Review
Fluoroquinolones’ Biological Activities against Laboratory Microbes and Cancer Cell Lines

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Abstract: Development of novel derivatives to rein in and fight bacteria have never been more demanding, as microbial resistance strains are alarmingly increasing. A multitude of new fluoroquinolones derivatives with an improved spectrum of activity and/or enhanced pharmacokinetics parameters have been widely explored. Reporting novel antimicrobial agents entails comparing their potential activity to their parent drugs; hence, parent fluoroquinolones have been used in research as positive controls. Given that these fluoroquinolones possess variable activities according to their generation, it is necessary to include parent compounds and market available antibiotics of the same class when investigating antimicrobial activity. Herein, we provide a detailed guide on the in vitro biological activity of fluoroquinolones based on experimental results published in the last years. This work permits researchers to compare and analyze potential fluoroquinolones as positive control agents and to evaluate changes occurring in their activities. More importantly, the selection of fluoroquinolones as positive controls by medicinal chemists when investigating novel FQs analogs must be correlated to the laboratory pathogen inquest for reliable results.

Keywords: ciprofloxacin; moxifloxacin; norfloxacin; fluoroquinolones; resistant bacteria; anticancer; minimum inhibitory concentration

1. Introduction
Antimicrobial prescriptions for the treatment of infections caused in particular by Staphylococcus aureus (S. aureus), Pseudomonas aeruginosa (P. aeruginosa), and Mycobacterium tuberculosis (M. tuberculosis) have been affected by bacterial resistance [1]. Alarmingly, the ever-increasing emergence of resistant strains has globally increased the mortality rates [2].

Several approaches have been followed to develop novel fluoroquinolones (FQs) with enhanced antimicrobial activity and/or enhanced pharmacokinetic properties to tackle bacterial resistance [3–8]. With more than 500 newly introduced structural modifications on FQs’ key scaffold [9]; 1-substituted 1,4-dihydro-4-oxo-pyridine-3-carboxylic acid (Figure 1) and the recent approval of delafloxacin in 2017, researchers have focused on embracing the biological activity of FQs, particularly against resistant bacterial strains [10,11].

Additionally, literature reviews pointed out FQs’ potential activities as anticancer, antitumor, antiviral, and antifungal agents in addition to their antibacterial activity where the latter is attributed to their ability to selectively inhibit bacterial type II topoisomerases, DNA gyrase, and/or topoisomerase IV [12–15].

Currently, FQs are one of the most widely used antimicrobial drugs, with a wide range of indications, covering respiratory infections, urinary tract infections (UTIs), gastrointestinal infections, and gynecologic infections [16]. Moreover, FQs are indicated as a prophylactic treatment in immune-compromised neutropenic patients [17].
FQs are usually classified into four generations with enhanced efficacy and spectrum of activity, along with enhanced safety and pharmacokinetic characteristics (Figure 2) [18,19]. Ciprofloxacin is the most prosperous derivative, both economically and clinically [20], and the newer generations such as levofloxacin, gemifloxacin, and moxifloxacin offer enhanced activity against aerobic Gram-negative bacilli and Gram-positive bacteria over ciprofloxacin, e.g., against *Streptococcus pneumoniae* (*S. pneumoniae*) and *S. aureus* [20]. Ciprofloxacin and moxifloxacin retain enhanced in vitro activity against *P. aeruginosa* [21]. In terms of potency, moxifloxacin is more potent against Gram-positive and anaerobes than ciprofloxacin and levofloxacin. Newer generations displayed potent activity against penicillin-resistant and multidrug-resistant (MDR) pneumococcus and anaerobic bacteria. Recently, delafloxacin was granted approval in 2017 for the systemic treatment of acute bacterial skin infections [22].

**Figure 1.** Fluoroquinolone’s nucleus: 1-substituted 1,4-dihydro-4-oxo-pyridine-3-carboxylic acid; R’, R” are responsible for pharmacokinetic properties, and R”’ is responsible for potency.

**Figure 2.** Spectrum and antimicrobial activities of fluoroquinolone based on their generations. Widening of the antibacterial activity of fluoroquinolones in relation to their generation. Reproduced/adapted from ref. [13].

Appraisal of the newer FQs’ derivatives should be, in part, based on the relevant references. Herein, commonly employed FQ acting as positive controls in antimicrobial bioassays of up-to-date papers were reviewed. These results were reported in a constructive and comparative manner to facilitate the process of developing novel FQs’ analogues. The chemical structures and key physical properties of the frequently adopted standard FQs, namely norfloxacin 1, ciprofloxacin 2, levofloxacin 3, and moxifloxacin 4 are summarized in Table 1. This should provide a facile referral guide to recent research areas concerning FQs derivatives antibacterial inhibitory effect, the adopted testing protocols, and generations-based comparison between different FQs to be applied in innovative research. Choosing...
standard FQs will not only affect the assessment of the new counterparts, but also provide a more comprehensive and efficient performance in assays.

Table 1. Most adopted standard fluoroquinolones, their chemical structures, and key physical properties.

| Fluoroquinolone | Structure | Generation | Physical Properties | References |
|-----------------|-----------|------------|---------------------|------------|
| Norfloxacin     | ![Structure](image1.png) | 2nd        | ClogP 1.81          | [23,24]    |
| Ciprofloxacin   | ![Structure](image2.png) | 2nd        | LogP 1.60, ClogP 0.725 | [23,25–27] |
| Levofloxacin    | ![Structure](image3.png) | 3rd        | ClogP 1.35, ClogP 0.51 | [24,26]    |
| Moxifloxacin    | ![Structure](image4.png) | 4th        | ClogP 2.53, LogP 1.60 | [24,28]    |

2. Comparison of the In Vitro Antimicrobial Assays

A variety of methods and tactics could be adopted to evaluate the antibacterial activity of potential agents, and to draw constructive conclusions. In this regard, choosing and performing these assays varies according to the antimicrobial agents, availability of equipment, and cost-related reasons. The most known and basic standard methods are disk-diffusion [29] and broth or agar dilution methods [30]. The advantages and disadvantages of these assays are summarized in Table 2 and reviewed elsewhere [31,32], being apart from the scope of this article. In brief, standardized antimicrobial bioassays (antimicrobial susceptibility testing) are nowadays published and approved by the Clinical and Laboratory Standards Institute (CLSI) for bacteria and yeasts testing [33], herein the most commonly reported bioassays and the antimicrobial values of various FQs analogues are reported.
Dilution methods afford quantitative evaluation of the in vitro antimicrobial activity, which are usually expressed as minimum inhibitory concentration (MIC) values and represent the lowest concentration of the tested antimicrobial agent that inhibits the visible growth of tested microorganism. A number of approved guidelines for dilution antimicrobial susceptibility testing of fastidious or non-fastidious bacteria, yeast, and filamentous fungi are reported [30].

