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REVIEW

Fluoroquinolones Metal Complexes as Potent Antibacterial Agents

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In this review article, a brief discussion of fluoroquinolones (FQs) and their tendency to form metal complexes is presented. The effect of FQs-M complexes on disease causing microorganisms is also summarized. The antibacterial activity of various metal complexes of various fluoroquinolones [norfloxacin (NOR), ciprofloxacin (CIP), levofloxacin (LEVO), ofloxacin (OFL), gemifloxacin (GEMI), gatifloxacin (GATI), moxifloxacin (MOX), enrofloxacin (ENRO), sparfloxacin (SPRX)] is reviewed by comparing zone of inhibition and MIC values of metal complexes. It is found to be either corresponding with the parent fluoroquinolone or in some cases their respective metal complexes exhibit stronger antibacterial activity. New approach towards synthesis of FQ-metal complexes has led to formation of compounds with the anticancer and antiviral activity.

Keywords: Fluoroquinolones, Metal chelates, IR spectra, Antibacterial activities.

INTRODUCTION

The outbreak of contagious diseases brought about by various pathogenic microbes and the emergence of antibiotic resistance has drawn the worldwide attention of researchers for novel antibacterial agents. Quinolones are antibiotics with broad-spectrum activity, excellent capability of oral absorption and good bioavailability. The basic chemical structure of all quinolones includes a carboxyl (-COOH) group at the 3rd position, a carbonyl or keto group at the 4th position and mostly a heterocyclic ring with N-atom or basic piperazinyl ring at position 7, so they can behave as bidendate, unidentate and bridging ligand which is the basis of their extraordinary capacity to bind metal ion. The moiety present at C-7 and N-1 position in the ring has a great influence on the microbiological and pharmacological properties of drugs. However, several derivatives of quinolones, having different atoms at various positions of the ring structure, impart various desirable properties to the quinolones. For example, a fluorine atom at position 6 of ring structure of quinolone had given rise to a new subclass of this family, referred to as "fluoroquinolones" [1,2].

Fluoroquinolones led to extreme advancement in the field of synthetic bactericidal agents [3-5]. This class of drugs have emerged as an important drug with a high opportunity to gain much effective antimicrobial activity. Fluoroquinolones exhibit a comparatively higher broad spectrum behaviour, enhanced efficiency, better oral bioavailability, upgraded pharmacokinetics and good tolerability [6-8]. The area of bioinorganic chemistry, which manages the investigation of the role of metal ions in biological frameworks, has unfastened another perspective for scientific research toward this path. The pharmacokinetic behaviour of these metal complexes is profoundly reliant on the nature of metal cation, its ligands and the structure of the complex. It is realized that specific metal cation infiltrate into microorganism membrane and inactivate their enzymes or some metal ions can produce hydrogen peroxide, accordingly eliminating microscopic organisms. This exceptional property of metal complexes tends to offer favourable circumstances for the advancement of new drugs. Number of studies confirmed that various drugs possess mutated pharmacological and toxicological properties in their metal complexes.

Fluoroquinolone complexes of Cu^{2+} have demonstrated to be useful in several diseases such as rheumatoid arthritis, tuberculosis, gastric ulcers and cancers [9-12]. Similar studies reveal that in Mg^{2+} complexes of drug, the metal ion is highly helpful in destroying the gyrase-DNA complex and thus, enhances its antibacterial activity [13]. These results encouraged researchers to research in the area of complexes of antibiotics with transition and lanthanide metal ions in an attempt to investigate biological activities. In this review article, metal complexes of FQs-norfloxacin (NOR), ciprofloxacin (CIP), levofloxacin (LEVO), ofloxacin (OFL), gemifloxacin (GEMI), gatifloxacin (GATI), moxifloxacin (MOX), enrofloxacin (ENRO), sparfloxacin (SPRX) and their comparative antibacterial activities are reviewed.

Fluoroquinolones: Modified quinolones

Quinolones: Quinolones as antibacterial agents have been in medicinal use since 1960s. The first quinolone (nalidixic acid) was introduced as a curative agent of urinary tract infections in 1963, since then quinolones have been in use as an important means to treat numerous infections such as soft tissue infections, respiratory infections, acute bronchitis, bone-joint infections, sexually transmitted diseases, prostatitis and typhoid fever [14]. Quinolones act by effectively interfering in DNA replication of microorganisms by inhibiting the activity of two enzymes-DNA gyrase (topoisomerase II) and Topoisomerases IV, responsible for replication process. The broad spectrum behaviour of these drugs leads to development of a plethora of novel quinolone derivatives, exhibiting diverse structural modifications and advanced biological activities.

On the basis of their chemical structures, this group of drugs can be classified into four classes [15]:

(i) **Naphthyridine:** Examples–nalidixic acid, enoxacin, gemifloxacin, tosufloxacin.

(ii) **Cinnoline:** Example–cinoxacin.

(iii) **Pyridopyrimidine:** Example–pipemidic acid, piromidic acid.

(iv) **4-Quinolone:** Example–oxolinic acid, flumequine, norfloxacin, ciprofloxacin, ofloxacin, levofloxacin, sparfloxacin.

General chemical structure of quinolones is given in Fig. 1, where R_1, R_2, R_5, R_6, R_7, R_8 indicate possible positions of structural modification and X, Y, Z varies with different classes.

Based on their antibacterial behaviour, their clinical indications and their pharmacological behaviour, the quinolones can be classified in four generations [16,17] as shown in Table-1. First-generation quinolones exhibit minimum serum levels,

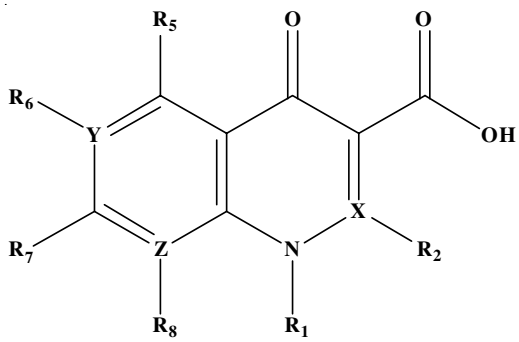

Fig. 1. (1) Naphthyridine (8-aza-4-quinolone): X = C, Y = C, Z = N; (2) Cinnoline (2-aza-4-quinolone): X = N, Y = C, Z = C; (3) Pyridopyrimidine (6,8-diaza-4-quinolone): X = C, Y = N, Z = N; (4) 4-Quinolone: X = C, Y = C, Z = C

second-generation drugs possess higher Gram-negative activity, third-generation drugs show enhanced antibacterial activity counter to Gram-positive bacteria and specific microorganisms whereas fourth-generation drugs achieve fascinating action against anaerobic pathogens.

