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RESEARCH ARTICLE – MEDICINE (MISCELLANEOUS)

The Efficacy of Quinolones and Fluoroquinolones in the Medicine: a review study

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Abstract

Background: Previous studies have shown that several antibiotics have significant side effects in addition to their antibacterial ones, which are indirectly mediated by altering and controlling the mediators of the immune system. The synthetic antibiotics fluoroquinolones (FQs) were discovered that fluoroquinolones (FQs) have an impact on humoral and cellular immunity. Typically, FQs only have their moderating effects when combined with another stimulant.

Conclusion: This review presented the suitability of fluoroquinolones for potential use in medicine in order to manage several infectious diseases. These FQs are highly effective antibiotics against the bacterial infections. They are therefore prone to misuse, which can result in patients experiencing unwanted side effects and the continued development of antibiotic resistance. Even though quinolones can be used empirically to treat patients in an outpatient setting, doctors still need to follow up with patients to make sure the course of antibiotics is completed and to confirm the success of the treatment. When culture and sensitivity data are available, patients should be switched to more focused antibiotics so that quinolones can be stopped. It is advisable for clinicians to use another antibiotic if a patient is at high risk for serious side effects. In order to discuss alternate antibiotics, confirm dosage, and find any drug-drug interactions, a pharmaceutical consultation may be beneficial. In order to prevent serious side effects from occurring when using quinolones, the patient and their healthcare providers should be informed by the pharmacist and the doctor. Physicians should exercise caution while treating life-threatening gram-positive infections with quinolone antibiotics, even if the more recent fluoroquinolones have demonstrated encouraging in vitro activity against gram-positive bacteria based on MIC data. Future quinolone efficacy is likely to be constrained by the ongoing abuse of these antibiotics in clinical care and agricultural feed, which will encourage gram-positive and gram-negative resistance.

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Keywords: Fluoroquinolones; Quinolones; Chemical Structure; Immunomodulatory Effect; Intracellular Penetration.

1. Introduction

Some Middle Eastern and Mediterranean countries still have endemic cases of some incurable diseases that affect animals, especially sheep. Numerous zoonotic diseases, including salmonellosis, campylobacteriosis, and brucellosis, are problematic in both human and veterinary medicine. Food, water, direct touch, and insect vectors are the ways that zoonotic illnesses can spread from animals to humans [1]. Cohabitation between husbandry and humans may provide a health danger to both. Many illnesses have spread across the food chain as a result of severe food-borne outbreaks that have been documented in recent decades [2]. Enterohaemorrhagic Escherichia coli, Salmonella, and Campylobacter were the most common bacterial infections that caused these outbreaks. These pathogenic microorganisms have withstood the majority of traditional, widely used antibiotics used in animals, particularly those found intracellularly. Antibiotic use to treat a variety of illnesses, such as zoonotic infections in domesticated animals, may raise the risk of bacterial resistance in people through direct and indirect contact or the food chain [3].

Although the innate immune system is the first line of defense against microbial invasion, it can become dysregulated during an infection, increasing the pathogen burden and causing an excess of pro-inflammatory cytokines and chemokines to be secreted. This condition results in intravascular protein leakage into the alveolar lumen and disruption to the pulmonary alveolar epithelial–endothelial barrier. Fluoroquinolones are artificial antimicrobials that have immunomodulatory qualities that can both reduce inflammation and stop bacteria from growing. The structure of fluoroquinolones, especially those containing a cyclopropyl group, has been shown to have immunomodulatory effects [4]. However, if antimicrobial therapy is used sometimes as a test-treatment approach in diseased herds, there is minimal concern regarding the development of such resistance. This is because it would be more acceptable from an ethical, humane, and economic standpoint than using a

test-slaughter procedure. Therefore, an effective antibacterial agent—preferably one that can enter cells—would be required to eradicate these germs, reduce the number of affected animals, and lower the risk of zoonosis.

2. Synopsis and history of Quinolone antibiotics

The discovery of penicillin in 1928 and sulphonamides in the middle of the 1930s marked the beginning of the antibiotic industry. Later, starting in the 1950s, novel agents such erythromycin, tetracycline, chloramphenicol, and quinolone antibiotics are still being developed. Regretfully, many of the first antibacterial medicines that work immediately cause some organisms to become resistant. The quinolones' general chemical structure is depicted in Fig. 1. Quinolone antibiotics (Qs) are divided into two related subgroups: quinolones (one nitrogen at ring position 1) and naphthyridones (two nitrogens in the ring at positions 1 and 8). Fluorination at ring position 6 creates the fluoroquinolones (FQs), a key class of Qs [5].

