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IMPORTANCE OF FLUOROQUINOLONES IN HUMAN HEALTHCARE: A COMPREHENSIVE REVIEW

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ABSTRACT: Fluoroquinoloes are a very important group of antibacterial agents that are widely prescribed for the treatment of infectious diseases in humans. These agents have excellent bioavailability and good tissue penetration with antimicrobial activity against pathogens especially resistance to other class of antimicrobial drugs. This article gives a comprehensive review on different aspects of fluoroquinolones such as discovery, structural modifications, pharmacokinetic properties, antibacterial activity, present status of important drugs in which pharmacists and medical microbiologists should be interested.

INTRODUCTION: Fluoroquinolones gained wide spread use as antibacterial drugs for the human healthcare after the development of norfloxacin and ciprofloxacin in 1980's. Thereafter more fluoroquinolones have been developed [1 - 2]. The usefulness of newer fluroquinolones has been greatly expanded due to their improved properties as compared to older members. Simultaneously fluoroquinolones resistance strains have also developed as a consequence of their heavy uses [3].

In view of this, the present article gives a comprehensive review on different aspects of fluoroquinolones especially present status of their clinical uses and development of resistance against bacteria.

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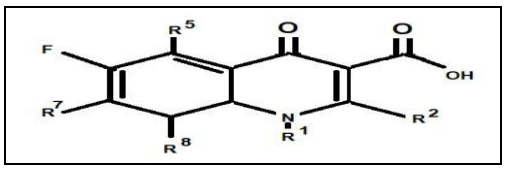
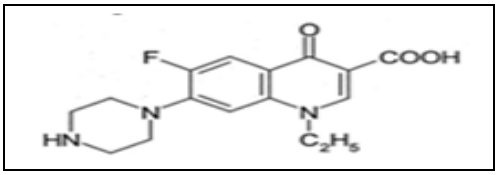
Background information:

The first quinolone discovered was nalidixic acid in 1962 as a byproduct of antimalarial research. Further structure modifications to the quinolone nucleus have resulted in the production of number of fluoroquinolones [1- 2, 4]. The selected important fluoroquinolones for human uses are present in Table 1 [4 - 6].

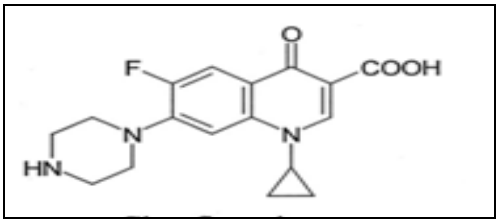
These structural modifications **Figure 1** have altered mainly to improve the pharmacokinetic and antimicrobial activity of the fluoroqunolones **Table 2** [5, 7- 8].