Fluoroquinolones: Microbes developing resistance to antibiotics is the greatest health risk of the modern world. The rise and spread of antimicrobial resistance is a mind boggling issue driven by many interconnected elements: the over consumption of antibiotics, not following completion of treatment courses, their misuse due to lack of access to appropriate treatment [18], alterations in membrane permeability of bacteria and accumulation of several bacterial mutations [6]. However different chemical replacements have occurred over the decades, trying to widen the range of spectrum of activity and strength of the quinolones. The fluoride substitution in the original ring structure of quinolone (R_6 in Fig. 1), is a step ahead in this direction which has led to a new subclass of quinolones, 'the fluoroquinolones' that have better potency, improved spectrum of antibacterial properties, better oral bioavailability, upgraded pharmacokinetics and good tolerability. Fluoride substitution at R_6 position has been proved to expedite the penetration of bacterial cells [16] and thus sufficiently increased the spectrum of activity. By comparing fluorinated and non-fluorinated quinolones, Domagala *et al.* [19] illustrated that gyrase-complex binding ability of the antibiotic is improved 2-17 times by substituting fluorine in the ring structure, which is essential for the antimicrobial action of the drug.

In general, the chemical structure of most FQ, a -COOH group and a >C=O group are present at position 3 and position 4, respectively so they are commonly referred to as 4-quinolones

TABLE-1
CLASSIFICATION OF QUINOLONES

Generation	Agents	Antimicrobial spectrum
First generation	Nalidixic acid, cinoxacin, pipemidic acid, piromidic acid, rosoxacin, oxolinic acid, flumequine	Gram-negative stain pathogens (but not *Pseudomonas* species)
Second generation	Norfloxacin, enoxacin, ofloxacin, ciprofloxacin, pefloxacin, enrofloxacin, lomefloxacin	Gram-negative stain pathogens (including *Pseudomonas* species) and some Gram-positive stain pathogens
Third generation	Levofloxacin, sparfloxacin, gatifloxacin, moxifloxacin, balofloxacin	Gram-negative and Gram-positive microorganism with enhanced activity against specific pathogens
Fourth generation	Trovafloxacin, alatrofloxacin, clinafloxacin, sitafloxacin	Similar to third generation drugs along with broad activity against anaerobic organisms

(Fig. 2). In addition to that presence of piperazine ring or methyl piperazinyl group at position 7 and fluorine atom at position 6, upgraded the spectrum of their activity. Different groups are present at the position N(1) and C(7), which has a robust influence on the microbiological and pharmacokinetic properties of drugs.

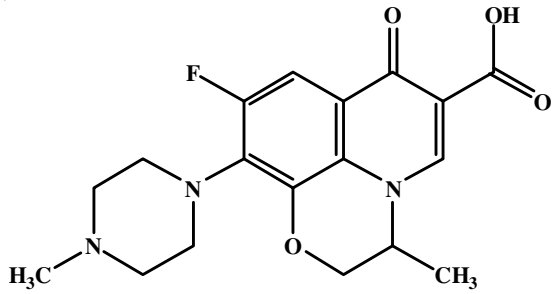

Fig. 2. 4-Quinolone: Fluoroquinolone

Broadly, bactericidal agents can be categorized on the basis of their principal mechanism of action. They are found to follow 5 primary modes of action: (i) interference in synthesis of cell membrane, (ii) interference in peptide synthesis, (iii) inhibition of replication process (iv) blockage of a metabolic pathway and (v) disruption of structure of bacterial membrane [17]. FQ's mode of action is through interference in nucleic acid synthesis by targeting DNA gyrase and topoisomerase enzyme, which helps in replication of bacterial DNA. Thus these drugs act as specific inhibitors of the bacterial DNA gyrase (topoisomerase II) and topoisomerase(IV), to finally hinder DNA transmission activity. Instead of DNA-enzyme binary complex, these drugs bind to form a ternary complex of DNA-enzyme-FQ, which deforms DNA-enzyme complex [13] and causes inactivation of these enzymes, thus helping in killing the bacteria. Because of the specific mode of action, FQ are recognized as broad-spectrum antibiotics which have furious action against Gram-negative and Gram-positive bacteria.

Between pH 3-11, FQ exists in the form of zwitterion, which is a legitimate species for efficiently penetrating the microbial cell membrane. At pH 1, it exists mostly(99.9%) in completely protonated form, whereas at pH 7.4 all the species are in comparable proportion [20]. These microspecies play a vital role in complex formation with metal ions. Quinolones and FQs possess admirable capability to form complexes with various metal ions. It is recommended that for metal chelates, the interaction of metal ions with parent drug is essential for their activity as bactericidal agents. The recognition of, role of metal ions in functioning of the biological system and use in medication process, has drawn attention for investigation of interaction between metal ions and FQs.

Metal chelates of fluoroquinolones: Like quinolones, FQs also possess extraordinary capability to bind to metal ions, the reason being the presence of donor atoms in their aromatic ring. The conduct of these drugs and their metal complexes has been analyzed in various ways. The interaction of metal ion with the FQ was suggested through the >C=O and -COOH group present in ring structure. FQs can bind to several divalent or trivalent metal ions, such as Mg^{2+}, Cd^{2+}, Ca^{2+}, Mn^{2+}, Ni^{2+}, Cu^{2+}, Co^{2+}, Zn^{2+}, $Fe^{2+/3+}$ and Al^{3+} and may result in alteration of their antimicrobial activity [20-22]. For example, complexes with Mg^{2+} and Al^{3+} were reported to show decline in the activity of the drugs, but the Fe^{3+} and Zn^{2+} complexes were proclaimed to have higher activity [12]. The FQs can behave in either way *i.e.* as bidentate, unidentate or bridging ligands in their metal complexes. Most commonly, when the FQs behave as bidentate ligand, they are chelated from one oxygen atom of carboxyl anion and the other oxygen of ring carbonyl group (Fig. 3a). However, less common possibility of their chelation as bidentate ligand is when FQs are coordinated either with both the carboxylic oxygen atoms (Fig. 3b) or with both piperazinyl nitrogen atoms (Fig. 3c). FQs can also act as unidentate ligand by binding through terminal piperazinyl nitrogen (Fig. 3d).

FQs can form complexes with metal-ligand ratio as 1:1 or 1:2 while binding to divalent cations (Mg^{2+}, Cu^{2+}, Fe^{2+}, Co^{2+} Zn^{2+}, Ca^{2+}, *etc.*) or as stoichiometric ratio 1:1, 1:2 or 1:3 with trivalent cations ($A1^{3+}$, Fe^{3+}, *etc.*). The FQs having a piperazinyl ring at 7th position in ring structure can form complexes as unidentate ligand with terminal piperazinyl nitrogen involving in the chelation to the metal ion. This bonding is observed in complexes of metals Ag^{+} Au^{3+} and Ru^{3+} [23]. In few complexes of Ru^{3+}, with general formula as $Ru(L)_2Cl_3(DMSO)_m{\cdot}xH_2O$, where L can be pipemidic acid, ciprofloxacin, enoxacin, norfloxacin, enrofloxacin, ofloxacin or levofloxacin, FQs act as unidentate ligand and are coordinated through the N-4 piperazinyl nitrogen [24,25]. Similarly in complexes $[Mg_2(H_2O)_6(NOR)_2]$-$Cl_4{\cdot}4H_2O$ and $[Ca_2(Cl)(NOR)_6]Cl_3{\cdot}10H_2O$ [26], FQ(norfloxacin) act as bidentate bridging ligand when bonding occurs *via* one oxygen atom of carboxylic group and other oxygen atom of pyridone group.