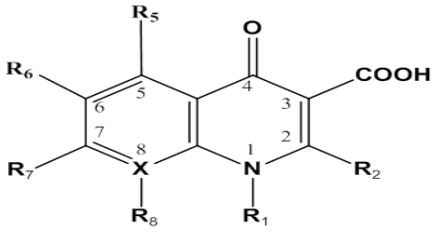

Fig. 1. The generic chemical structure of the quinolone antibiotics. (If X=N, the compounds are categorized as naphthyridones. If X=C, the compounds are termed quinolones. Fluoroquinolones are originated on the quinolone basic structure with fluorine at position 6

Nalidixic acid (Figure 2) was the first quinolone antibiotic to be nonfluorinated. When it was accidentally found, it was made available in 1962 to treat UTIs. Although flumequine Fig. 2 was the first FQ to be produced in the early 1970s, it was soon surpassed by more potent substances. Subsequently, structural alterations were made to naphthyridones, quinolones, and fluoroquinolones (such as substitutes at accessible locations on the quinolone ring) in order to improve the antibacterial activity of this antibiotic class. Since the 1990s, novel chemicals have been developed in response to the emergence of bacterial resistance. Compounds with improved potency, more extensive bacterial treatment, better dosage profiles, longer elimination half-lives, and appropriate safety features have been produced via structural changes. In order to treat a variety of bacterial illnesses, quinolone antibiotics are currently regarded as first-line treatments. The pharmacological characteristics of Qs have led to their classification into four generations [6], which will be covered in the next section..

Fig. 2. Chemical structures of initial quinolone antibiotics. (A) nalidixic acid, the first naphthyridone compound; (B) flumequine, the first fluoroquinolone

3. Chronology of development of Qs

During the manufacture of chloroquine, 7-chloro-1-ethyl-1, 4-dihydro-7 methyl-4-oxo-1, and 8-napthyrlidin-3-carboxylic acid was accidentally modified to produce naphthyridone quinolone compounds' basic structural core, naphixic acid Fig. 2. Two parallel paths have led to the production of Qs: (i) naphthyridones containing nalidixic acid's basic core, and (ii) FQs that emerge from fluorination at the basic quinolone nucleus's 6-position. The presence of a nitrogen (N) at position 8 in the naphthyridones and a carbon (C) at position 8 in the Qs is the primary distinction between them. Flumequine was the first FQ to be produced by altering the fundamental quinolone structure, while norfloxacin [7], was the first FQ to have greater antimicrobial activity. Quinolone agents have developed during the last 4 decades and are categorized into 4 generations.

4. Generations of Qs

In the 1960s, the first generation of Qs, which included naphthyridine and nalidixic acid, was created. Urinary tract infections were commonly treated with these Qs, which were somewhat effective against the majority of Gram-negative bacteria, with the exception of Pseudomonas aeruginosa as seen in Table 1. The 1970s saw the discovery of other Qs, including oxolinic acid, pipemidic acid, and cinoxacin; however, their effectiveness did not significantly increase until flumequine, the first monofluoroquinolone to be therapeutically utilized in domestic animals, was produced. This caused FQs to form more quickly [8]. The molecule known as norfloxacin Fig. 3 marked the beginning of the second generation of FQs at the end of the 1970s. This chemical exhibits more effectiveness against Gram-negative bacteria, including P. aeruginosa, a longer half-life, and less protein binding than the first generation. In 1980, it was approved for clinical usage. Following chemical changes to enhance FQs in the 1980s, fleroxacin, a trifluorinated quinolone, was produced with improved pharmacological characteristics. Ciprofloxacin and ofloxacin, which can be taken orally or intravenously, are examples of medications with increased bioavailability and antibacterial activity

that were produced as a result of further development of FQs. To combat a range of microorganisms, ciprofloxacin Fig. 3 is still often employed. The most effective second-generation veterinary FQ, particularly for poultry, was enrofloxacin until it was banned in the United States in 2005 [9]. Through the 1990s, a number of structural changes were made that produced compounds with antibacterial activity that also extended to Streptococci bacteria. Among them were levofloxacin, grepafloxacin, sparfloxacin, and temafloxacin [9, 12]. Their bioavailability was enhanced, which gave them a highly therapeutic efficacy in treating respiratory and urinary tract infections in addition to their broad spectrum antibacterial efficacy. Later, some of these quinolone compounds, like temafloxacin and grepafloxacin, were discontinued because of negative side effects [10].

