymes and hence stops replication, transcription, repair as well as recombination. The fluoroquinolones bind to the enzyme-DNA complex and forms a stable ternary complex. The complex of drug, topoisomerase IV and DNA collides with the DNA replication complex and forms a physical barrier that blocks the further progression of the replication fork [25]. On the other hand, the complex of drug, DNA gyrase and DNA blocks the passage of RNA polymerase and leads to the premature termination of transcription [27].

It has been observed that these drugs preferably bind to either DNA gyrase or topoisomerase IV. In gram negative organisms like *Escherichia coli*, fluoroquinolones bind to DNA gyrase as a primary target and topoisomerase IV as the secondary target. In contrast, in gram positive organisms like *Staphylococcus aureus*, fluoroquinolones bind to topoisomerase IV as the primary target and DNA gyrase as the secondary target [28]. However, there are certain exceptions to this rule. For example, in *S. pneumonia*, a gram positive organism, DNA gyrase was found to be more sensitive to fluoroquinolones than topoisomerase IV [29]. In *Mycobacterium tuberculosis* DNA gyrase was found to be the unique target for fluoroquinolones [30].

The cell is finally killed by the formation of irreversible complex of drug, enzyme and DNA and then the formation of double strand breaks in the DNA by denaturation of topoisomerase [25]. A DNA bubble is formed at the active site by the interaction of the DNA and fluoroquinolones and then the DNA is nicked, once at each strand to cleave the DNA [31].

4. PHARMACOKINETICS AND PHARMACODYNAMICS

The commercially available fluoroquinolones are levofloxacin, ofloxacin, moxifloxacin and ciprofloxacin. Some fluoroquinolones like garenoxacin are now under clinical trials [32]. Most of the fluoroquinolones are available in the intravenous or oral form. Such fluoroquinolones include ciprofloxacin, ofloxacin, levofloxacin and alatrofloxacin (alatrofloxacin is metabolised in the body into trovafloxacin). The bioavailability of the fluoroquinolones from an oral administration is the same as the intravenous administration, and hence gives the same effect as one administered intravenously. The bioavailability of fluoroquinolones ranges from 70% to greater than 90%. Ballow et al. reported that a 91.8% absolute bioavailability of moxifloxacin was observed after a 100mg dose administered as a 60 minutes infusion [33]. Another study reported the absolute bioavailability of gatifloxacin to be 96% [34]. The only disadvantage of an oral administration is that the absorption of the drug is affected by cations like aluminium, magnesium, zinc, iron and calcium. Lober et al analysed the effects of administration of aluminium magnesium hydroxide used mainly in antacids like gelusil, gaviscon, Maalox, etc with gatifloxacin [35]. They reported that there was a 45% decrease in peak plasma concentration when aluminium magnesium hydroxide was administered two hours before gatifloxacin and a 68% decrease when concomitantly administered. There was no change in the concentration when it was administered two or four hours after gatifloxacin. Moreover, ingestion with food delays the absorption of the drug: the drug takes an extra hour to reach peak plasma concentration [36]. Few fluoroquinolones like ciprofloxacin are also available as eye or ear drops.

The pharmacokinetics analysis reveals the time duration of the drug in the plasma corresponding to the dosage regimen. Comparison of different fluoroquinolones show that the fourth and higher generations, like trovafloxacin and moxifloxacin have better bioavailability, higher plasma concentrations, greater tissue penetration, longer elimination half life and higher volume of distribution [7,32,37,38]. The fourth generation fluoroquinolones have been shown to have higher protein binding than the third generation. This results in higher concentration of the drugs in the tissues and fluids. Penetration of the fluoroquinolones into various tissues like kidney, lung, bronchial mucosa, gallbladder, genital tract and prostate are found to be very high.