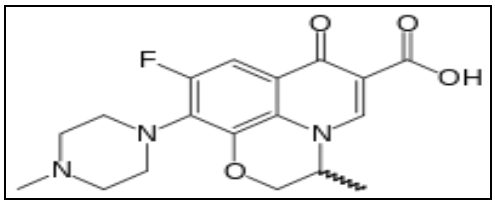
QUINOLONE



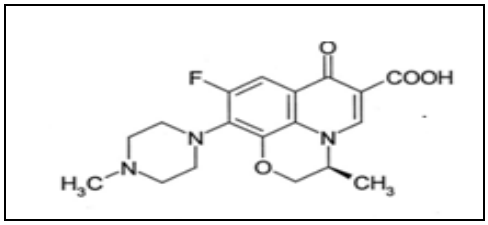
NORFLOXACIN



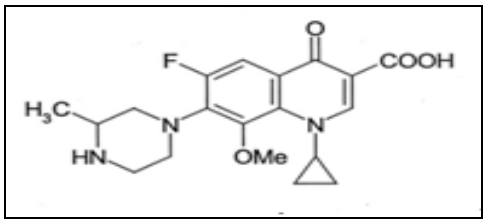
CIPROFLOXACIN



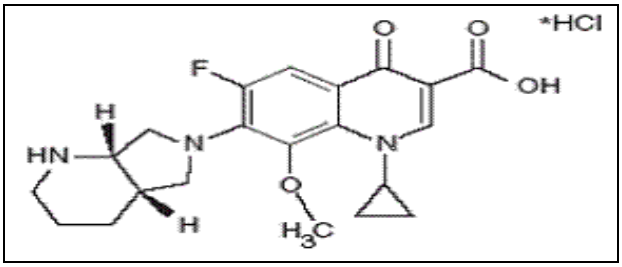
OFLOXACIN



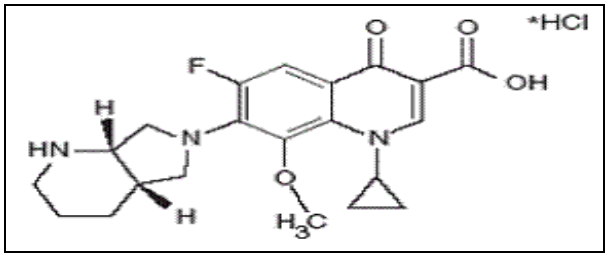
LEVOFLOXACIN



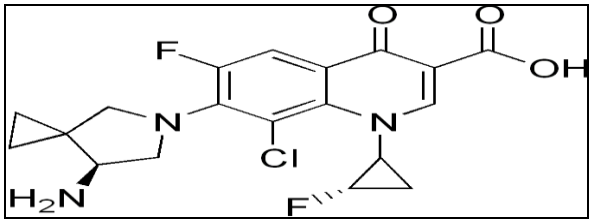
GATIFLOXACIN



MONOFLOXACIN



GEMIFLOXACIN



SITAFLOXACIN

FIGURE 1: CHEMICAL STRUCTURE OF CLINICALLY IMPORTANT FLUOROQUINOLONES AVAILABLE IN MARKET FOR HUMAN USE

TABLE 1: SELECTED CLINICALLY IMPORTANT FLUOROQUINOLOES

First generation	Second generation	Third generation	Fourth generation
Nalidixic acid	Norfloxacin, Enoxacin, lomefloxacin,Ciprofloxacin Ofloxacin, Levofloxacin Pefloxacin	Sparfloxacin, Gatifloxacin, Grepafloxacin,Temafloxacin, Tosufloxacin	Trovafloxacin, Moxifloxacin, Gemifloxacin, Sitafloxacin, Prulifloxacin

TABLE 2: STRUCTURAL MODIFICATIONS OF FLUOROQUINOLONES WITH SUPERIOR PROPERTIES.

- The fluoroquinolones have a basic structure of 4 quinolone–3–carboxylic acid. The common feature of all fluoroquinolones is that they have a COOH group at position 3 and a CO group at position 4 and a fluorine at position 6. The COOH group at position 3 and a CO group at position 4 increases hydrophobicity and therefore facilitates drug entry into gram negative bacteria by passive diffusion while fluorine at position 6 increase activity against gram negative organisms
- The addition of second fluorine group at position C-8 results in increased absorption and a longer elimination half life but also increased phototoxicity.
- The addition of piperazine group as in norfloxacin at position C-7 results in improved activity against aerobic gram negative bacteria and staphylococci species.
- Alkylation of the C-7 ring improved the activity against aerobic gram positive bacteria and half life.
- The addition of methyl group to distal nitrogen of the C-7 piperazine ring also increased the elimination of half life and improved bioavailability.
- The addition of a cyclopropyl group at position N-1 yield ciprofloxacin which has increased antibacterial activity against aerobic gram positive and gram negative pathogens.
- The addition of methoxy group instead of a halide at C-8 position decrease the possibility of the development of resistance to fluroquinolones.