Fig. 3. The chemical structural formulae of norfloxacin and ciprofloxacin

When Qs was first released in the late 1990s and early 2000s, its greater activity against gram-positive microorganisms and its efficiency against anaerobic microbes were its most important features. Moxifloxacin and gatifloxacin, two fourth-generation FQs, are useful in ophthalmology because of their exceptional efficacy against certain gram-positive cocci that cause keratitis and endophthalmitis. The novel FQ besifloxacin is most effective when applied topically as an antibacterial agent for the eyes. The majority of gram-positive bacteria, including anaerobic microbes and those resistant to ciprofloxacin, are effectively combatted by trovafloxacin, a naphthyridone quinolone of this generation. Among the agents in this generation, sitafloxacin and clinafloxacin are probably the most effective against a range of microorganisms. Two further newly created FQs, delafloxacin and garenoxacin, are currently undergoing clinical trials [11].

5. Mechanism of action of quinolones

The replication mechanism necessary for bacterial DNA synthesis primarily relies on two topoisomerase enzymes: topoisomerase II (DNA gyrase) and IV. DNA-enzyme cleavage complexes are produced by these enzymes Table 1. Qs inhibits both enzymes and stops the formation of DNA-enzyme complexes [12] . The interaction between the DNA-gyrase enzyme and the variable group at the quinolone's C-7 location is one way that this happens. According to Gootz and Brighty, the ternary complex that forms between DNA, DNA-gyrase, and the bound quinolone may be the cause of FQs' inhibitory function in DNA synthesis. Thus, Qs has bactericidal activity due to its suppression of bacterial DNA synthesis. Based on the presence of dividing bacteria and the requirement for RNA and protein synthesis, Morrissey divided quinolone antibacterial processes into four kinds (A, B, B1, and C). All Qs use Mechanism A, which necessitates bacterial growth and the creation of RNA or proteins. Another mechanism that works against bacteria that do not divide is mechanism B, which does not require active RNA or protein synthesis. Like mechanism B, mechanism B1 requires dividing bacteria but does not require RNA or protein synthesis. In contrast, Mechanism C does not divide bacteria but necessitates the creation of proteins or RNA.has subcategorized quinolone antibacterial mechanisms into four types (A, B, B1 and C) based on the existence of dividing bacteria and the need for RNA and protein synthesis. Mechanism A is basic for all Qs and requires bacterial multiplication and RNA or protein synthesis. Mechanism B is an additional mechanism active against non-dividing bacteria and does not require active protein or RNA synthesis. Mechanism B1, similar to mechanism B, does not require RNA or protein synthesis, but does need dividing bacteria. Mechanism C, in contrast, requires protein or RNA synthesis, but not dividing bacteria [12,13].

Table 1. Generations of Qs, mechanism of action and bacterial coverage [12]

Generation (years)	Representative agents (Year approved)	Targets		Bacterial Coverage		
		DNA gyrase	Topoisomerase IV	Anti-gram-Negative	Anti-gram-Positive	Anti-Others
1 st (1960s)	Nalidix acid (1962)	Yes	No	Narrow	No	No
2 nd (1970s-1980s)	Norfloxacin (1986) Ciprofloxacin (1987) Ofloxacin (1990) Enoxacin (1991) Lomefloxacin (1992)	No	Yes	Expanded	Limited	Limited atypical pathogens
3 rd (1960s)	Levofloxacin (1996) Trovafloxacin (1997) Gatifloxacin (1999)	Yes	Yes	Expanded	Expanded. Featured by activities against *S. pyogenes*	Expanded atypical pathogens
4th (2000s-)	Moxifloxacin (1999)	Yes	Yes	Expanded	Further improved	Anaerobic pathogens

6. Mechanism of resistance development

One of the main concerns when administering antibiotics is bacterial resistance, which can result from overuse of antibacterial medicines. The gyrase enzyme mutation or alteration, and less commonly the topoisomerase IV enzyme, is the primary mechanism of bacterial resistance to FQs. The bacterial species and the particular quinolone determine which target enzymes the bacterium will use to create resistance. The

decreased intracellular drug accumulation brought on by the active efflux of the Qs by antibiotic efflux pumps may be another cause of resistance [34, 35]. This method mostly involves hydrophilic FQs, such as norfloxacin. The transmission of resistance from one bacterium to another, known as plasmid-mediated quinolone resistance, is a recently reported mechanism that speeds up and expands resistance to this class of antibiotics [2,14].