On the other hand, agar disk-diffusion method is the standard qualitative method for routine antimicrobial susceptibility testing. This method provides qualitative results by categorizing bacteria as susceptible, intermediate, or resistant based on the obtained growth zones of inhibition (ZOI) diameters. However, important parameters, including the growth media, temperature, period of incubation, and the required inoculum size should be optimized to fulfil CLSI standards [22].

Differently, measuring the inhibition of supercoiling activity (catalytic activity) of DNA gyrase or the concentration of compounds required for inhibiting 50% of gyrase supercoiling activity (IC$_{50}$) has been widely reported as an alternative assay to test the antibacterial activity of different FQs derivatives, particularly if the mechanistic and catalytic activity of the developed analogues are of concern [34,35].

**Table 2.** Advantages and disadvantages of commonly applied technique for the evaluation of drugs antimicrobial activity.

| Testing Technique | Advantages | Disadvantages | Reference |
|-------------------|------------|---------------|-----------|
| Disk-diffusion     | - Can be used to for routine susceptibility testing  
                   | - Ability to adjust the tested discs  
                   | - Simple  
                   | - Standardized  
                   | - Low cost  
                   | - Reproducible | - Diffusability of drug from disc must be considered  
                   | - Results are qualitative  
                   | - Requires large inoculum size [1–2 × 10$^8$ CFU/mL]  
                   | - Can only approximate MIC based on diameter of the zones of inhibition | |
| Dilution methods   | - Includes agar dilution, broth microdilution and broth macrodilution methods  
                   | - Can be used to accurately calculate MIC against various bacteria, yeasts, and fungi  
                   | - Can be used to monitor resistance emergence  
                   | - Reproducible  
                   | - Low cost  
                   | - Can test multiple bacteria in one plate using agar dilution method  
                   | - Agar dilution method can be semi-automated | - Broth macrodilution has higher risk of error  
                   | - Broth microdilution may not detect contamination, inoculum viability and the inhibitory effect of cosolvents used (e.g., dimethyl sulphoxide)  
                   | - Agar dilution method requires intense labor and high cost unless it is automated | [31,38] |

3. FQ’s Antibacterial Biological Activity

3.1. FQ’s Antibacterial Activity against Gram-Positive Bacteria

According to the reviewed literature in the past five years, and for the sake of including up-to-date activities on the most common FQs applied as golden antimicrobial positive controls in laboratories, herein, standard FQs and their antimicrobial activity against a panel of laboratory microbes are reported (Table 3).

As reported, norfloxacin was used as a positive control in the pipeline publications, including norfloxacin derivatives synthesis. Norfloxacin MIC against Gram-positive is presented in Table 3 [1,23,24,26,28,34–71]. In brief, norfloxacin inhibitory activity against a panel of Gram-positive bacteria regardless of the strain varied relatively. For example, norfloxacin in vitro antibacterial activity reported by Mentese et al. against *E. faecalis* ATCC 29212 varied from
that reported by Seliem et al. (MIC ranged from \(<0.128 \mu M \) [46]–100.207 \(\mu M \) [47]). Similarly, norfloxacin MIC against \(S. \) aureus ATCC 25923 ranged from \(<0.128 \mu M \) [46]–156.170 \(\mu M \) [45] in the above-mentioned two different studies.

**Table 3.** Fluoroquinolones’ antibacterial activity against Gram-positive bacterial strains.

| Fluoroquinolone Generation | Name          | G +ve Bacteria         | Strain          | MIC (µM) | Reference |
|----------------------------|---------------|------------------------|-----------------|----------|-----------|
| Second Generation          | Norfloxacin   |                        |                 |          |           |
|                            |               | \(B. \) subtilis        | NCDC 71         | 15.658   | [42]      |
|                            |               |                        | 8035            | 4.697    | [44]      |
|                            |               | \(B. \) cereus          | Roma 702        | \(<0.128\) | [46]      |
|                            |               |                        | Roma 709        | 8.267    | [28]      |
|                            |               | \(B. \) polymyxna       | NCDC 64         | 78.289   | [42]      |
|                            |               |                        |                 | \(<0.128\) | [46]      |
|                            |               | \(E. \) faecalis        | ATCC 29212      | 8.267    | [28]      |
|                            |               |                        |                 | 100.207  | [47]      |
|                            |               | \(L. \) acidophilus     | RSKK 06029      | 2113.794 | [28]      |
|                            |               | \(L. \) monocytogenes   | ATCC 43251      | 8.267    | [28]      |
|                            |               |                        | NCDC 110        | 31.315   | [42]      |
|                            |               |                        | ATCC 29213      | 3.132    | [43]      |
|                            |               | \(S. \) aureus          | ATCC 25923      | 4.134    | [28]      |
|                            |               |                        |                 | \(<0.128\) | [46]      |
|                            |               | \(S. \) aureus 209p     |                 | 1.221    | [44]      |
|                            |               |                        | MRSA            | 1.879    | [28]      |
|                            |               | \(S. \) pneumonia       | ATCC 49619      | 19.572   | [43]      |
| Lomefloxacin               |               | \(B. \) cereus          | 8035            | 17.931   | [44]      |
|                            |               | \(S. \) aureus          | 209p            | 2.220    |           |
| Ciprofloxacin              |               | \(A. \) baumannii       | 24.144          | [24]     |           |
|                            |               |                        | ATCC 19606      | 2.354    | [50]      |
|                            |               | \(B. \) cereus          | ATCC 10876      | 0.360    | [57]      |
|                            |               |                        | Roma 702        | 0.181    | [46]      |
|                            |               |                        | Roma 709        | 3.954    | [28]      |
|                            |               | \(B. \) polymyxna       | NCDC 64         | 30.180   | [42]      |
|                            |               |                        |                 | 0.090    | [57]      |
|                            |               | \(B. \) subtilis        | ATCC 6633       | 0.030    | [58]      |
|                            |               |                        |                 | 8.149    | [34]      |
|                            |               | \(B. \) subtilis        | NCDC 71         | 60.361   | [42]      |
|                            |               |                        |                 | 72.433   | [59]      |
|                            |               |                        |                 | 3.018    | [56,60,61]|
|                            |               |                        |                 | 1.360    | [51]      |
|                            |               | \(E. \) Faecalis        | ATCC 29212      | 0.368    | [46]      |
|                            |               |                        |                 | 1.509    | [55,62]   |
|                            |               |                        |                 | 7.878    | [28]      |
Table 3. Cont.