Numerous investigations have revealed that these metal complexes exhibit an admirable antimicrobial activity as compared to the free antibiotic [27-32]. Central metal cations are fit for arranging surrounding ligands to obtain pharmacophore geometries. Metals have assumed a significant part in the

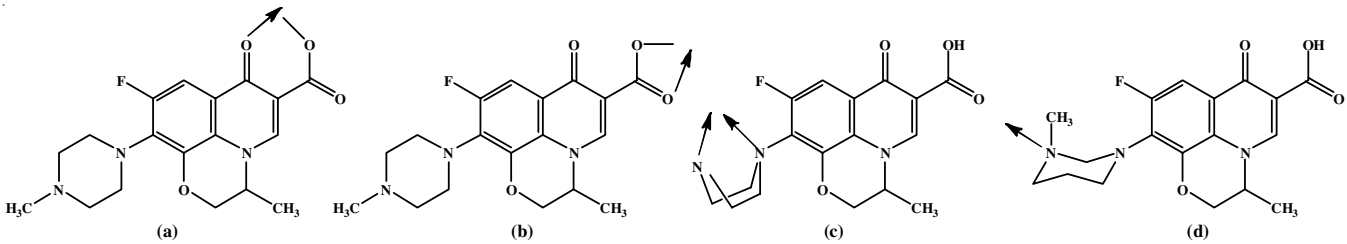

Fig. 3. Ligand coordinated through carbonyl oxygen and carboxylate oxygen (a), through both the carboxylic group oxygen (b), through both piperazinic nitrogen atoms (c) and through terminal piperazinyl nitrogen (d)

medicines field for quite a long time, since the time human beings began to stroll on the planet. Ancient Egyptians utilized copper metal for purification of water whereas gold was utilized in a number of prescriptions in Arab and China. Metal ions have a decisive role towards interactions of these drugs with different biomolecules [33]. Metal complexes have been utilized to treat different infections and illnesses for a long time and seem to give a rich stage to the plan of novel chemotherapeutic medications.

However initially, metal chelates were found to exhibit declined activity as compared to drugs. In 1985, there was first information that antacid containing Mg^{2+} and Al^{3+}, when taken along with ciprofloxacin, caused a nearly complete loss of activity of the drug [34]. But nowadays it has been established that the metal chelate of FQs exhibits not only magnificent bactericidal properties but also good antiviral, anticancer, anti-inflammatory properties. FQ-metal complexes are extremely helpful in the combat counter to bacterial resistance, as they possess greater lipophilicity which is attributed to the chelation effect [35]. Thus it offers a different way of action, which also includes their capacity to combine with DNA. Various researchers proclaimed that the antimicrobial activities of FQs were enhanced due to involvement of divalent cations [36]. The *in vivo* behaviour of FQs as bactericidal agents was robustly influenced by their capacity to form complexes with metal ions [37]. Latest researcher's data described the important role of the Cu^{2+} and Mg^{2+} ions in the mechanism of action of FQs.

Truel *et al*. [38] reviewed the interaction of metal ions with quinolones and debated the physico-chemical properties and crystal structure of quinolone-metal complexes [38]. Further in 2008, Serafin *et al*. [39] reviewed the biological activities and structural characteristics of few FQ metal complexes. Later in 2013, Psomas *et al*. [17] and Valetina [40] separately updated a comprehensive review of structural and biological properties of quinolone metal complexes. Recently, Ana-Madalina *et al*. [41] explained in their review, the chemical and biological properties of various quinolone-metal complexes of lanthanide ions along with analytical applications for their quantitative determination. In this review article, antibacterial activities of various FQ-metal complexes were also reviewed by comparing their MIC values and zone of inhibition.

Antibacterial activities of metal complexes: The effect of formation of metal complex on the antimicrobial behaviour of quinolones was explained first of all as a negative phenomenon and some results indicating decrease in the antimicrobial behaviour of quinolones due to the presence of metal ions [42,43] further toughen this assumption. However, for most of the solid state metal complexes of FQs, similar or superior antimicrobial behaviour was reported when compared with that of parent ligand drugs. The chelation theory and overtone concept of cell permeability was helpful in explaining enhanced biological activity of metal chelates. Consequent to chelation, the polarity of a metal ion is decreased. Reason for decrease in polarity can be explained because of the positive charge being shared partially with the donor ligand and due to overlap with the orbitals of ligand. The delocalization of π-electron cloud over the entire ring increases due to chelation and which leads to increase in lipophilic nature of the central metal ion. This enhanced lipophilicity leads to increase in the penetration of complex through the lipid biomembranes of microorganisms and thus penetrating in cells [44-46].

Various factors that should be considered to study antimicrobial activity of metal complexes include: (i) the nature of the metal ion and ligand; (ii) chelate effect; bidentate ligands show higher antimicrobial activity than monodentate ligands. (iii) the overall charge of the complex; mostly the antimicrobial activity follows the order: cationic complex > neutral complex > anionic complex, (iv) quality or type of the ion neutralizing the ionic complex; and (v) the nuclearity of the metal centre in the complex [47-51].

The results to indicate the antibacterial activity is expressed as MIC values (minimum inhibitory concentration, μg mL^{-1}) or as zone of inhibition (mm). MIC is the minimum concentration of compound which is sufficient to inhibit the growth of microorganism. Inhibition zone diameter in mm, can be measured *via* disc diffusion method, qualitative antimicrobial susceptibility test. Antibacterial activities of metal complexes of various FQs are reviewed in this article. The MIC values in μg mL^{-1} and diameter of zone of inhibition in mm of FQs and its metal complexes are collected from various research papers to compare their antibacterial activities. The interaction of one metal complex with one microorganism is considered as one case for analysing and comparing the antibacterial behaviour of complexes with parent FQ.