7. Antimicrobial spectrum: strucure-activity relationships

The chemical structure of microorganisms determines how effective Qs is against them. Quinolone activity against Gram-negative bacteria like Enterobacteriacae (measured by MIC90) has not significantly increased since the creation of the first fluoroquinolone (norfloxacin) [3,15]. With distinct binding substituents at eight bondable locations of the basic quinolone unit or pharmacore, the quinolone structure affects the antibacterial action Fig. 4.

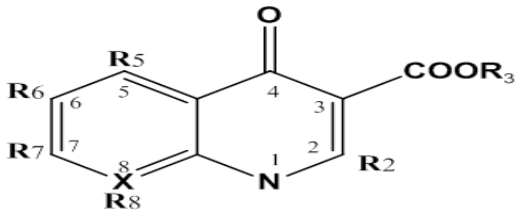

Fig. 4. The quinolone or naphthyridone pharmacore with 8 bondable positions. Adapted from. Where X is a carbon atom, the molecule is a quinolone. Where X is a nitrogen atom the molecule is a naphthyridone

The following are some possible sites for quinolone molecule modifications [4,16] :

7.1. Position 1. Strong activity against Gram-negative bacteria is provided by ethyl, cyclopropyl, or difluorophenyl groups . Position 1In vivo efficacy and increased activity against anaerobes are linked to the 2,4-fluorophenyl replacement. Additionally, pharmacokinetic characteristics may change if this position is modified.

7.2. Position 2. In order to offer antibacterial activity, this site must bind with DNA gyrase (or topoisomerase IV). Occasionally, this position complements positions 3 and 4.

7.3. Position 3,4: Due to their chelating properties, the 3-carboxylate and 4-carbonyl groups are thought to be essential for both transit into the bacterial cell and antimicrobial action through interacting with the DNA-gyrase complex.

7.4. Position 5. By changing the molecular shape, substituents at this position influence activity. The best groups at this location for action against Gram-positive bacteria are NH_2, OH, and CH_3. The gains in in vitro antibacterial activity brought about by modifications at this location, however, are not necessarily translated into improvements in in vivo activity in animal models for currently unknown reasons.

7.5. Position 6. The addition of a fluorine molecule at this location significantly increases bacterial cell penetration and gyrase inhibition, enhancing antibacterial efficacy, particularly against Gram-positive bacteria. The groups at sites 1, 7, and 8 continue to be important factors in determining the biological activity of these compounds, regardless of the substituent at this location.

7.6. Position 7. It is thought that the R7 substituent directly interacts with DNA gyrase or topoisomerase IV, greatly influencing the pharmacokinetics, spectrum, and efficacy of antibiotics. The most prevalent substituents are piperazines, which often offer increased potency against Gram-negative germs and higher efficacy *in vivo*, and pyrrolidines, which confer the greatest potency against Gram-positive bacteria. Quinolone pharmacokinetic characteristics are improved by the insertion of alkyl substituents at this location.

*7.7. Position 8***.** Like position 5, which largely regulates in vivo efficacy and increased antibacterial action, substitution at this point is thought to impact the overall molecular stearic structure. The groupings N, CF, and CC1 are the best ones. Oral pharmacokinetics and antibacterial effectiveness are influenced by certain groups, such as CF and CC1, usually against anaerobic species. The impact of these modifications can be clearly shown in Fig. 5.

The effectiveness of quinolone medicines against atypical, Gram-positive, and Gram-negative bacteria serves as an example of their progression. Since norfloxacin was first introduced, the potency against the *Enterobacteriaceae* group, as determined by MIC90 data, has not altered significantly. While second-generation drugs like ciprofloxacin are highly powerful anti-pseudomonal antibiotics, first-generation Qs like nalidixic acid and cinoxacin are thought to be ineffective against *Pseudomonas aeroginosa*. Many of the newer Qs, including moxifloxacin, garnefloxacin, and gatifloxacin, are less effective than ciprofloxacin against *Pseudomonas aeroginosa*, despite the fact that they are active against atypical microbes such as *Mycoplasma pneumonae*, *Chlamydia* species, *Mycobacterium*, and some have enhanced activity against anaerobes. The anti-Gram-positive activity of quinolones is one of the other noteworthy advancements in their potency. The most significant advancement has been in the ability of certain of these medications, particularly those with C-8-methoxy in their structures, to combat Group A streptococci, Streptococcus pneumoniae, and *S. aureus* that are resistant to ciprofloxacin.