| Fluoroquinolone | G +ve Bacteria | Strain      | MIC (µM) | Reference |
|-----------------|----------------|-------------|----------|-----------|
| Generation      | Name           |             |          |           |
|                 |                | ATCC 33186  | 2.384    | [50]      |
|                 |                | ATCC 51875  | 1.360    | [51]      |
|                 |                | ATCC 51299  | 1.509    | [55]      |
|                 |                | JH2-2       | 6.036    | [63]      |
|                 |                | UCN41       | 3.018    | [63]      |
| E. Faecalis     |                |             |          |           |
|                 |                | ATCC 19434T | 3.018    | [63]      |
|                 |                | BM-4147     | 12.072   | [63]      |
|                 |                | ATCC 27270  | 2.651    | [56]      |
|                 |                | ATCC 700221 | >386.308 | [55]      |
|                 |                | 13-7        | >386.308 | [55]      |
|                 |                | 14-2        | 96.577   | [53,54]   |
|                 |                | 14-5        | 386.308  | [53,54]   |
|                 |                | 14-6        | >386.308 | [53,54]   |
|                 |                | ATCC 10541  | 24.144   | [48]      |
|                 |                | K. pneumonia| 193.154  | [24]      |
|                 |                | RSKK 06029  | 252.277  | [28]      |
| L. acidophilus  |                | ATCC 43251  | 3.954    | [28]      |
|                 |                | EGD         | 12.072   | [64]      |
|                 |                | CLIP21369   | 48.288   | [64]      |
|                 |                | ATCC 6538   | 26.015   | [65]      |
|                 |                | ATCC 29213  | 1.509    | [48]      |
|                 |                | ATCC 25923  | 0.755    | [64]      |
| S. aureus       |                | ATCC 29213  | 0.400    | [66]      |
|                 |                | 0.082       | [67]      |
|                 |                | 0.296       | [50]      |
|                 |                | 0.680       | [51]      |
|                 |                | 0.755       | [55]      |
|                 |                | 0.755       | [64]      |
|                 |                | 2.960       | [57]      |
|                 |                | 0.010       | [52]      |
|                 |                | 0.755       | [26]      |
|                 |                | 0.368       | [46]      |
|                 |                | 3.954       | [28]      |
|                 |                | 3.018       | [62]      |
## Table 3. Cont.

| Fluoroquinolone | G +ve Bacteria | Strain                                      | MIC (µM) | Reference |
|-----------------|----------------|---------------------------------------------|----------|-----------|
| Generation      | Name            | S. aureus ATCC 25923 (clinical isolate)     | 0.755    | [63]      |
|                 |                 | SAI                                         | 24.144   | [64]      |
|                 |                 | SA124                                        | 48.289   | [64]      |
|                 |                 | SA036                                        | 96.577   | [64]      |
|                 |                 | N41120032                                    | 193.154  | [64]      |
|                 |                 | SG511                                        | 0.470    | [58]      |
|                 | Microbank       | 14001 (MRSA)                                | 1.480    | [57]      |
|                 | S. aureus D15   | MRSA                                        | 3.100    | [66]      |
|                 | S. aureus D17   | MRSA                                        | 3.100    | [66]      |
|                 | S. aureus CIPR  |                                             | 50.000   | [66]      |
|                 | S. aureus NCTC  | 4163                                        | 0.755    | [48]      |
|                 | S. aureus HG001 | (laboratory strain)                         | 0.377    | [63]      |
|                 | MSSA 12-1       |                                             | 0.755    | [26]      |
|                 | MSSA 12-2       |                                             | 0.755    | [26]      |
|                 | MSSA 12-4       |                                             | 0.755    | [26]      |
|                 | MSSA 12-5       |                                             | 0.755    | [26]      |
|                 | MSSA 14-1       |                                             | 96.577   | [53,54]   |
|                 | MSSA14-3        |                                             | 0.377    | [53,54]   |
|                 | MSSA 14-4       |                                             | 1.509    | [53,54]   |
|                 | MRSA            |                                             | 3.954    | [28]      |
|                 | MRSA 14-4       |                                             | ≥386.308 | [53,54]   |
|                 | MRSA 14-5       |                                             | 48.288   | [53,54]   |
|                 | MRSA 12-2       |                                             | 193.154  | [26]      |
|                 | MRSA 12-4       |                                             | 193.154  | [26]      |
|                 | MRSA 12-5       |                                             | 96.577   | [26]      |
|                 | CMCC 26003      |                                             | 1.509    | [53,54]   |
|                 | S. aureus ATCC  | 700699 (resistant isolate)                 | ≥24.144  | [63]      |
|                 | Healthcare-acquired MRSA NRS70 | | 0.604 | [50] |
|                 | Community-acquired MRSA USA300 | | 19.014 | [50] |
|                 | (MRSA) ATCC 33591 |                                             | 1.509    | [60,61]   |
|                 |                 |                                             | 0.755    | [55]      |
|                 |                 |                                             | 0.680    | [54]      |
|                 | MRSA ATCC 33592 |                                             | ≤0.083   | [56]      |
|                 | NCDC 110        |                                             | 150.901  | [42]      |
|                 | 12.072          |                                             | 1.59    | [47]      |
|                 |                  |                                              | 0.589    | [49]      |
|                 |                  |                                              | 0.377    | [24]      |
### Table 3. Cont.