Fluoroquinolones have favorable pharmacokinetic properties that have encouraged their widespread clinical usages **Table 3** [6, 9-10]. They are well absorbed and have good tissue penetration but absorption is inhibited by coadministration with antacids containing divalent metals such as magnesium, calcium and iron which they form insoluble chelates. Most fluoroquinolones are eliminated via the kidney. Moxifloxacin which is eliminated via the hepatic route is lacking antimicrobial activity against genitourinary infections.

The currently marketed fluroquinolones have safety profiles similar to that of other antimicrobial classes. Some of the serious effects occur with fluroquinolones includes CNS and tendon toxicity [11].

Fluoroquinolones have broad spectrum activity against many clinically important bacteria which are mainly responsible for the bacterial infections of urinary tract, gastrointestinal, respiratory tract and skin **Table 4** [12-17]. Fluoroquinolones exhibit concentration dependent antibacterial activity and inhibit the two bacterial enzyme, DNA gyrase [target for gram negative bacteria] and topoisomerase IV [target for gram positive bacteria].

TABLE 3. PHARMACOKINETICS OF CLINICALLY IMPORTANT FLUOROQUINOLONES.

Drug	Bioavaibality [percentage]	Protein binding [percentage]	Half life [Hours]
Norfloxacin	35-45	15	4-6
Ciprofloxacin	60-80	20-40	3-5
Ofloxacin	85-95	25	8
Levofloxacin	99	40	7
Moxifloxacin	90	50	13
Gemifloxacin	71	60	7
Sitafloxacin	70-94	50	7

TABLE 4: ANTIBACTERIAL ACTIVITY OF SELECTED IMPORTANT FLUOROQUNOLONES.

Drug	Clinical indication	Clinically important bacteria
Ciprofloxacin	Urinary tract infections	GNB-*- *Escherichia coli, Klebsiella pneumoniae Enterobacter cloacae,Serratia Serratia marcesce Proteus mirabilis, Providencia rettgeri, Morganella morganii, Citrobacter spp. , Pseudomonasa aeruginosa,* GPB**- *Staphylococcus epidermidis, Enterococcus faecalis*
	Respiratory tract infections	GNB*- *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis,Pseudomonas aeruginosa, Moraxella*m *catarrhalis, Haemophilus influenzae* GPB** -*Streptococcus pneumoniae.*
	Skin infections	GNB*- *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae,Proteus spp. Providencia, stuartii, Morganella morganii, Citrobacter freundi Pseudomonas aeruginosa.* *GPB*- Staphylococcus aureus, Staphylococcus epidermidis Streptococcus pyogenes*
	Bone and joint infections	GNB* - *Enterobacter cloacae, Sterratia marcescens, Pseudomonas aeruginosa.*
	Gastrointestinal infections	GNB* - *Escherichia coli, Campylobacter jejuni, Salmonella typhi*
Ofloxacin	Respiratory tract infections	GNB * - *Haemophilus influenza, Moraxella cutarrhalis* *GPB** - Streptococcus pneumoniae.*
	Urinary tract Infections	*GNB* - Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa Neisseria gonorrhoeae* *OB***- Chlamydia trachomatis*
	Skin infections	GNB* - *Proteus mirabilis* GPB – *Staphylococcus aureus, Streptococcus pyogenes*
Levofloxacin	Respiratory tract Infections	GNB* - *Haemophilus influenzae, Moraxella catarrhali Legionella pneumophila* *GPB**-Multidrug resistant Streptococcus pneumoniae, Staphylococcus aureus*