All the fluoroquinolones undergo either renal or hepatic elimination. All hydrophilic drugs, namely levofloxacin and ofloxacin, undergo renal elimination, whereas, all lipophilic fluoroquinolones, mainly third and fourth generation fluoroquinolones like sparfloxacin, gatifloxacin, moxifloxacin, etc, undergo hepatic metabolism alone [36]. In the liver, they are usually metabolised by cytochrome P450. Some are also metabolised by glucoronidase and sulphate conjugation. Hence, in case of any problems in renal or hepatic function, the respective fluoroquinolones should not be administered as increase in the plasma concentrations of these drugs will lead to adverse drug reactions.

Pharmacodynamics deals with the relationship between the drug concentration and the antimicrobial activity. At concentrations above the MIC, all fluoroquinolones exhibit both post antibiotic effect and concentration-dependent bactericidal activity. In addition to acting on DNA gyrase and topoisomerase, certain fluoroquinolones like ciprofloxacin and fleroxacin act on the cell membrane of bacteria [38]. At high concentrations, fluoroquinolones have been found to disintegrate the inner and outer membranes of the bacteria. They are hypothesised to act as chelating agents removing cations, majorly magnesium ions. Thereby, they lead to a 35% increase in cell hydrophobicity as well as an increased sensitivity to lysis by SDS and other detergents [39].

5. ACTIVITY

In vitro testing of the activity of fluoroquinolones showed that they act on a variety of gram positive and gram negative organisms. Though the older generations of fluoroquinolones were majorly active against gram negative microorganisms, the newer fourth and higher generations have been synthesised so as to target gram negative micro-organisms equally as their previous generations as well as to have a greater degree of activity against gram positive micro-organisms than their previous generations. In a study it was shown that moxifloxacin, a fourth generation fluoroquinolone, has greater activity against gram positive organisms and has similar activity against gram negative organisms as that of older fluoroquinolones as observed in levofloxacin, a third generation, and ciprofloxacin and ofloxacin, second generation drugs [40].

Various gram negative bacilli and cocci are targeted. They include *Neisseria gonorrhea, Pseudomonas aeroginosa, Aeromonas hydrophila, Haemophilus influenzae, and Legionella pneumophila.* Fluoroquinolones can also be used against pathogens of the gastrointestinal tract like *E. coli,* Salmonella spp., Shigella spp*., Yersinia enterocolitica, Clostridium jejuni* and *Vibrio spp*. [8] As some of the fluoroquinolones are eliminated by renal excretion, their concentration in the urine is very high and hence helps to overcome a number of urinary tract infections. They can also be used against pathogens that have developed multiple antibiotic resistances like methycillin resistant *Staphylococcus aureus* and β-lactamase producing *N. gonorrhoea*. The only problem associated with this usage is the high risk of development of resistance to fluoroquinolones [41]. The most commonly targeted gram positive micro-organisms are penicillin sensitive and resistant *Streptococcus pneumoniae, Staphylococcus aureus, Streptococcus pyogenes* and *Streptococcus agalactiae* [42].

Ciprofloxacin is the most potent drug against *Pseudomanas aeroginosa*. Fluoroquinolones are most active against *Pseudomonas* than any other bacterial species. The third and fourth generations of fluoroquinolones are active against *Streptococcus pneumonia*. In addition, the fourth generation fluoroquinolones, especially trovafloxacin, are lethal to anaerobic bacteria, namely *Actinomyces spp., Bacteroides spp., Bactriodes distasonis, Bacteroides thetaiotaomicron, Bacteroides fragilis, Clostridium perfringens,* and certain species of *Eubacterium, Lactobacillus* and *Peptostreptococci* [43]. Biowarfare micro organisms like strains of Bacillus anthrax and *Y. pestis* are also sensitive to fluoroquinolones [44]. The aminoglycoside inactivating enzymes aminoglycoside acetyltransferase that can inactivate the fluoroquinolone as well [45]. All generations of fluoroquinolones are prescribed against *Enterobacteriaciae*.