| Fluoroquinolone | G +ve Bacteria | Strain | MIC (µM) | Reference |
|------------------|----------------|--------|----------|-----------|
| **Ciprofloxacin** | **S. epidermidis** | ATCC 12228 | 0.400 | [66] |
|                  |                | ATCC 14990 | 1.480 | [57] |
|                  |                | ATCC 35984 | 0.377 | [63] |
|                  |                | ATCC 12228 | 0.755 | [48] |
|                  |                | MSSE CANWARD-2008 81388 | 0.589 | [49] |
|                  |                | MSSE ATCC 12228 | ≤0.181 | [63] |
|                  |                | MSSE 12-1 | 0.377 | [63] |
|                  |                | MSSE 12-3 | 0.340 | [55] |
|                  |                | MSSE 12-6 | 0.755 | [26] |
|                  |                | MSSE 12-8 | 0.589 | [49] |
|                  |                | MSSE 14-2 | 6.036 | [26] |
|                  |                | MRSE CAN-ICU 61589 (CAZ > 32) | ≤0.083 | [56] |
|                  |                | MRSE 12-1 | 12.072 | [26] |
|                  |                | MRSE 12-6 | 0.377 | [55] |
|                  |                | MRSE 12-8 | 0.340 | [51] |
|                  |                | MRSE 14-2 | >386.308 | [53,54] |
|                  |                | MRSE 14-39 | 386.308 | [53,54] |
|                  |                | MRSE 16-3 | 386.308 | [53,54] |
|                  |                | MRSE 14-21 | 32.897 | [54] |
|                  |                | MRSE 12-1 | 32.897 | [54] |
|                  |                | MRSE 12-6 | 32.897 | [54] |
|                  |                | MRSE 12-8 | 32.897 | [54] |
|                  |                | MRSE 14-22 | 32.897 | [54] |
|                  |                | MRSE 14-37 | 32.897 | [54] |
|                  |                | MRSE 14-39 | 32.897 | [54] |
|                  |                | MRSE 14-39 | 32.897 | [54] |
|                  |                | MRSE 14-39 | 32.897 | [54] |
|                  | **S. pneumoniae** | ATCC 19615 | 6.036 | [54] |
|                  |                | ATCC 49619 | 0.331 | [56] |
|                  |                | R6 | 1.177 | [50] |
| **Cipro HCl** | **B. cereus** | Roma 709 | 1.636 | [28] |
|                  | **E. faecalis** | ATCC 29212 | 3.435 | [28] |
|                  | **L. acidophilus** | RSKK 06029 | 219.385 | [28] |
|                  | **L. monocytogenes** | ATCC 43251 | 3.435 | [28] |
|                  | **S. aureus** | ATCC 25923 | 6.843 | [28] |
|                  |                | MRS | 3.435 | [28] |
| **Third Generation Levofoxacin** | **E. faecalis** | ATCC 29212 | 2.770 | [51] |
|                  |                | ATCC 51575 | 2.767 | [55] |
|                  |                | ATCC 700221 | 1.384 | [51] |
|                  |                | 14-1 | 44.276 | [68] |
|                  |                | 14-1 | 354.210 | [53,54] |
| Fluoroquinolone Generation | Name     | Strain | MIC (µM) | Reference |
|---------------------------|----------|--------|----------|-----------|
| **E. faecalis**           |          |        |          |           |
|                          | 14-2     | 88.552 |          | [68]      |
|                          | 14-3     | 2.767  |          | [53,54]   |
|                          | ATCC 700221 | 88.552 |          | [55]      |
|                          | 13-7     | 88.552 |          | [55]      |
|                          | 14-1     | 354.210|          | [68]      |
|                          | 14-2     | 88.552 |          | [53,54]   |
|                          | 14-2     | 2.767  |          | [68]      |
|                          | 14-5     | 177.105|          | [53,54]   |
|                          | 14-6     | 177.105|          | [53,54]   |
|                          | 16-4     | 44.300 |          | [51]      |
|                          | ATCC 25923 | <0.022 |          | [26]      |
|                          | ATCC 29213 | 1.66   |          | [69]      |
|                          | CMCC 26003 | 0.350  |          | [51]      |
|                          |          | 0.350  |          | [51]      |
|                          |           | 0.346  |          | [68]      |
|                          |           | 0.346  |          | [53,54]   |
|                          | MSSA 12-2 | 0.346  |          | [26]      |
|                          | MSSA 12-4 | 0.166  |          | [69]      |
|                          |           | 0.344  |          | [26]      |
|                          | MSSA 12-5 | 0.346  |          | [26]      |
|                          | MSSA 14-1 | 22.138 |          | [53,54]   |
|                          | MSSA 14-2 | 0.692  |          | [68]      |
|                          | MSSA 14-3 | 0.346  |          | [53,54,68]|
|                          | MSSA 14-4 | 1.384  |          | [53,54,68]|
|                          | MRSA 12-1 | 177.105|          | [69]      |
|                          | MRSA 12-2 | 88.552 |          | [26]      |
|                          | MRSA 12-4 | 88.552 |          | [26]      |
|                          | MRSA 12-5 | 88.552 |          | [26]      |
|                          | MRSA 14-4 | 177.105|          | [53,54,68]|
|                          | MRSA 14-5 | 22.138 |          | [26,53,54]|
|                          | NARSA 10198 | 88.552 |          | [70]      |
|                          | NARSA 10193 | 88.552 |          | [70]      |
|                          | ATCC 29213 | 1.384  |          | [70]      |
|                          | MSSE ATCC 12228 | 0.350 |          | [51]      |
|                          |          | 0.346  |          | [55]      |
| **S. aureus**             |          |        |          |           |
|                          | MSSA 14-2 | 0.692  |          | [68]      |
|                          | MSSA 14-3 | 0.346  |          | [53,54,68]|
|                          | MSSA 14-4 | 1.384  |          | [53,54,68]|
|                          | MRSA 12-1 | 177.105|          | [69]      |
|                          | MRSA 12-2 | 88.552 |          | [26]      |
|                          | MRSA 12-4 | 88.552 |          | [26]      |
|                          | MRSA 12-5 | 88.552 |          | [26]      |
|                          | MRSA 14-4 | 177.105|          | [53,54,68]|
|                          | MRSA 14-5 | 22.138 |          | [26,53,54]|