Levofloxacin: The antibacterial properties of metal chelates of LEVO against various Gram-negative and Gram-positive bacteria were studied. Several metal ions *viz*. Mn^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} exhibited higher activity than the drug itself in more than 50% cases (Fig. 4), whereas Co^{2+} exhibited higher and lower antibacterial activity than the ligand in almost equal cases. It is reported that Mn^{2+} and Cu^{2+} complex showed enhanced bactericidal properties than parent drug against all the test strains except *C. hofmannii*. The Co^{2+}, Ni^{2+} and Zn^{2+} complex

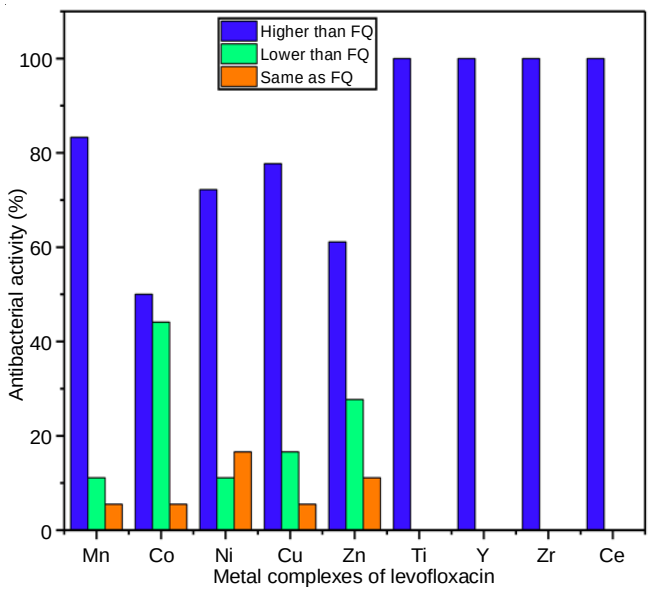

Fig. 4. Antibacterial activity of LEVO-metal complexes

exhibited better activity against *S. aureus* [52], whereas heavy metal complexes like Ti^{4+}, V^{4+}, Y^{3+}, Ce^{4+} and UO_2^{4+} were found to show higher activity against all microorganisms investigated by Sadeek *et al.* [53].

Sparfloxacin: Comparing the antibacterial activity of SPRX with its metal complexes, almost all complexes are found to be more potent than the parent drug. In 2010, complexes of Mg^{2+}, Cr^{2+}, Mn^{2+}, Zn^{2+}, Ca^{2+}, Co^{2+}, Cu^{2+}, Cd^{2+}, Ni^{2+} Fe^{3+} and Fe^{2+} with SPRX were synthesized, characterized and analyzed for antimicrobial properties by Sultana *et al.* [54]. Experimental data against a series of Gram-positive and Gram-negative bacteria suggest that most of the complexes exhibited extra-ordinary capability to act as antibacterial agents. Fe^{2+}–SPRX complex was found to exhibit superb activity against almost all strains whereas Mn^{2+}, Mg^{2+} and Cr^{2+} displayed a little activity. The platinum complexes of SPRX analyzed by Patel & Patidar [55] showed the higher antimicrobial behaviour of the complexes as compared with the parent drug El-Gamel & Zayed [56] synthesized binary complexes by mixing metal chlorides for Cu^{2+}, Co^{2+}, Ni^{2+}, Mn^{2+}, Cr^{3+} and Fe^{3+}, nitrate for UO_2^{4+} and La(III) with SPRX. Ternary complexes of the same metal ions were also synthesized with DL-alanine. Analysis of antimicro-bial behaviour of these complexes suggested that bactericidal properties of binary and ternary complexes of Cu^{2+}, Co^{2+}, Ni^{2+}, Mn^{2+}, Cr^{3+} and Fe^{3+} was superior than SPRX whereas its similar to SPRX for UO_2^{4+} and La^{2+} complexes (Fig. 5).

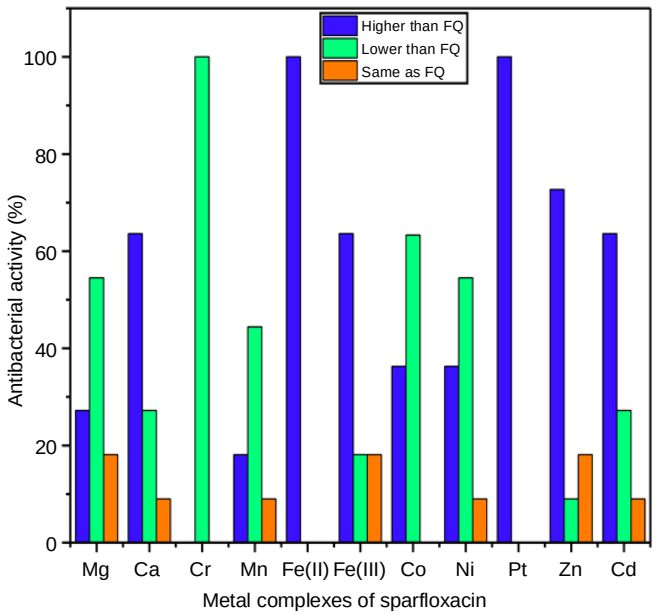

Fig. 5. Antibacterial activity of SPRX-metal complexes

Gatifloxacin: Gamil *et al.* [57] studied the ternary complexes of GATI with few transition metal ions. Coloured complexes of Mn, Fe, Co, Ni, Zn were prepared by using $CoCl_2{\cdot}6H_2O$, $FeSO_4$, $NiCl_2{\cdot}6H_2O$, $CuCl_2{\cdot}2H_2O$ and $ZnSO_4$ in acetone, respectively, in 1:1:1 (M^{2+}:GFLX:Preg) molar ratio. Their antibacterial and antifungal properties were compared and found to show remarkable antibacterial but no fungal activity. Sultana *et al.* [58] studied the bactericidal behaviour of Mg, Ca, Cr, Mn, Fe, Co, Ni, Cu, Zn, Cd with GATI and concluded that all metal complexes, except Cd displayed excellent activity against Gram-positive strain of bacteria whereas envisioned varied activity against Gram-negative strain. *In vitro* biological properties of ternary complexes of GATI with Cu^{2+} and Zn^{2+} metal ions and 2,2′-bipyridine (bipy), 1,10-phenanthroline (phen) and 2,2′-bipyridylamine (bipyam) as co-ligands, were analyzed separately by Kostelidou *et al.* [59] and Kakoulidou *et al.* [60], respectively. All the ternary complexes exhibited better antibacterial activity than GATI. Fe^{2+} exhibited higher or similar activity with respect to the complex against almost all strains whereas Cd^{2+} was found to show minimum activity (Fig. 6).