6. CLINICAL USES

The use of earlier antimicrobials, like penicillin, cephalosporins, etc is decreasing due to the development of resistance to these drugs [46]. This led to the requirement of newer antimicrobials that could kill or inhibit the growth of micro-organisms that could not be killed by existing antimicrobials. Starting from nalidixic acid, a number of newer and more potent fluoroquinolones were developed with broader spectra of activity and broader applications for the treatment of genital, gastrointestinal and respiratory tract infections and those of the bone and joint [47]. Ciprofloxacin and ofloxacin were the most commonly used drugs in the early nineties of the twentieth century.

S. pneuminae responsible for community-acquired respiratory tract infections is found to be resistant to penicillins and cephalosporins. These strains were also cross-resistant to other antibiotics used in treatment, like macrolides [48,49]. Hence the use of fluoroquinolones has been encouraged in such cases of respiratory tract infections [48]. Levofloxacin and trovafloxacin has been shown to have superior activity against *Bacteroides fragilis, Chlamydia spp., Mycoplasma pneumoniae,* and *Mycobacterium spp*. A study by Ersnt *et al*. demonstrated the use of levofloxacin for the treatment of community-acquired respiratory-tract infections, genitourinary infections, skin and skin-structure infections, acute bacterial sinusitis, and infections of the head and neck. Trovafloxacin is still under clinical studies and may be used to treat skin and skin-structure or soft-tissue infections respiratory-tract infections, sexually transmitted diseases, and meningitis after proper testing. Both trovafloxacin and levofloxacin are well tolerated by the body [50,51]. Though not yet in use, trovafloxacin has been shown to have similar clinical outcomes as imipenem when administered in combination with metronizadole and ciprofloxacin for the treatment of intra-abdominal infections [52].

Temafloxacin was withdrawn from use in June 1992, the use of trovafloxacin was restricted to the treatment of only serious infections in June 1999, and grepafloxacin was withdrawn globally in October 1999. Some of the recently developed fluoroquinolones, such as moxifloxacin and gatifloxacin, are indicated for the treatment of respiratory tract infections because of the improved Gram-positive activity that is seen with gatifloxacin, as well as the additional anaerobic activity that is seen with moxifloxacin. Serious toxic effects have developed with the use of three agents: temafloxacin, grepafloxacin and trovafloxacin. The 'temafloxacin syndrome' was characterized by hemolytic anemia, renal impairment, hepatotoxicity, disseminated intravascular coagulation and hypoglycemia [53]. Some of the fluoroquinolones are discontinued in the clinical conditions and the rates are: levofloxacin 3.7%; gatifloxacin 2.9%; and gemifloxacin 3.2% [54].

Fluoroquinolones like ofloxacin, ciprofloxacin, sparfloxacin, and pefloxacin are shown to exhibit clinical efficacy against mycobacterial diseases, especially tuberculosis and leprosy [55]. Their in vitro activity against *Mycobacteria* and their efficacy in murine models has been documented. The substitution of moxifloxacin for isoniazid during the treatment of tuberculosis has the greatest potential to reduce the duration of therapy that originally included 2 months of rifampin, isoniazid and pyrazinamide followed with 4 months of rifampin and isoniazid. This is hypothesised to be due to the synergism of rifampin, moxifloxacin and pyrazinamide when compared to rifampin, isoniazid and pyrazinamide [56,57]. A study reports their activity against most strains of *Mycobacterium spp.* like *M. tuberculosis, M. leprae, M. bovis, M. kansasii, M. marinum,* and *M. xenopi* with their MICs ranging between 0.5 mg/L and 2.0 mg/L [58,59].

The use of norfloxacin in the treatment of urinary tract infections has been reported [60]. These compounds have shown potential bactericidal activity to cure patients with uncomplicated and complicated cases of infection [61,62]. A comparative study reported that norfloxacin cured 19 out of 20 patients whereas amoxicillin cured only 15 patients and hence proved its potential activity against urinary tract infections than other groups of antibacterial compounds [63].