		*OB***-, Mycoplasma pneumonia*
	Skin infections	GNB*- *Proteus mirabilis* *GPB ** -Streptococcus pyogenes*
	Urinary tract infections	GNB- *Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* *GPB* - Enterococcus spp., Staphylococus epidermidi*
Moxifloxacin	Respiratory tract infections	GNB*- *Haemophilus influenzae, Moraxella cantarrhalis, Klebsiellal pneumoniae.* *GPB**-Multidrug resistant Streptococcus pneumoniae*
	Skin infections	GNB * -*Escherichia coli, Klebsiella pneumoniae Enterobacter cloacae.* *GPB **- Strptococcus pyogenes*
	Gastrointestinal infections	GNB* *Escherichia coli, Proteus mirabilis* *GPB**- Enterococcus faecalis, Clostridum perfringens.*
Gemifloxacin	Respiratory tract infections	GNB* *Haemophilus influenzae, Moraxella catarrhalis.* *GPB** Multidrug Sreptococus pneumonae,* *OB***Chlamydia pneumoniae, Mycoplasma pneumoniae*

** Gram Negative bacteria, ** Gram positive bacteria *** Other bacteria*

Present status:

General clinical use: Nalidixic acid, the first generation agent has moderate gram negative activity and minimal systemic distribution and today less often used [1].

Second generation fluoroquinolones such as ciprofloxacin, ofloxacin and levofloxacin have expanded gram negative activity but limited gram positive activity. Norfloxacin is primarily used to treat gastrointestinal or genitourinary infections [12]. It is good for bacterial diarrhea because high concentrations are present in the gut and anaerobic flora is not disturbed [9]. Ciprofloxacin is the one of the most potent fluoroquinolone active against a broad range of bacteria and used worldwide. It is used for the treatment of urinary tract infections, respiratory tract infections, skin, bone, joint and gastrointestinal infections caused by gram negative and gram positive bacteria [13.] Ofloxacin has intermediate antibacterial activity between ciprofloxacin and norfloxacin against gram negative bacteria but more potent than ciprofloxacin for gram positive organisms [9].

It is generally used for respiratory tract infections and urinary tract infections [14]. Ofloxacin is available worldwide. Levofloxacin [levoisomer of ofloxacin] having improved activity against *Strep. pneumoniae* and some other gram positive and gram negative bacteria [9.] The antibacterial spectrum of enoxacin, lomefloxacin and pefloxacin is similar to that of norfloxacin and use of these fluoroqunolones is now limited due to availability of newer highly active fluoroqunolones [18].

Third generation fluoroquinolones retain expanded gram negative and atypical intracellular activity but have improved gram positive coverage. The main advantages of sparfloxacin over older fluoroquinolone are its improved activity against gram positive pathogens (especially *Streptococcus pneumoniae, Staphylococcus aureus,* Enterococcus spp,), *Bacteroides fragilis and Mycobacteria* [9].

Sparfloxacin was withdrawn from USA market due to severe photosensitivity but remains available in Japan, India and some parts of Europe. Gatifloxacin has good activity against many gram positive and negative respiratory pathogens, atypical organism and some anaerobes [19]. However, gatifloxacin is associated with the risk of hypoglycemia and hyperglycemia [20]. Grepafloxacin and temafloxacin had a broad range of activity against gram positive as well as gram negative pathogens with some advantages but due to a high rate of reported adverse reactions including several death these were discontinued [21].

Tosufloxacin is used for the treatment of respiratory and gastrointestinal tract infections as well as genitourinary, hepatobiliary and orthopedic infections [22]. It has a controversial safety profile and associated with severe thrombocytopenia and nephritis, and hepatotoxicity [23]. It is available in Japan and some Asian countries.

Fourth generation agents improve gram positive coverage maintaining gram negative coverage and gram anaerobic coverage. Trovafloxacin had better positive bacterial coverage and less gram negative coverage than previous fluoroquinolones [22].

However it was withdrawn from the market due to the risk of hepatotoxicity [24]. Moxifloxacin has a broad spectrum activity and is used for the treatment of respiratory, skin and gastrointestinal infections [25, 26, 27]. Other clinical conditions in which moxifloxacin may be considered for use includes diabetic foot infections, intra-abdominal sepsis, pelvic inflammatory diseases and TB [28].