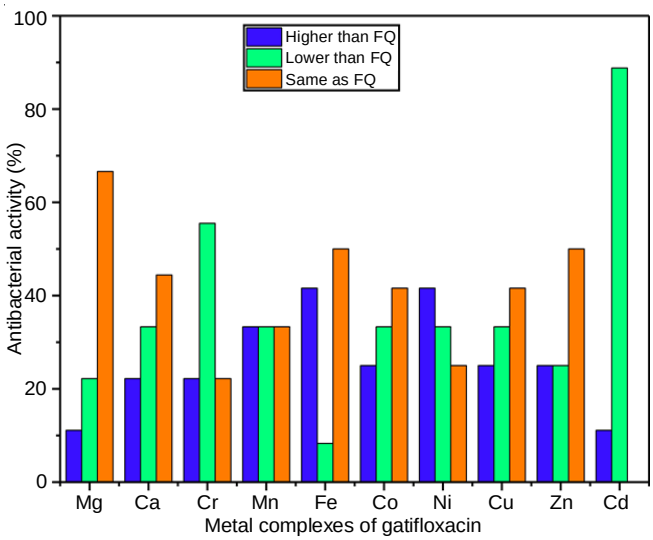

Fig. 6. Antibacterial activities of GATI-metal complexes

Enrofloxacin: Antibacterial activity of ENRO-metal complexes with Mn^{2+}, Fe^{2+}, Ni^{2+}, Co^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+} were reviewed by Cuprys *et al.* [53] and concluded that bactericidal behaviour of complexes was either higher or similar to the ligand. Efthimiadou *et al.* [61] studied the binary and ternary complexes of Cu^{2+} and ENRO. Ternary complexes, [Cu(ENRO)-(phen)]Cl and [Cu(ENRO)(bipy)(H_2O)]Cl were obtained by replacing one ENRO unit from binary complex, $Cu(ENRO)_2$-(H_2O), with the co-ligand. It was observed that binary complexes had better antimicrobial behaviour than ternary complexes. Few complexes *viz.* Mn^{2+}, Ni^{2+}, Cd^{2+} complexes exhibited activity similar to ENRO in almost all cases and Fe^{3+} exhibited higher activity than the parent against all microorganisms (Fig. 7).

Gemifloxacin: Mixed ligand solid complexes of GEMI as primary ligand, 1,10-phenanthroline as auxiliary ligand and metal ions of Zn^{2+}, Zr^{2+}, La^{3+}, Ce^{4+}, Th^{4+} and U^{4+} were reported by Sadeek & El-Hamid [62]. The complexes were synthesized by mixing ethanolic solution of GEMI and 1,10-phen with aqueous solution of $Zn(CH_3COO)_2{\cdot}2H_2O$, $ZrOCl_2{\cdot}8H_2O$, $LaCl_3{\cdot}7H_2O$, $Ce(SO_4)_2$, $Th(NO_3)_4{\cdot}5H_2O$ and $UO_2(CH_3COO)_2{\cdot}2H_2O$. The complexes possess highly significant antimicrobial behaviour against *E. coli* compared with GEMI. The activity index data indicated that La^{3+} complex has highest activity against *B. subtilis*. Similarly, Sadeek *et al.* [63] also studied biological

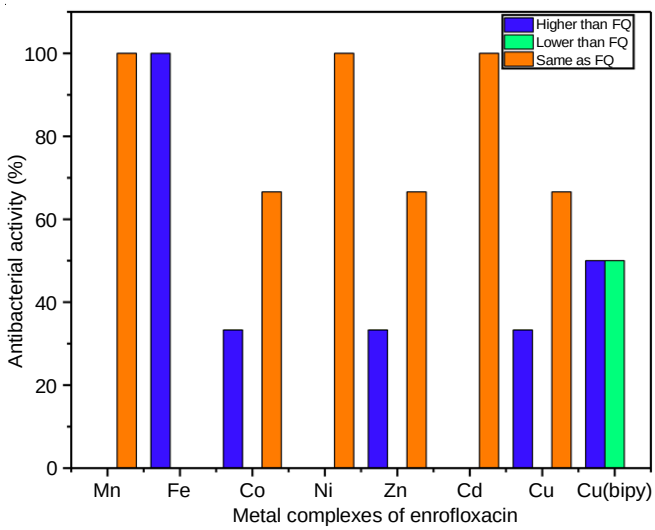

Fig. 7. Antibacterial activities of ENRO-metal complexes

properties of the ENRO complexes of Zn^{2+}, Zr^{2+}, La^{3+}, Ce^{4+}, Th^{4+} and U^{4+}-metal ions with 2,2′-bipyridyl as auxiliary ligand. The metal complexes exhibited remarkable antibacterial activity with higher value of inhibition zone as compared to the parent drug. Comparing the data collected from various research articles, it is summarized that metal complexes of GEMI exhibited excellent and higher bactericidal behaviour than the uncomplexed ligand (Fig. 8).

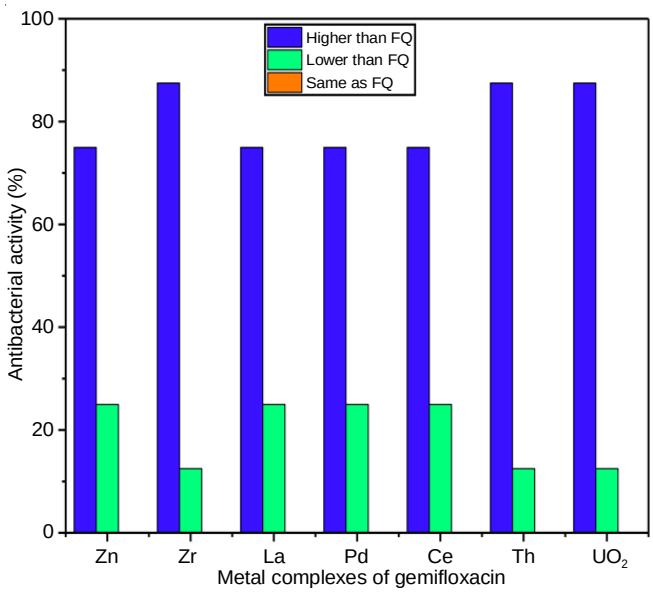

Fig. 8. Antbacterial activities of GEMI-metal complexes

Ofloxacin (OFL): Patel *et al.* [64] studied eight ternary complexes of OFL with Cu^{2+}. Various co-ligands included in complex formation are pyridine-2-carbaldehyde, 2,2-bipyridylamine, thiophene-2-carbaldehyde, 2,9-dimethyl-1,10-phenanthroline, 2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline, 4,5-diazafluoren-9-one, 1,10-phenanthroline-5,6-dione and 5-nitro-1,10-phenanthroline. Comparing the antimicrobial properties of the ternary complexes, it was observed that all complexes showed moderate to good antimicrobial behaviour. Sadeek *et al.* [65] compared the biological properties of ternary complexes of OFL with Zn^{2+}, Zr^{4+}, U^{4+} and 1,10-phenanthroline as coligand. Similarly, El-Hamid *et al.* [66] investigated the ternary complexes of Zn^{2+}, Zr^{4+}, Ce^{4+}, $Th4^{+}$, U^{4+} with 2,2′-bipyridyl as co-ligand. Both researchers separately confirmed an increase in antimicrobial activity in complexes as compared to the parent drug. Data collected from research papers demonstrated that OFL-metal complexes displayed outstanding antibacterial activity and were found to be higher than OFL in maximum cases (Fig. 9).