|                          | NARSA 10198 | 88.552 |          | [70]      |
|                          | NARSA 10193 | 88.552 |          | [70]      |
|                          | ATCC 29213 | 1.384  |          | [70]      |
|                          | MSSE ATCC 12228 | 0.350 |          | [51]      |
|                          |          | 0.346  |          | [55]      |
| **S. epidermidis**        |          |        |          |           |
|                          | 12-1     | 0.346  |          | [26]      |
|                          | 12-3     | 1.384  |          | [26]      |
|                          | 12-6     | 0.346  |          | [26]      |
| Fluoroquinolone Generation | Name          | G +ve Bacteria          | Strain   | MIC (µM)   | Reference |
|----------------------------|---------------|-------------------------|----------|------------|-----------|
| Third Generation           | Levofloxacin  | S. epidermidis          |          |            |           |
|                            |               |                         | 12-8     | 11.069     | [26]      |
|                            |               |                         | 12-1     | 11.069     | [26]      |
|                            |               |                         | 12-6     | 88.552     | [26]      |
|                            |               |                         | MRSE 12-1| 0.083      | [69]      |
|                            |               |                         | MSSE 14-2| 354.210    | [68]      |
|                            |               |                         |          | >354.210   | [33,54]   |
|                            |               |                         |          | 354.210    | [68]      |
|                            |               |                         |          | 1.384      | [69]      |
|                            |               |                         |          | 2.767      | [68]      |
|                            |               |                         |          | 5.534      | [68]      |
|                            |               |                         |          | 88.552     | [55]      |
|                            |               |                         |          | 177.105    | [53,54]   |
|                            |               |                         |          | 88.552     | [53,54,68]|
|                            |               |                         |          | 177.105    | [53,54,68]|
|                            |               |                         |          | 177.105    | [53,54,68]|
|                            |               |                         |          | 5.540      | [51]      |
|                            |               | S. pneumoniae           |          |            |           |
|                            |               | ATCC 49619              | 0.346    | [69]      |
|                            |               | ATCC 19615              | 1.384    | [53,54,68]|
|                            | Sparifloxacin  | B. cereus               | 8035     | 0.484      | [44]      |
|                            |               | S. aureus               | 209p     | 0.484      |           |
|                            |               | B. subtilis             | NCDC 71  | 213.109    | [42]      |
|                            |               | B. polymyxa             | NCDC 64  | 26.639     | [42]      |
|                            | Gatifloxacin   | S. aureus               | NCDC 110 | 13.319     | [42]      |
|                            |               | ATCC 29213              | 0.333    | [71]      |
|                            |               | MSSA clinical isolates   | 0.333    | [71]      |
|                            |               | MRSA clinical isolates   | 42.622   | [71]      |
|                            |               | ATCC 12228              | 0.160    | [71]      |
|                            |               | S. epidermidis          | MSSE clinical isolates | 0.160 | [71] |
|                            |               | MRSE clinical isolates   | 0.160    | [71]      |
|                            | Moxifloxacin HCl| B. cereus                | Roma 709 | <1.370     | [28]      |
|                            |               | ATCC 33186              | 0.891    | [50]      |
|                            |               | E. faecalis             | 14-1     | 18.296     | [68]      |
|                            |               |                         | 14-2     | 36.539     | [68]      |
|                            |               |                         | 14-3     | 18.296     | [68]      |
|                            |               | ATCC 29212              | <1.370   | [28]      |
|                            |               | 14-1                   | 73.077   | [68]      |
|                            |               | 14-2                   | 1.142    | [68]      |
|                            |               | E. faecium              | MSSE 12-3| 0.284      | [26,69]   |
|                            |               | MSSE 12-6               | 0.069    | [26]      |
|                            |               | MSSE 12-8               | 2.284    | [26]      |
As illustrated in Table 3, ciprofloxacin was the most commonly adopted reference by the cited researchers against different Gram positive and negative bacterial stains, ciprofloxacin
MIC against Gram-positive bacteria including *B. cereus* spp. ranged from 0.181 µM [46]–3.954 µM [28], *S. aureus* ATCC 6538 (ranged from 1.509 µM [48]–146.978 µM [49]), *S. aureus* ATCC 29213 (MIC ranged from 0.082 µM [67]–1.509 µM [48]), and *S. aureus* ATCC 25923 (MIC ranged from 0.010 [52] µM –3.954 µM [28]). Remarkably, ciprofloxacin MIC varied within similar bacterial species, one example is *S. epidermidis* species, according to Liu et al., strain MSSE 12-1 of *S. epidermidis* species was susceptible to ciprofloxacin (MIC 0.755 µM) [26], whereas it showed very limited activity against MSSE14-2 strain (MIC > 386.308 µM) [53,54]. Interestingly, discrepancy in MIC values was observed between similar bacterial strains as reported by different research groups with 100-fold MIC difference [48,49]. Minor variation between the adopted testing protocol for MIC determination, such as incubation temperature might be the driving factor for such a difference [48,49].