Three key advantageous aspects of antibiotics are combined in FQs [1,17] :

- Improved antimicrobial action, especially against streptococci and other Gram-positive bacteria; enhanced activity against anaerobes.
- Better tissue dissemination and absorption pharmacokinetic profiles with a respectably extended half-life.
- A decreased metabolism of the liver.

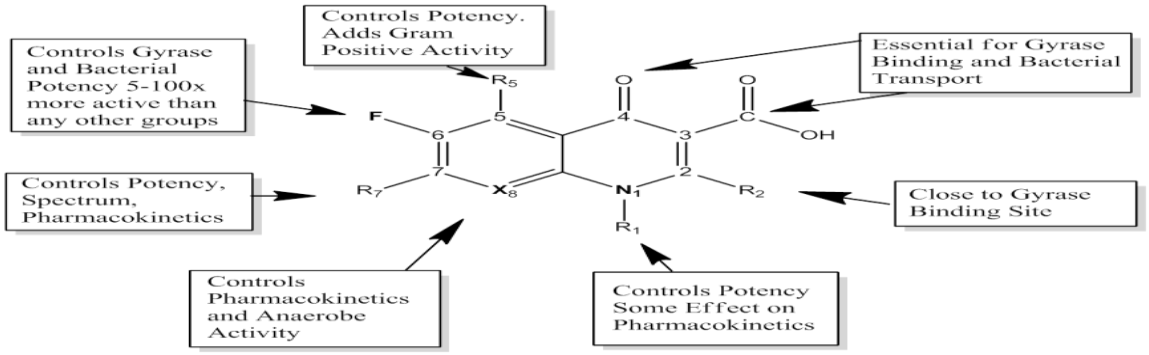

Fig. 5. A diagram demonstrations the effect of alteration at different positions of quinolone molecule. Adapted from [17]

8. Importance in humans and animals (clinical uses)

FQs have a wide range of actions against a variety of pathogens, which makes them suitable for treating both local and systemic infectious disorders brought on by a variety of Gram-positive, Gram-negative, and atypical bacteria. As a result, Qs is widely used in illness management for both humans and animals. Qs was most frequently used to treat urinary tract infections after nalidixic acid was introduced. Since FQs have a wider range of microorganisms, they are most frequently used to treat respiratory tract infections, particularly community-acquired pneumonia, which is typically caused by *S. pneumoniae*, *Haemophilus influenza*, or certain common bacteria like *Chlamydia pneumoniae*, *Legionella pneumophila,* and *Mycoplasma pneumonia*. Furthermore, FQs are commonly used to treat infections of the gastrointestinal tract, intra-abdominal tract, STIs, infections of the bones and joints, and disorders of the skin and soft tissues. Recently, certain FQs, such besifloxacin and moxifloxacin, have been created for topical use, specifically for ocular infections [1, 5, 18]. In the late 1980s, the first veterinary FQ to be licensed was enrofloxacin. Five additional FQ agents—difloxacin, danofloxacin, marbofloxacin, orbifloxacin, and sarafloxacin—then became accessible for use in animal medicine in the United States. The use of antibiotics as growth promoters in veterinary medicine has been prohibited due to the consequences of antimicrobial resistance in humans. However, certain FQs are now being studied, and others are currently being utilized therapeutically in animals. Qs is mostly used in animal medicine to treat respiratory infections, especially chronic respiratory disorders (CRD) in poultry that are brought on by *Mycoplasma synoviae* linked to E. coli. Additionally, they work wonders in treating respiratory illnesses in sheep and cattle that are brought on by *Pasteurella* and *Mannheimia* species and cattle and pigs that are brought on by *Mycoplasma* spp. For both topical and systemic treatment of cow mastitis, FQs are highly efficacious [6,19].

9. Quinolone pharmacokinetics in general

The pharmacokinetic characteristics of Qs are excellent. After oral administration, they are typically quickly absorbed, quickly distributed into bodily fluids, and primarily removed by the kidneys. After oral administration, Qs has a moderate to high bioavailability (60–95%). The majority of FQs have good penetration into bodily tissues like the skin, bones, and lungs; diseased tissue may have even greater penetration [20].