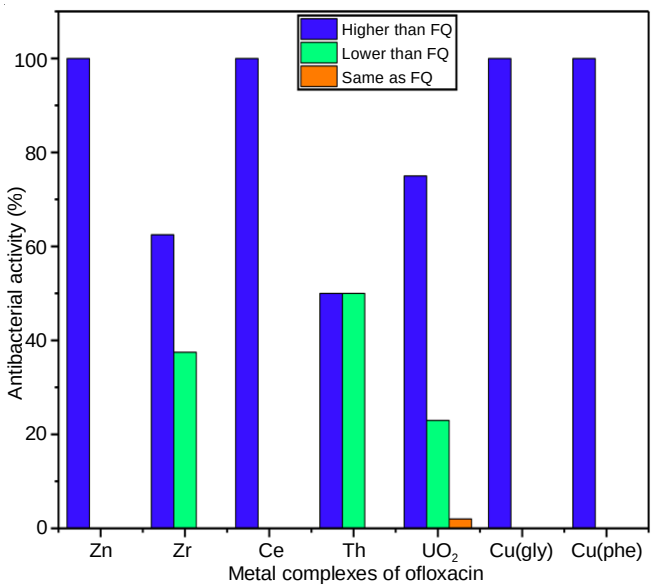

Fig. 9. Antibacterial activities of OFL-metal complexes

Moxifloxacin (MOX): Gold and silver metal complexes of MOX were synthesized and their antimicrobial behaviour were analyzed by Seku *et al.* [67]. The complexes were found to display magnificent bactericidal activity against *S. aureus, E. coli* and *P. aeruginosa* even much higher than MOX. But exhibited lesser activity against *B. subtilis* and *S. features*. Sadeek *et al.* [38] synthesized and characterized the four new complexes of metal ion of MOX with Ti^{4+}, Y^{3+}, Pd^{2+} and Ce^{4+}. The chemical formula of complexes was reported as $[Ti(MOX)_2](SO_4)_2{\cdot}7H_2O$, $[Y(MOX)_2Cl_2]Cl{\cdot}12H_2O$, $[Pd(MOX)_2(H_2O)_2]Cl_2{\cdot}6H_2O$ and $[Ce(MOX)_2](SO_4)_2{\cdot}2H_2O$. The antibacterial activity was studied by measuring the diameter of the zone of inhibition. The zone of inhibition of all complexes was found to be higher than the MOX except for Y and Pd with *S. aureus*. Sadeek *et al.* [69] also investigated the antimicrobial properties of the new solid complexes formed by interaction of MOX with $VOSO_4{\cdot}H_2O$, $ZrOCl_2{\cdot}8H_2O$ and $UO_2(NO_3)_2{\cdot}6H_2O$. The antibacterial activity against *S. aureus* was undetected in all the complexes whereas exhibited superb activity against other all strains even higher than MOX (Fig. 10).

Ciprofloxacin (CIP): Ciprofloxacin was reacted with metal ions (Mn^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cr^{2+}, Cd^{2+}, Mg^{2+} and Ca^{2+}) and the complexes were characterized and investigated for antimicrobial properties by Sultana *et al.* [70]. Antibacterial study was done through disc diffusion technique against 13 bacteria of different strains. The bactericidal beha-

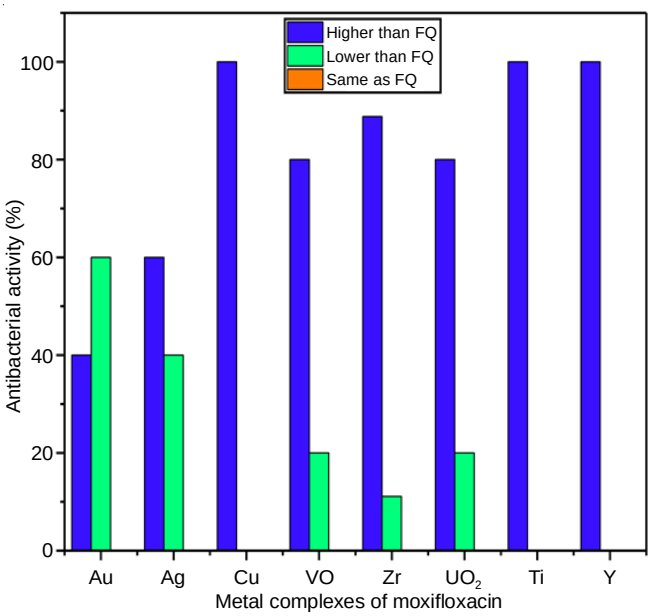

Fig. 10. Antibacterial activities of MOX-metal complex

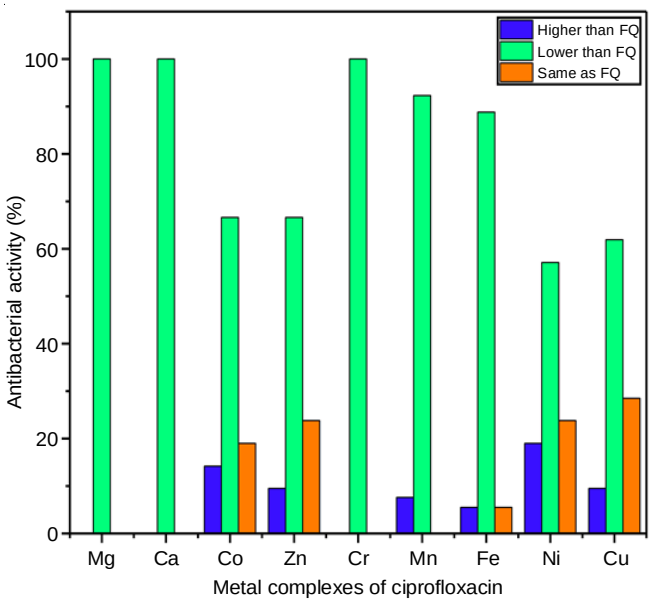

Fig. 11. Antibacterial activities of CIP-metal complexes

viour of almost all complexes was intensely reduced and the zone of inhibition was found to be lesser than CIP. But Ca^{2+} and Cd^{2+} complexes against *S. aureus* exhibited higher activity, similarly Ni^{2+} and Cd^{2+} complexes against *S. pyogenes* also show better antimicrobial activity than the reference standard.