The problem with fluoroquinolones usage is that they are largely prescribed for the wrong indications. Even if prescribed correctly, the patients are given wrong dose levels or the drug is given for the wrong duration of therapy. This results in the development of resistance in the micro-organisms or the prevalence of adverse affects. Hence, it might become difficult to

cure diseases like certain abdominal infections and drug resistant tuberculosis that can only be treated with fluoroquinolones. Due to these reasons the fluoroquinolones are generally prescribed when all other antibiotics fail or cannot be used in case of resistant micro-organisms. If administered, the dose and the dosage regime will depend on the severity and type of infection, the susceptibility of the causative organism, the host-defence mechanism and the renal and hepatic function. Since the fluoroquinolones have a broad spectrum of activity even on resistant trains, they should be prescribed appropriately.

7. RESISTANCE

Resistance to fluoroquinolones is developed majorly due to three reasons. The first involves mutation of any one or both the enzymes: DNA gyrase and topoisomerase IV. This kind of mutation decreases the binding of the fluoroquinolones to the enzyme-DNA complex. If a mutation occurs only on one enzyme, the degree of resistance observed depends on the sensitivity of the enzyme targeted by the fluoroquinolones [25]. Mutations in the primary target will lead to higher degree of resistance than those in the secondary target. A stepwise mutation is built up by spontaneous mutations in the genes *gyrA, gyrB, parC* and *parE*, as well as mutations leading to the increased expression of efflux pumps, such as mutations abolishing the expression of a transcriptional repressor for the pump [64-66]. Here, the initial mutation may not have a significant effect in the development of resistance but may be important for the occurrence of subsequent mutations that lead to higher levels of resistance [67]. Such mutations, both single and stepwise, may lead to cross-resistance to other quinolones. Davis *et al* reported that all levofloxacin resistant strains of *Streptococcus pneumoniae* were not susceptible to gatifloxacin and moxifloxacin. They were also cross-resistant to ciprofloxacin [68]. Examples of mutations include *S. aureus* and *P. aeroginosa* that require only one mutation for sufficient degree of resistance. *E. coli* on the other hand, requires more than one mutation to confer resistance, especially to the newer class of fluoroquinolones. In *S. aureus*, mutations were observed in Ser-80 to Tyr of grlA, which is a homologue of parC [69]. In *Bacteriodes fragilis*, mutation was observed at Ser-82 to Tyr of gyrA [70]. Majority of the mutations in resistant *M. tuberculosis* are seen at codons 90, 91, 94 and 95 with the residue being Asp94 [71,72]. These mutations are equivalent to the mutation at Ser-83 of gyrA in *E. coli*, which is the resistance hot spot. An Asn 90Val mutation led to low level resistance, Asp 94 Ala and Asp 94 Val led to moderate level resistance and Ser91Pro, Asn 94 asp and Asn 94 asp led to high level resistance with the MIC of <16 µg/ml, and >64 µg/ml respectively. Because of the homology between DNA gyrase and topoisomerase IV, it has been concluded that the fluoroquinolones act on the same structural motif [73]. Acquisition of fluoroquinolone resistance in *C. difficile* has been associated with mutations in the active site of DNA gyrase is reported in few studies. Sequence analysis of subunits *gyrA* and *gyrB* showed that most drug-resistant isolates sharing the same single transition mutation (ACT to ATT) in *gyrA*, resulting in the amino acid substitution Thr-82→Ile. Few other isolates possessed a Thr-82→Ile and Asp-71→Glu (GAC to GAA) mutation and also showed a Thr-82→Ala (ACT to GCT) change [74]. The primary structures of these enzymes are conserved probably due to the importance of their function.