10. Side effects

The majority of antibiotics, including FQs, have some side effects, even though they are usually well tolerated. Both individual medications and diverse antibiotic classes have varied side effect intensity and quality. According to numerous studies, Qs's molecular structure plays a critical part in producing unwanted consequences Fig. 6. Therefore, in an effort to lessen the toxicity profiles of quinolones, scientists have tried to alter their structure [5,11].

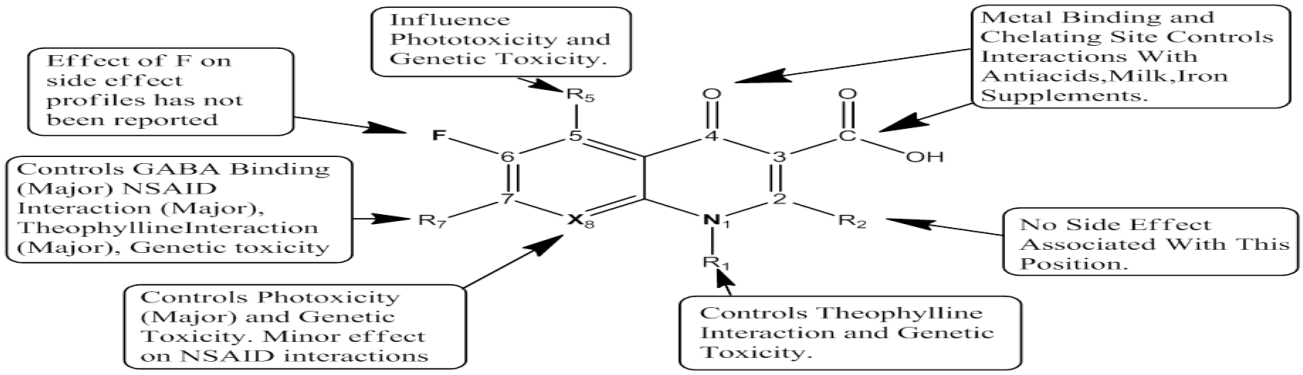

Fig. 6. A diagram presenting chemical structure-side effect relationships for the quinolone antibiotics. Adapted from [12,14]

10.1. Specific side effects

Some FQs exhibit specific side effects which might pose a significant risk to human or animal life.Some Qs may produce cardiovascular disturbances like hypotension, tachycardia, and QTC interval prolongation. Grepafloxacin and sparfloxacin were withdrawn from markets after severe cardiovascular events were reported [9,21]. Hepatotoxicity can result from extended use or high doses of antibiotics including Qs. Hepatic injury is most commonly associated with 8 methoxyquinolone agents. Most Qs show low frequencies of hepatotoxicity, but trovafloxacin was found to cause serious hepatic injury and was subsequently withdrawn from markets.Photosensitivity is a significant adverse effect of some FQs, particularly sparfloxacin, and to a lesser extent perfloxacin and lomefloxacin. The phototoxicity is affected by substitution at position 1, 5 and 8 of the quinolone pharmacore and is likely to be augmented in dihalogenated FQs such as clinafloxacin. The phototoxic reaction can be clinically manifested by erythema of sun-exposed areas with possible severe bullous eruptions. The response of fair-skinned persons is greater than dark- skinned persons. Uncommon dermatological adverse reactions not related to phototoxicity might occur during FQs therapy, including pruritis, edema, rash urticaria, dermatitis and hyperpigmentation [10,22].

About 1% of people who have taken FQs may have arthropathy problems that can be manifested by joint pain, stiffness and swelling of weight-bearing joints, especially knees. Arthropathy seems to be a general class effect that is not related to chemical structure of these agents; almost all Qs are reported to cause arthropathy at some doses [23]. Recently, tendinopathy has been identified as a side effect of these drugs, manifested by tendonitis and tendon rupture. The Achilles tendon is most commonly affected, with shoulder joints and hand less affected; these disorders may occur either unilaterally or bilaterally. Qs have been shown to cause some haematological abnormalities such as anemia, leukopenia, methemoglobinemia, granulocytopenia, and altered platelet counts or prothrombin time. DW-116, a new FQ with excellent pharmacokinetic and potency profiles, was shown to cause a transitory dose-dependent increase in the total white blood cells (WBCs) which resulted from the elevation of lymphocytes when it was taken orally for 26 weeks. A case report has shown a trovafloxacin-associated leucopenia during treatment of trauma. Severe thrombocytopenia associated with intravenous administration of ciprofloxacin, and alatrofloxacin therapy has been reported recently. Another study showed that concurrent administration of ciprofloxacin and tazobactam/piperacillin led to manifest thrombocytosis. A syndrome of hemolytic anemia, combined with renal and hepatic dysfunction, and/or coagulopathy (so-called temafloxacin syndrome) has been described in 95 patients, leading to the rapid withdrawn of temafloxacin from the market in 1992 [24].