Considering the third FQ reference, levofloxacin was adopted by many researchers’ as a reference control, and exhibited variable antimicrobial activity against *E. faecalis* (MIC ranged from 1.384 µM for *E. faecalis* 51575 [55], 177.220 µM for *E. faecalis* ATCC 700221 [51]) as an example. A notable difference in levofloxacin potency against different *staph* strains, including methicillin-sensitive *S. aureus* (MSSA) [26,53,54,68,69], methicillin-resistant *S. aureus* (MRSA) [26,53,54,68,69], *S. epidermidis*, and *S. pneumoniae* was observed (Table 3).

Following scientific reports in the literature, levofloxacin exhibited superior antibacterial activity against Gram-positive *S. epidermis* strains [51,55,63] and moxifloxacin is generally the most potent amongst FQs against Gram-positive and negative bacteria [26]. Moxifloxacin was the latent agent against the food poisoning pathogen *L. monocytogenes* ATCC 43251 (MIC < 1.370 µM [28]) when compared with other FQs as ciprofloxacin (MIC 3.954 µM–12.072 [28,64]) and norfloxacin (MIC < 8.267 µM [28]).

### 3.2. FQs Antibacterial Activity against Gram-Negative Bacteria

A summary of common laboratory tested Gram-negative bacteria and standard fluoroquinolones antibiotics are presented in Table 4. It is noticeable that ciprofloxacin has potential antibacterial activity against Gram-negative bacteria as *P. aeruginosa* and *E. coli*. [28,48]. Moreover, ciprofloxacin had prospective growth inhibitory activity against *H. pylori* NCTC 11916 and 12 more *H. pylori* clinical isolates as reported by Abu-Sini et al. [72]. Ciprofloxacin broad spectrum of activity against aerobic and anaerobic Gram-negative bacteria is shown in Table 4.

Nevertheless, Gorityala et al. [56] reported that ciprofloxacin potency against *P. aeruginosa* were superior compared to moxifloxacin. This pattern was also noticed in results published by Türe et al. and Garza et al., [28,50].

Norfloxacin inhibitory activity against a panel of Gram-negative bacterial type, and on the same bacterial strain is noted to be varied. For instance, norfloxacin in vitro antibacterial activity reported by Pardeshi et al. against *E. coli* ATCC 25922 varied from that reported by Leyva-Ramos et al. (MIC ranged from < 0.094 µM [24]–117.433 µM [45]). Moreover, norfloxacin and ciprofloxacin MIC against different *P. aeruginosa* strains ranged from 1.002 µM [1]–1565.773 µM [45] and <0.091 [62] µM–150.901 µM [42], respectively, in different studies. On the contrary, ciprofloxacin MIC against a panel of Gram–negative pathogens looks more consistent (*A. haemolyticus* ATCC 19002 (MIC 0.755 µM) [62], *A. baumannii* ATCC17961 (MIC 0.24 µM) [58], *A. calcoaceticus* ATCC 19606 (MIC 1.509 µM) [55], and *C. freundii* ATCC 43864 (MIC 1.38 µM) [51]. However, a wide range in ciprofloxacin MIC against *E. coli* ATCC 25922 is perturbing as MIC reported ranged from 0.002 µM [24]–61.869 µM [49] in different publications. This fluctuation in ciprofloxacin antibacterial activities may explain the current abundant application of levofloxacin and moxifloxacin as positive standards by medicinal chemists when designing and synthesizing novel FQs analogues [24,28,53–55,68–70,73–75].
### Table 4. Fluoroquinolones’ antibacterial activity against Gram-negative bacterial strains.

| Fluoroquinolone Generation | Name | G−ve Bacteria | Strain | MIC (µM) | Reference |
|---------------------------|------|---------------|--------|----------|-----------|
| Second Generation         | Norfloxacin | ATCC 8739 | E. coli | <0.251 | [1] |
|                           |       | ATCC 25922   |        | 3.132 | [43] |
|                           |       | ATCC 35218   |        | <0.094 | [24] |
|                           |       | F-50         |        | <1.879 | [28] |
|                           |       | NCDC 134     |        | 0.128 | [46] |
|                           |       | ATCC 9027    | K. pneumoniae | 9.708 | [44] |
|                           |       | ATCC 27853   |        | 1.002 | [1] |
|                           |       | ATCC 43288   | P. aeruginosa | >1565.773 | [45] |
|                           |       | ATCC 911     | Y. pseudotuberculosis | 4.134 | [28] |
| Lomefloxacin              |       | ATCC 911     |        | 1.879 | [28] |
|                           |       | F-50         |        | 0.128 | [46] |
|                           |       | 9027         | P. aeruginosa | 8.823 | [44] |
|                           |       | 19002        | A. haemolyticus | 0.240 | [58] |
|                           |       | 19002        | A. baumannii | 0.755 | [62] |
|                           |       | ATCC17961    |        | 0.240 | [58] |
|                           |       | CIP 7010     |        | 0.377 | [62] |
|                           |       | CAN-ICU 63169|        | 6.036 | [21] |
|                           |       | ATCC 43864   | A. coaceticus | 1.509 | [55] |
|                           |       | ATCC 4360    |        | 1.360 | [51] |
|                           |       | ATCC 43560   | E. aerogenes | ≤0.091 | [55] |
|                           |       | ATCC 13048   |        | 1.380 | [51] |
|                           |       | ATCC 14-11   | E. cloacae | ≤0.091 | [55] |
|                           |       | ESBLs(+)     |        | 24.144 | [54] |
|                           |       | 14-1         | E. coli | 24.144 | [54] |
|                           |       | 14-2         |        | 24.144 | [54] |
| Fluoroquinolone Generation | G−ve Bacteria Strain | MIC (µM) | Reference |
|---------------------------|----------------------|----------|-----------|
| ATCC-29213                | ≤0.755 [21,52]       |          |           |
|                           | <1.811 [28,63]       |          |           |
|                           | 0.024 [54,57]        |          |           |
|                           | 0.031 [48]           |          |           |
| ATCC 25922                | 0.010 [66]           |          |           |
|                           | 61.869 [49]          |          |           |
|                           | 0.091 [62]           |          |           |
|                           | 0.002 [24]           |          |           |
| NR 17663                  | 0.002 [24]           |          |           |
| NR 17666                  | 0.045 [24]           |          |           |
| NR 17661                  | 96.577 [24]          |          |           |
| ATCC 25922 ESBLs(−)       | ≤0.091 [55]          |          |           |
|                           | ≤0.080 [51]          |          |           |
| ATCC 25922 (wild type)    | ≤0.091 [76]          |          |           |
|                           | 0.045 [60,61]        |          |           |
| ATCC 35218                | 16.961 [34]          |          |           |
|                           | ≤0.080 [51]          |          |           |
| BW5328/pAH69 (wild type)  | ≤0.091 [76]          |          |           |
| CAN-ICU 61714 (GEN-R)     | ≤0.755 [21]          |          |           |
| CAN-ICU 63074 (AMK 32)    | ≤0.755 [21]          |          |           |
| CANWARD-2011 97615        | 772.616 [21]         |          |           |
| gyrA S83LD87N, parC S801 E84G, AcrA+ | >96.577 [76] |          |           |
| DC0                       | 0.470 [58]           |          |           |
| DC2                       | 0.240 [58]           |          |           |
| F-50                      | 0.573 [44]           |          |           |
| K12                       | 0.604 [50]           |          |           |
| K12 ΔlacI169              | 0.005                |          |           |
| K12 ΔlacI169 tolC::Tn10   | 0.001                |          |           |
| K12 ΔlacI169 tolC::Tn10 gyrA S83L | 0.019 [67] |          |           |
| K12 ΔlacI169 tolC::Tn10 gyrA D87Y | 0.009                |          |           |
| imp-4213 (permeable outer membrane) | ≤0.091 [76] |          |           |
| JW5503-1 (ΔtolC)          | ≤0.0.091 [76]        |          |           |
| MC4100 (wild type)        | ≤0.091 [76]          |          |           |
| NB27005-CDY0039 (ΔtolC, gyrA S83L D83G, parC S801) | 6.036 [76] |          |           |
| Fluoroquinolone | G–ve Bacteria | Strain | MIC (µM) | Reference |
|----------------|--------------|--------|----------|-----------|
| Generation     | Name         |        |          |           |