Horozic *et al.* [71] synthesized complexes $Co(CIP)_2(H_2O)_2$, $Mn(CIP)_2(H_2O)_2$ and $Ni(CIP)_2(H_2O)_2$ by mixing ligand and metal ions in ratio 1:2. *In vitro* antibacterial activities of the metal complexes were decreased as compared to CIP, however Co^{2+} and Mn^{2+} complexes were found to have better bactericidal behaviour against *E. faecalis.* Ternary metal complexes of Cu^{2+}, Zn^{2+}, Mn^{2+} with CIP and glycine were studied for their kinetic, thermodynamic and antibacterial activities by Panda *et al*. [72]. The complexes with general formula $[M(CIPgly)(H_2O)_3]\cdot H_2O$, exhibited significant antimicrobial activity but lesser than CIP. However Cu^{2+} complex did not display any activity against *S. aureus*, *K. pneumoniae* and *Enterococcus*. Eugene-Osoikhia *et al.* [73] discussed the synthesis, characterization and antimicrobial studies of Fe^{2+} and Cu^{2+} complexes of acetylated and benzoylated derivatives of CIP. The *in vitro* antimicrobial activities revealed that the complexes did not exhibit any antifungal behaviour, however acetylated complexes envisioned better activity than the parent drug CIP against *B. subtilis*, *P. aeruginosa* and *K. pneumonia*, while benzoylated derivative displayed decreased activity in comparison to CIP against all the bacterial strains. The oxovanadium(IV) complex of CIP, $[VO(CIP)(H_2O)]$ was evaluated for antibacterial properties against 8 Gram-positive and 9 Gram-negative strains of bacteria by Turel *et al.* [74]. The complex demonstrated the lesser or similar activity with respect to CIP, against all strains of bacteria except for *B. subtilis* against which the complex exhibited higher activity. In most cases, the bactericidal behaviour of CIP-metal complexes was reduced drastically as compared to the parent drug (Fig. 11).

Norfloxacin (NOR): The solid state complexes of metal cation Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+} with NOR were reported. Bactericidal properties were investigated by the disk diffusion method against *S. aureus*, *E. coli*, *P. aeruginosa* and *L. monocytogenes* [75]. Complexation increases the antibacterial activity of NOR against all strains except *L. monocytogenes* for which activity is reduced on complex formation. Norfloxacin in the Cu^{2+} complex, surprisingly lost its antibacterial activity. Shaikh *et al.* [76] studied the antimicrobial behaviour of Bi-NOR complex and Ahmadi *et al.* [77] studied the same for Zn-NOR complex. *In vitro* evaluation of antibacterial properties of the metal complexes was done by adopting Agar diffusion method and then comparing the MIC values. In both cases, the activity of NOR increased on complexation. Silver, copper and gold complexes of NOR with chemical formula: $Ag_2(NOR)_2](NO_3)_2$, $[Cu(NOR)_2(H_2O)_2]SO_4\cdot 5H_2O$, $[Au(NOR)_2(H_2O)_2]Cl_3$ were synthesized and characterized by Refat *et al*. [78]. Antibacterial activity of all the complexes was higher than NOR against *P. aeruginosa* but lesser than NOR against *B. subtilis*. Two novel complexes of NOR with the formula $[ZrO(NOR)_2Cl]Cl\cdot 15H_2O$ and $[UO_2(NOR)_3](NO_3)_2\cdot 4H_2O$ were reported by Sadeek *et al.* [79]. Comparative study of their zone of inhibition revealed that the metal-complexes have higher antibacterial activity as compared to the ligand. Refat *et al.* [80] synthesized the complexes of NOR with Zn^{2+}, Cd^{2+} and Hg^{2+} with the general formula $[M(NOR)_2]X_2\cdot nH_2O$. The antibacterial evaluation of the complexes indicated impressive activity of complexes against *B. subtilis.* However Hg^{2+} complex was found to show better activity than Zn^{2+} and Cd^{2+} against *Trichoderma* [80]. Comparing the antibacterial properties of all the cases of NOR-metal complexes, Co^{2+}, Mn^{2+} and Ni^{2+} complexes was found to show better activity than NOR in almost all cases whereas Cu^{2+} exhibited higher and lower activity almost equally (Fig. 12).

A metal complex interacting with a microorganism is considered one case and thus considering all the cases of metal complexes, it is summarized that in maximum cases FQs metal complexes were found to exhibit similar or enhanced antibacterial activity as compared with uncomplexed ligands. Out of

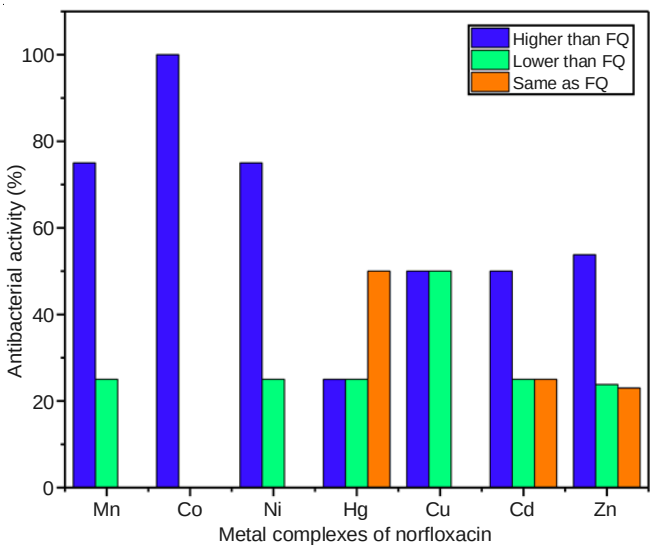

Fig. 12. Antibacterial activities of NOR-metal complexes

all the metal complexes studied, only metal complexes of ciprofloxacin and gatifloxacin show lesser antibacterial activity as compared to the respective FQs (Fig. 13). The CIP-metal complexes were found to show lesser antibacterial activity than ciprofloxacin in maximum cases (Table-2), whereas out of various cases reviewed for MOX-metal complexes, higher antibacterial activity is shown in more than 80% cases. Similarly GEMI-metal complexes also show higher antibacterial activity than the respective antibiotic in more than 80% cases whereas in case of ENRO-metal complexes the antibacterial activity remains same as that of antibiotic in almost 50% cases.

Other applications of FQ metal complexes: Medication of infectious diseases emerged as a challenging problem due to a combination of factors such as the emergence of new diseases and the increasing number of microbes becoming resistant to available drugs. Resistance of drugs was first of all noticed in the 1950s, in chloroquine-an antimalarial drug and afterward to others [81]. Antimicrobial activity of these drugs, for which