10.2. Immunomodulatory effects and mechanism of action

The immune system plays a very important role in the prevention and therapy of bacterial infection. In addition to the direct interaction between antibiotics and bacteria, antibiotics can indirectly affect bacterial organisms by modulation of the immune system. Sepsis is considered a systemic immune reaction to severe infections and is mediated by systemic release primarily of pro-inflammatory cytokines (e.g., IL-1, IL-2, tumour necrosis factor α (TNFα)) and secondarily of anti-inflammatory molecules such as IL-10 [25]. FQs may interact directly (negatively or positively) with the immune system, or indirectly through their antibacterial activity to affect the immune system response. The interaction may involve changes of chemotaxis, phagocytosis, endotoxin release, cytokine production, and tumoricidal effects of specific cells, as well as induction or inhibition of apoptosis. Many studies have clearly shown that FQs demonstrate several immunomodulatory actions, primarily affecting cellular and humeral immunity via attenuating cytokine responses. Generally, they inhibit the production of IL-1, IL-6, IL-12, and TNFα and considerably enhance the synthesis of IL-10 and granulocyte-macrophage colony stimulating factor (GM-CSF). These mechanisms may be related to their capability to interfere with protein transcription, which may favour bacteria, as the interaction between Qs and type II topoisomerases is reported to be more selective for bacteria than mammals.

Previous studies have shown that Qs such as ciprofloxacin, sparfloxacin, clinafloxacin, and moxifloxacin were capable of enhancing immunity through a cyclopropyl moiety at position 1. Some Qs like ciprofloxacin and moxifloxacin induce increased production of certain cytokines such as interlukin-2 (IL-2) and IL-3, GM-CSF and gamma interferon (IFN-γ) in cultured human peripheral blood lymphocytes *in vitro* and in some models of immunosuppressed animals *in vivo*, and the effect of both compounds was dose dependent [26]. It has been shown that fluoroquinolones' structures, especially those containing a cyclopropyl group, have immunomodulatory effects. Inhibiting phosphodiesterase activity causes intracellular cAMP to build up, which in turn increases PKA activity, which in turn inhibits transcriptional factor NF-κB and activates cAMP response element-binding protein (CREB). TLR and ERK signaling pathway suppression is another mechanism that has been documented. The exact mechanisms behind the immunomodulatory effects of fluoroquinolones have been better understood, despite the fact that the exact sequence of events is still unclear [3,22]. Grepafloxacin inhibited the production of IL-1γ, IL-1β, tumor necrosis factor γ (TNFγ), IL-6 and IL-8 mRNA in lipopoly-saccharide-stimulated human peripheral blood cells. Generally, however, the concentrations of Qs required to produce a significant cytokine response in *in vitro* studies (apart from those showing IL-2 stimulation) were higher than those reached in clinical practice [2,15].

11. Penetration into phagocytes

Penetration of antibiotics into various host cells especially immune cells is very important to their effectiveness against various microbes, particularly intracellular bacteria. Penicillins, cephalosporins, and aminoglycosides enter cells very poorly and for that reason, they are inactive against intracellular bacteria, although they are highly effective antibiotics. In contrast, macrolides, lincosamines, rifamycins and FQs are considered to penetrate cell membranes well. Among various immunological cells, previous studies have been shown that Qs can penetrate into different white blood cells such as phagocytes, monocytes, macrophages and human neutrophils [88]. Some drugs such as clindamycin and ciprofloxacin are able to be concentrated into the phagocytic cell cytoplasm or vacuole while others like penicillins may fail to enter or bind with phagocytic cells after incubation of the antibiotics with phagocytes Fig. 7. The antibacterial agent that fails to enter or bind to the phagocyte membrane will be rapidly eliminated from the cell during washing and centrifugation, that takes merely few minutes for the macrolides and FQs [5,27]. In order to be active intracellularly, an antibiotic need to be in direct contact with bacteria which mostly exist in the phagosome of the phagocytic cell. Difloxacin and ciprofloxacin and to a lesser extent pefloxacin and flerofloxacin were found to be active against intraphagocytic *Staphylococcus aureus* and *Listeria monocytogenes* in normal neutrophils. Nguyen *et al* suggested that a lower concentration of levofloxacin in the phagosome compared to its concentration in other subcellular compartments contributed to its decreased activity against intracellular *S. aureus* in THP-1 monocytes [28,29].