Another involves the differential expression of efflux mechanisms. These energy-dependent efflux pumps, on recognising an antibacterial compound as a potential substrate, force it out. The recognised compounds are usually hydrophilic. Over-expression of the efflux pumps will lead to multidrug resistance. Over-expression of *AcrAB, MdfA* and *NorE* efflux genes in *E. coli* has been shown to contribute individually and simultaneously as a group to fluoroquinolone resistance [75]. *Mycobacterium smegmatis* has the LfrA efflux pump to flush out the fluoroquinolones [76]. These pumps are translocases with 12-14 membrane-

spanning regions and transport out fluoroquinolones and other drugs in exchange of protons. Rv2687 gene coding for ABC transporter is responsible for conferring resistance to ciprofloxacin and to a lesser extent, norfloxacin, moxifloxacin and sparfloxacin in *M. Tuberculosis* [77]. Studies in *S. aureus* showed that the NorA efflux pump is involved in antibacterial resistance. Over-expression of the NorA efflux pump, brought about by a mutation, resulted in the increase in the MICs of various fluoroquinolones to various degrees [78]. Another efflux pump related to NorA was found in *S. pneumonia*, called PmrA. Its over-expression led to the increase in sensitivity to certain fluoroquinolones like ciprofloxacin and norfloxacin but had no effect on the newer generation of quinolones like moxifloxacin and sparfloxacin, which are hydrophobic in nature [79]. When sodium orthovanadate was used as it is an ATPase inhibitor and inhibits ATP-dependent efflux systems, such as ABC transporters.Sodium orthovanadate had no effect upon accumulation of any of the quinolones used in the study, suggesting that no ATP-dependent efflux pumps exist in anaerobic *B. fragilis* [80].

Another mechanism for resistance is due to the presence of a plasmid generally found in gram negative organisms that can be horizontally transferred [81]. This plasmid encodes for Qnr proteins (qnrA, qnrB and qnrS) that belong to a pentapeptide repeat family and bind mainly to DNA gyrase, thus preventing the binding of the drug to the enzyme. They are also known to have structures similar to DNA and thus act as a substrate to DNA gyrase. These factors greatly reduce the action of fluoroquinolones [82,83]. A multiresistance plasmid (pMG252) with a wide host range and that expresses quinolone resistance was isolated from *Klebsiella pneumonia* by Martinez et al. [84]. It leads to an 8 to 32-fold increase in the MIC of fluoroquinolones. There has been no plasmid mediated resistance observed in *M. tuberculosis*.

Resistance can be overcome by synthesizing drugs that act equally on both the enzymes: DNA gyrase and topoisomerase IV. This would require a concomitant mutation in both the enzymes to confer high level of resistance and this has less probability to occur than sequential mutations. Newer fluoroquinolone derivatives developed with the consideration of factors like hydrophobicity and structural features could avoid being pumped out by the efflux mechanisms [85]. In addition, the use of a quinolone as monotherapy or as the sole active agent in a multidrug regimen has often resulted in the emergence of resistance to the quinolone. Therefore, to forestall rapid selection of mutant strains resistant to the fluoroquinolones, these drugs are mostly used successfully in combination with at least one other active agent.

7.1 Bio Transformation

The different pathways are likely to be used by different microorganisms that involved in the bioconversion of fluoroquinolones in the environment. Fluoroquinolones are usually attacked at the piperazine or the *N*-methylpiperazine ring, or at the carboxyl group in animals and in fungi, it demethylates the *N*-methylpiperazine ring [86].

8. ADVERSE DRUG REACTION

The adverse effects of fluoroquinolones are the major reasons for using them as a last resort for therapy. Most of the side effects are mild to moderate like those related to the gastrointestinal tract or Central Nervous System (CNS). On some occasions the side effects can be serious like dysglycemia, Torsades de Pointes and hepatotoxicity [87]. Some of the