Gemifloxacin is used for the treatment of acute bacterial exacerbations of chronic bronchitis and commonly occurred pneumonia of mild to moderate severity [29]. Sitafloxacin was recently approved in Japan for the treatment of respiratory and urinary tract infections and especially very effective against methicillin resistant *Staphylococci*, *Streptococcus pneumonia* [30]. Prulifloxacin has been used in Italy and Japan for the treatment of urinary tract infection and also in several European countries for the treatment of urinary tract infections and exacerbations of chronic bronchitis [31].

Newer fluoroquinolones such as delafloxacin [32], zalbofloxacin [33] and finafloxacin [34] are undergoing different phases of clinical trials. Delafloxacin has an anionic character which results in a 10 fold increase in delafloxacin accumulation in both bacteria and cells at acidic pH. This property is believed to confer to delafloxacin an advantage for the eradication of *Straphylococcus aureus* in acidic environments including intracellular infections [32].

It is under phase III clinical trials for the study of acute bacterial skin infections [35]. Zabofloxacin is undergoing phase II clinical trials for the treatment of community acquired pneumonia. Finafloxacin is with the unique property of increasing antibacterial activity at pH values lower than neutral. It is undergoing safety profile studies in human.

Ophthalmic uses:

Topical fluoroquinolones are used as antibacterial for the treatment of ocular infectious diseases such as conjunctivitis, keratitis and endophthalmitis. Ciprofloxacin (0.3% solution), ciprofloxacin (3mg/g ointment), ofloxacin (0.3% solution), gatifloxacin (0.3% solution), levofloxacin (0.5% and 1.5 % solution) and moxifloxacin (0.5%solution) are most commonly used [36- 37].

A comparative study indicated that levofloxacin was highly active against *streptococcal pneumonia* and *streptococcus viridians* [isolated from keratitis and endophthalmitis patients] than ofloxacin and ciprofloxacin [38]. Further another study indicated that gatifloxacin and moxifloxacin were more potent than ciprofloxacin, ofloxacin and levofloxacin for gram positive bacteria and equally potent against gram negative bacteria. Duggirala and her colleagues [40] reported that levofloxacin, gatifloxacin and moxifloxacin were more effective against gram positive bacteria and ciprofloxacin was most effective fluoroquinolone against gram negative bacteria.

Emerging resistance:

With increasing utilization of fluoroquinolones in human health, emerging resistance for these agents has also increased. Various studies indicated that bacterial resistance to the fluoroqunolones is an emerging problem especially in Asia, America and other countries. [3 - 4]. Major resistance is developed due to three reasons [41]. The first involves mutation of any one or both the enzymes, DNA gyrase and topoisomerase IV. The second reason involves the differential expression of efflux mechanism and third is due to the presence of a plasmid generally found in gram negative organisms that can be horizontally transferred.

As fluoroquinolone resistance increase worldwide, enormous challenge will be placed on physicians and industry. Efforts to promote their judicious clinical use are therefore essential.

Research efforts are required for further modifications in the quinolone nucleus that may produce newer compounds which may have greater potency, better penetration into the CNS and cerebrospinal fluid, better patient tolerability with lower incidence of adverse reactions and serious toxicity. Further 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.

CONCLUSION: From all the information collected from various sources, it is observed that the fluoroquinolones have many favorable properties including broad spectrum activity. As a result they are widely used clinically and their uses as constantly growing. Misuse of these drugs has resulted in one of the problem of bacterial resistance that we face today. it is advised to use these drugs judiciously for specific condition.

In Australia [42] the use of fluroqiunolones in human and animals has been restricted through its national pharmaceutical subsidy scheme and through regulation. As a consequence resistance to fluoroquinolones in the country has been slow in emergence and has remained at low levels in key pathogens therefore appropriate use of fluoroquinolones will preserve its choice as an antibacterial drug for longer clinical uses**.**

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