The mechanism of Qs penetration into cells is not well defined. Using a radioisotopic technique in human neutrophils, Vazifeh *et al* postulated that intracellular accumulation of levofloxacin occurred by a solely passive process. On the other hand, Mémin *et al* reported that pefloxacin was actively transported at 42 °C in *in vitro* studies. Qs may penetrate into cells passively under normal physical conditions, while some may be actively transported when the temperature or pH is modified. While pefloxacin and fleroxacin were active in normal human neutrophils, they were not active in neutrophils with impaired phagocytic function from individuals with chronic granulomatous disease. In addition, difloxacin and ciprofloxacin were active in diseased neutrophils only at high concentrations. The author suggested that intraphagocytic antibiotic concentrations must be sufficient to activate an intact or impaired O_2-dependent intraphagocytic antimicrobial mechanism [30,31,32,33].

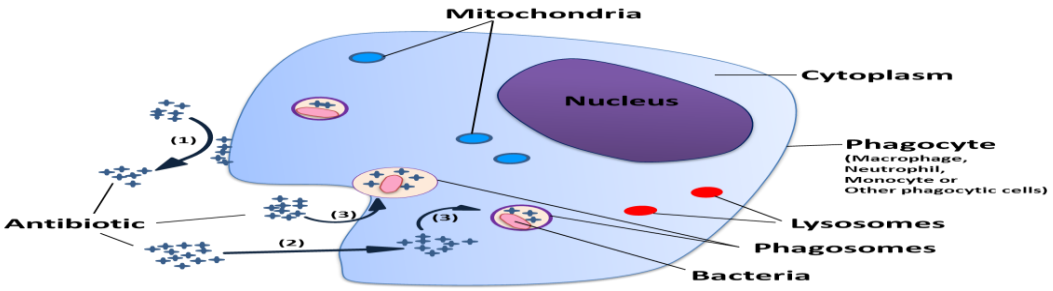

Fig. 7. The interaction between the antibiotic and phagocytic cell in relation to site of intracellular bacteria. (1) Antibiotic may bind to or fail to enter phagocytic cell; (2) antibiotic may penetrate into the cell and be concentrated in the cytoplasm; (3) antibiotic may penetrate into the cell and become localized in the phagosome containing bacteria. Adapted from [24].

12. Conclusion

This review presented the suitability of fluoroquinolones for potential use in medicine in order to manage several infectious diseases. These FQs are highly effective antibiotics against the bacterial infections. They are therefore prone to misuse, which can result in patients experiencing unwanted side effects and the continued development of antibiotic resistance. Even though quinolones can be used empirically to treat patients in an outpatient setting, doctors still need to follow up with patients to make sure the course of antibiotics is completed and to confirm the success of the treatment. When culture and sensitivity data are available, patients should be switched to more focused antibiotics so that quinolones can be stopped. It is advisable for clinicians to use another antibiotic if a patient is at high risk for serious side effects. In order to discuss alternate antibiotics, confirm dosage, and find any drug-drug interactions, a pharmaceutical consultation may be beneficial. In order to prevent serious side effects from occurring when using quinolones, the patient and their healthcare providers should be informed by the pharmacist and the doctor. Physicians should exercise caution while treating life-threatening gram-positive infections with quinolone antibiotics, even if the more recent fluoroquinolones have demonstrated encouraging in vitro activity against gram-positive bacteria based on MIC data. Future quinolone efficacy is likely to be constrained by the ongoing abuse of these antibiotics in clinical care and agricultural feed, which will encourage gram-positive and gram-negative resistance. Overuse of one agent will eventually cause the class as a whole to become resistant.

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Nomenclature & Symbols			
FQs	Fluoroquinolones	UTIs	Urinary Tract Infections
Qs	Quinolones	CRDs	Chronic Respiratory Disorders
IL1	Interleukin 1	WBCs	White Blood Cells
IL 2	Interleukin 2	TNF α	Tumour Necrosis Factor α
IL 6	Interleukin 6	GM-	Granulocyte-Macrophage Colony Stimulating Factor
IL 10	Interleukin 10	IFN-γ	Gamma Interferon
IL 12	Interleukin 12	CREP	cAMP Response Element-Binding Protein

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