**E. coli**
- NCDC 134: 75.451 [42]
- NCTC 8196: 0.031 [48]
- ATCC 8739: 28.007 [65]
- Penicillin Resistant E. coli: 0.377 µM (68.9% survival of bacteria) [77]

**H. pylori**
- NCTC 11916: 1.811 [72]
- Clinical isolate: 0.905 [72]

**K. pneumoniae**
- ATCC 13883: ≤0.755 [21], 1.811 [28], 0.755 [62], 0.050 [66]
- ATCC 35657: 0.021 [60,61], 1.509 [55], ≤0.091 [55]
- ATCC 700603 ESBLs (+): 1.360 [51], 0.755 [63]
- 7 ESBLs(-): ≤0.091 [55], ≤0.080 [51]
- ESBL+ 14–17: 1.509 [54]
- ESBL+ 14–18: 1.509 [54]
- ESBL+ 14–19: 193.154 [54]
- 14-1: 96.577 [54]
- 14-2: 48.288 [54]
- 14-3: >386.308 [54]
- 14-4: 96.577 [54]

**M. catarrhalis**
- ATCC 25238: 0.091 [60,61]

**M. morganii**
- ATCC 25830: ≤0.091 [55], ≤0.080 [51]

**P. aeruginosa**
- ATCC 9027: 0.720 [57], 1.177 [41]
- ATCC 15442: 0.755 [46]
- ATCC 43288: <0.091 [62], 3.954 [28], 1.509 [48]
- ATCC 27853: 1.509 [54], 0.680 [51], 0.755 [55]
Table 4. Cont.

| Fluoroquinolone | G−ve Bacteria | Strain | MIC (µM) | Reference |
|-----------------|---------------|--------|----------|-----------|
| Generation | Name | | | |
| | ATCC 27853 | 0.755 | [62,63] |
| |  | 3.018 | [21] |
| | CAN-ICU 62308 (GEN-R) | 6.036 | [21] |
| | CANWARD-2011 96846 | 12.072 | [21] |
| | DSM 1117 Mueller–Hinton | 0.755 | |
| | DSM 1117 Succinate minimum medium | 0.755 | |
| | DSM 1117 Succinate minimum medium + FeCl₃ (1 lM) | 0.755 | [79] |
| | AM 85 Mueller–Hinton | 48.288 | |
| | AM 85 Succinate minimum medium | 48.288 | |
| | AM 85 Succinate minimum medium + FeCl₃ (1 lM) | 96.577 | |
| P. aeruginosa | K799/wt | 0.470 | [58] |
| | K799/61 | 0.240 | [58] |
| | K1542 (ΔmexX, DmexB) | 0.181 | [76] |
| | NCDC 105 | 150.901 | [42] |
| | NBS2023-CDK005 (ΔmexX, DmexB, gyrA T83I) | 1.509 | [76] |
| | NBS2023-CDK006 (ΔmexX, ΔmexB, gyrA T83I, parC S87L) | 12.072 | [76] |
| | PAO1 | 1.177 | [50] |
| | PA01 (Wild type) | 0.377 | [76] |
| | - | 5.030 | [47] |
| | - | 0.589 | [49] |
| | 14-9 | 1.509 | [54] |
| | 14-14 | 3.018 | [54] |
| | 14-15 | 3.018 | [54] |
| | 14-16 | 3.018 | [54] |
| P. mirabilis | ATCC 12453 | 0.045 | [57] |
| | ATCC 49565 | ≤0.080 | [51] |
| | 13-1 | ≤0.091 | [55] |
| P. rettgeri | ATCC 31052 | ≤0.091 | [55] |
| |  | ≤0.080 | [51] |
| P. vulgaris | ATCC 29905 | ≤0.091 | [55] |
| |  | ≤0.080 | [51] |
| Fluoroquinolone | G–ve Bacteria         | Strain                  | MIC (µM) | Reference |
|----------------|-----------------------|-------------------------|----------|-----------|
| **Generation**| **Name**              |                         |          |           |
|                | **S. marcescens**     | ATCC 21074              | 0.160    | [51]      |
|                |                       |                         | 0.181    | [55]      |
|                | **S. maltophilia**    | ATCC 13636              | 5.450    | [51]      |
|                |                       | CAN-ICU 62584           | 1.325    | [56]      |
|                | **S. pneumoniae**     | ATCC 49619              | 0.755    | [26]      |
|                |                       | 12-18                   | 3.018    | [26]      |
|                | **Y. pseudotuberculosis** | ATCC 911              | 1.812    | [28]      |
|                | **E. aerogenes**      | ATCC 13048              | 0.086–0.172 | [64] |
|                |                       | CM64                    | 0.022 (pH 7.4) | [64] |
|                |                       |                         | <1.636   | [28]      |
|                | **K. pneumoniae**     | ATCC 13883              | ≤0.083   | [51]      |
|                | **P. aeruginosa**     | ATCC 43288              | ≤0.083   | [51]      |
|                | **Y. pseudotuberculosis** | ATCC 911              | <1.636   | [28]      |
|                | **A. coaceticus**     | ATCC 19606              | 0.346    | [55]      |
|                |                       |                         | 0.350    | [51]      |
|                | **C. freundii**       | ATCC 43864              | ≤0.083   | [55]      |
|                |                       |                         | ≤0.080   | [51]      |
|                | **E. aerogenes**      | ATCC 13048              | 0.166    | [55]      |
|                |                       |                         | 0.170    | [51]      |
|                | **E. cloacae**        | ATCC 43560              | ≤0.083   | [55]      |
|                |                       |                         | ≤0.080   | [51]      |
|                | **E. coli**           | ATCC 25922              | 0.346    | [55]      |
|                |                       |                         | 0.0412   | [24]      |
|                |                       |                         | <0.022   | [69]      |