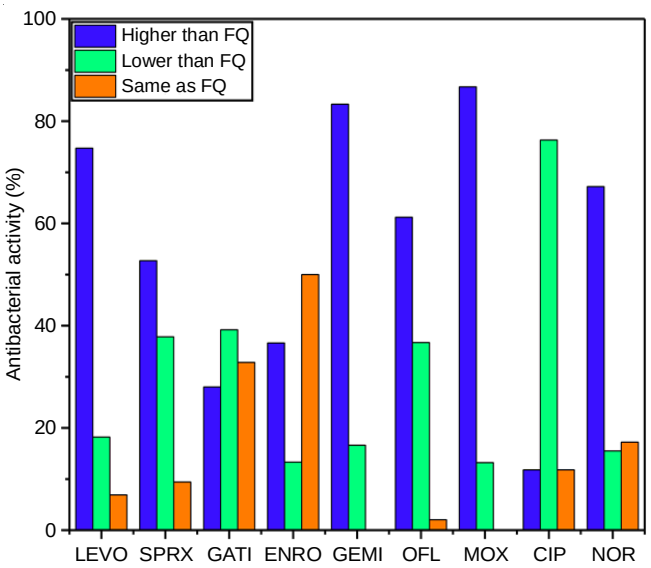

Fig. 13. Summary of antibacterial behaviour of FQ-metal complexes

TABLE-2
SUMMARY OF ANTIBACTERIAL BEHAVIOUR OF FQ-METAL COMPLEXES REVIEWED

	Total cases	Higher activity than FQ	Lesser activity than FQ	Similar activity
LEVO	115	86	21	8
SPRX	127	67	48	12
GATI	125	35	49	41
ENRO	30	11	4	15
GEMI	48	40	8	0
OFL	98	60	36	2
MOX	53	46	7	0
CIP	211	25	161	25
NOR	58	39	9	10

resistance has developed, can be restored by modifying the structure of the drug by means of embodying a metal ion in its structure. Fluoroquinolone-metal complexes exhibit not only magnificent antibacterial properties but also several other applications in the medical field.

Pharmacological aspects: Complexes of quinolones with trivalent cations possess enhanced solubility in comparison to uncomplexed ligands and this property could be advantageous for pharmacological formulation. For example some Al^{3+} complexes of CIP and NOR were reported to be more soluble than the parent drug. Such complexes can be helpful in advancement of more dose-efficient medications, such as compressed tablet dosage [82,83]. Reducing the oral bioavailability of quinolones is an important aspect of pharmaceuticals and it is reported in the presence of the metal ions-quinolones interaction. Reduction in bioavailability of FQs were reported by researchers in Fe^{2+}/Fe^{3+} complexes of CIP and NOR [84,85]. The effect of Ca^{2+}, Mg^{2+}, Fe^{2+} was analyzed with CIP, whereas the consequence of complexing with Al^{3+} was evaluated with CIP, NOR and OFL. The results disclosed that the chelation of fluoroquinolone with metal ions resulted in a decreased intestinal permeability in comparison to that of the respective fluoroquinolone, which leads to lesser drug bioavailability.

Antiparasitic and antifungal properties: Along with the antibacterial potential, some FQ-metal complexes exhibited antiparasitic, antifungal and antiviral activities [81]. However, FQs do not show any antifungal behaviour but its metal complexes have proven to show noticeable fungicidal behaviour. Complexes of LEVO with Cr^{3+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Th^{4+}, Mn^{2+}, Zn^{2+} and UO_2^{2+} having 1:1 stoichiometry displayed antifungal effect better than the drug against *C. albicans* [86]. Similarly, complexes with 1:2 stoichiometry of GATI and metal ions (Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, Fe^{3+}, Ca^{2+}, Mg^{2+},Cr^{3+}, Mn^{2+} and Co^{2+}) also exhibited excellent antifungal activity against *T. rubrum*, *C. albicans* and *F. solani* [58]. Mn^{2+} and Co^{2+} complexes of SPAR and NOR displayed sufficient antiparasitic activity against *Trympanosoma cruzi*. Mn^{2+} complex was found not to enhance the antiparasitic behaviour of NOR but Co^{2+} complex increased the antiparasitic behaviour four times the parent drug [87].

Anticancer activity: Fluoroquinolones have been studied and examined extensively for the anticancer activities in the past few years [81,88] depending on their capability to block topoisomerase II, thus suppressing its activity to repair DNA. Various investigations with respect to the biological action of

quinolone metal complexes depend on their ability to associate with DNA and accordingly go about as an unparalleled tool as anticancer agent. Enormous achievement was accomplished in the zone of anticancer and antimicrobial medications. Cisplatin has been extensively in use as an anticancer drug since 1978 to treat various types of cancer including carcinoma, germ cell tumours and sarcomas. The FQ-boron hybrid complex showed proliferation inhibition in SiHa and CasKi cells, thus increasing the chances of using them as efficient tools for the treatment of cervical cancer [89]. A palladium-based photodynamic treatment specialist was endorsed in 2019 for the therapy of cervical cancer by the European Medicines Agency (EMA) [90]. A lot more components are effectively being researched for a scope of clinical applications [86,91]. Studies have shown ruthenium, gold, gallium, titanium salts and silver to be an interesting agent for anticancer and antiviral therapies. Some of cobalt and zinc complexes of lomefloxacin, $[Co(Lfx)(H_2O)_4]Cl_2$ and $[Zn(Lfx)(H_2O)_4]Cl_2$ were investigated to be quite efficient against the breast cancer cell line MCF7 [92]. The Cu(II) complexes of pefloxacin were found to efficiently inhibit the proliferation of HCT 116 cancer cells and suggested cell apoptosis mechanism for anticancer activity [93]. Metal complexes of drugs are frequently and extensively used in chemotherapy.

Anti-inflammatory properties: Metal based drugs of fluoroquinolones have also found to exhibit anti-inflammatory and antiarthritic properties. Significant examinations are being conducted into FQ complexes of Cu^{2+}, Au^{+} and Zn^{2+} having great antinflammatory properties and have fewer side effects with comparative or higher viability than the respective FQ [94,95]. A low molecular weight copper complexes of quinolones have been found to show positive effect against various diseases such as rheumatoid, gastric ulcers, tuberculosis and cancers [11,96].

Analytical applications: Lanthanide complexes of fluoroquinolones, can be used for analytical applications for the quantitative determination of fluoroquinolones or metal ions. Their complexes with Tb^{3+} and Eu^{3+} exhibit strong luminescence and chemiluminescent properties, which are highly helpful for detection methods [97]. The detection method is based on the interactions of the parent drug and metal ion, which leads to formation of complex with magnificent luminescent properties. It is extensively employed to detect the presence of enrofloxacin [98], trovafloxacin [99], ciprofloxacin [100], ofloxacin [101], levofloxacin [102] or gatifloxacin [103] in the biological systems.

Conclusion

Excellent properties of fluoroquinolones (FQs) to form complex with divalent and trivalent metal ions, make them a very useful moiety of the medical field. The potency of the drugs on chelating with metal cation is intensified in various cases. This review article discussed some of the literature of the FQ-metal complexes and their antimicrobial behaviour was compared with respect to free FQs. In most of the FQ-metal complexes, the FQs act as bidentate ligands, due to the involvement of >C=O group at position C-4 and one of the oxygen atoms of -COOH group at position C-3 in coordi-nation sphere. The rise and spread of antimicrobial resistance is the greatest health risk of the modern world, it is thus relevant to explore and evolve the new antibacterial drugs to constrain infections occurring due to these resistant strains. Analysts have investigated the likely toxic conduct of FQ-M complexes to microorganisms and the investigation uncovered that the majority of the metal complexes displayed comparative or upgraded antimicrobial action when contrasted with the parent drugs. These complexes have capability to be used as bactericidal agents and can be explored further.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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