fluoroquinolones, like gatifloxacin tend to disturb the sugar levels in the blood leading to hypoglycaemia and hyperglycaemia (diabetes). Four cases of severe hyperglycemia were observed in non-diabetic patients with end-stage renal disease, when they were treated with maximum non-renally adjusted dose of gatifloxacin for bronchitis [88]. Some fluoroquinolones prolong electrocardiographic QTc interval because they block human cardiac K^+ channel HERG [89]. It has been reported that the C-5 substituent like a methy group as in sparfloxacin or an amine group as in grepafloxacin is responsible for prolonging the QTc interval by 14ms and 11ms respectively [90]. A prolonged QTc interval is indicative of arrhythmias like Torsades de Pointes and is considered a risk factor for sudden death. They are one of the most likely antibiotics which would cause the development of *Clostridium difficile* and MRSA infections. It has been observed that fluoroquinolones are responsible for 55% of all occurring *C. difficile* infections [91]. In different studies, ciprofloxacin and levofloxacin were found to be associated with *C. difficile* associated diarrhoea (CDAD) [92,93]. Sparfloxacin is associated with phototoxicity. It has been found that the reactive oxygen species, like superoxide anions, hydrogen peroxide and hydroxyl radicals produced by the UV illumination of fluoroquinolones leads to destruction of the target tissue, namely skin, mitochondria, etc. [94].

They also lead to toxicity of various organs such as liver, brain, CNS, heart etc. Hepatotoxicity occurs rarely, caused by the fluoroquinolones trovafloxacin and tosufloxacin [95]. A case study showed the occurrence of hepatocellular necrosis after the administration of gatifloxacin as a 10 day course. It was proved that there were no other causes of hepatotoxicity in the patient [96]. Fluoroquinolones, with fleroxacin and pefloxacin being the most potent, are known to cause Achilles tendon lesions in mice, with their severity dependent on the substituent in the seventh position [97]. They are also avoided in pediatric patients as they are prone to permanent musculoskeletal injuries. They may result in cardiovascular toxicity and cardiac arrhythmias [98]. Moreover, fluoroquinolones like moxifloxacin, are associated with side effects relating to the CNS namely convulsions and neurological and psychiatric toxicity which include confusion, agitation, anxiety, tremor, insomnia and in severe cases psychosis [99,100]. Fluoroquinolones also have been linked to several forms of ocular toxicity such as corneal perforations, optic neuropathy, and retinal hemorrhages [101]. These effects are caused because the position 7 substituents like piperazine or pyrrolidone are similar in structure to GABA and so competes for the GABA A receptor. These effects are augmented by the co-administration of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) [102].

In addition to direct effects on the body, they may also produce harmful effects by their interaction with other drugs. Administration of fluoroquinolones together with drugs namely theophylline, methylxanthines, and tizanidine that are metabolised by cytochrome P450, especially CYP1A2, leads to increased plasma concentrations of these drugs because they alter its biotransformation and hence increases the toxicity of the drugs due to their concomitant use [103]. Some fluoroquinolones are known to affect the metabolism of caffeine that increases the concentration of caffeine and hence causes the symptoms of caffeine overdose [104]. Coadministration with drugs that contain metal ions will delay absorption and hence if necessary, they must be separately administered with a gap of more than two hours. They are avoided in persons with a history of hypersensitivity to it, any member of the quinolone class of antimicrobial agents or any of the product components. Fluoroquinolones administration is often discouraged in pregnant women because they can easily traverse the placental barrier or through milk and get distributed in the fetus. This may cause abortions as well as birth defects and arthropathy in the immature child [105].

9. CONCLUSION

There are a lot of diseases that are caused by bacterial pathogens. They can be cured by administering antimicrobial compounds. The most commonly used antimicrobial are β-lactams, aminoglycosides, tetracyclins, macrolides, etc. Because of their indiscriminate or long term usage, micro-organisms have high probabilities of developing resistance to these compounds. This leads to the development of multiple and extensive drug resistance. Hence new antimicrobials that are effective against such micro-organisms are required. Fluoroquinolones are a new class of antibiotics that have potent antimicrobial activity against a wide range of gram positive and gram negative organisms. They have high bioavailability in the range of 70% to (in some cases) greater than 90%, even when given orally. Moreover, they attain high plasma concentrations and have high tissue penetration capacity. Their adverse effects are quite low when given for short durations of time, and some are found to be less frequent. Due to these reasons, fluoroquinolones have been increasingly used in the recent past. But care must be taken while prescribing the dose and the dosage regime so that the micro-organisms do not develop resistance to fluoroquinolones also.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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