**Ciprofloxacin HCl**

| Generation | **Name** | Strain                  | MIC (µM) | Reference |
|------------|----------|-------------------------|----------|-----------|
|            | **E. coli** | ATCC 25922 | <0.083   | [55]      |
|            |           | ATCC 25922 ESBLs−     | 88.610   | [51]      |
|            |           | ATCC 35218 ESBLs+     | ≤0.080   | [51]      |
|            |           | NR 17663              | 0.083    | [24]      |
|            |           | NR 17666              | 0.083    | [24]      |
|            |           | NR 17661              | 88.552   | [24]      |
|            |           | 12-6                  | 0.692    | [69]      |
|            |           | 12-11                 | 11.069   | [69]      |
|            | **ESBL+ 14-1** |              | 11.069   | [54]      |
|            |           |                       | 44.276   | [69]      |
|            |           |                       | 5.534    | [68]      |
Table 4. Cont.

| Fluoroquinolone Generation | G–ve Bacteria | Strain       | MIC (µM)       | Reference |
|----------------------------|---------------|--------------|----------------|-----------|
| Third Generation           | Levofloxacin  | ATCC 700603 ESBLs⁺ | 1.364          | [55]      |
|                            |               | ATCC 700603 ESBLs⁻ | 1.380          | [51]      |
|                            |               | ESBLs⁺        | ≤0.082         | [55]      |
|                            |               | ESBLs⁻        | 0.170          | [51]      |
|                            |               | 12-4          | 0.082          | [69]      |
|                            |               | 12-7          | 1.363          | [69]      |
|                            |               | ATCC 27853    | 2.726          | [54,55,68]|
|                            |               | 14-9          | 1.363          | [54]      |
|                            |               | 14-11         | 2.726          | [68]      |
|                            |               | 14-14         | 5.453          | [68]      |
|                            |               | 14-15         | 5.453          | [54,68]   |
|                            |               | 14-16         | 5.453          | [54]      |
|                            |               | 14-19         | 5.453          | [68]      |
|                            |               | 12-12         | 1.363          | [69]      |
|                            |               | 12-14         | 87.241         | [69]      |
|                            |               | 12-20         | 21.810         | [69]      |
|                            | M. morganii    | ATCC 25830    | ≤0.083         | [55]      |
|                            |               |               | ≤0.080         | [51]      |
|                            | K. pneumoniae | ESBL⁺ 14-2    | 21.810         | [54]      |
|                            |               | 14-1          | 21.810         | [68]      |
|                            |               | 14-2          | 10.905         | [68]      |
|                            | K. pneumoniae | ESBL⁺ 14-17   | 1.363          | [54]      |
|                            |               | 14-18         | 2.276          | [68]      |
|                            | K. pneumoniae | ESBL⁺ 14-19   | 174.482        | [54,68]   |
|                            |                | 14-1          | 43.621         | [54,68]   |
|                            |                | 14-2          | 21.810         | [54]      |
|                            | P. aeruginosa  | ATCC 27853    | 2.726          | [54,55,68]|
|                            |                | 14-9          | 1.363          | [54]      |
|                            |                | 14-11         | 2.726          | [68]      |
|                            |                | 14-14         | 5.453          | [68]      |
|                            |                | 14-15         | 5.453          | [54,68]   |
|                            |                | 14-16         | 5.453          | [54]      |
|                            |                | 14-19         | 5.453          | [68]      |
|                            |                | 12-12         | 1.363          | [69]      |
|                            |                | 12-14         | 87.241         | [69]      |
|                            |                | 12-20         | 21.810         | [69]      |

ESBL: Extended Spectrum Beta-Lactamase
| Fluoroquinolone | G−ve Bacteria | Strain     | MIC (µM) | Reference |
|-----------------|---------------|------------|----------|-----------|
| **Third Generation** Levofloxacin |             |            |          |           |
|                 | *P. mirabilis* | 13-1       | 0.166    | [55]      |
|                 |               | ATCC 49565 | ≤0.080   | [51]      |
|                 | *P. rettgeri* | ATCC 31052 | ≤0.080   | [51]      |
|                 |               |            | ≤0.83    | [55]      |
|                 | *P. vulgaris* | ATCC 29905 | ≤0.080   | [51]      |
|                 |               |            | ≤0.083   | [55]      |
|                 | *S. maltophilia* | ATCC 13636 | 2.767    | [55]      |
|                 |               |            | 1.380    | [51]      |
|                 | *S. marcescens* | ATCC 21074 | 0.350    | [51]      |
|                 |               |            | 0.356    | [55]      |
|                 | *S. pneumoniae* | ATCC 49619 | 0.345    | [26]      |
|                 |               | 12-18      | 2.535    | [26]      |
| **Sparifloxacin** |             |            |          |           |
|                 | *E. coli*     | F-50       | 0.484    | [44]      |
|                 | *P. aeruginosa* | ATCC 9027 | 0.484    | [44]      |
| **Gatifloxacin** |             |            |          |           |
|                 | *E. coli*     | ATCC 700603 | 0.160    | [71]      |
|                 |               | NCDC 134   | 266.387  | [42]      |
|                 | *K. pneumoniae* | ATCC 25922 | 2.664    | [71]      |
|                 | *P. aeruginosa* | NCDC 105  | 106.555  | [42]      |
|                 | *A. baumannii* | ATCC 19606 | 0.972    | [50]      |
|                 |               | ATCC 25922 | 0.137    | [68]      |
|                 |               |            | <0.018   | [69]      |
|                 |               |            | 0.037    | [24]      |
|                 |               |            | <1.370   | [28]      |
|                 | *E. coli*     | NR 17663   | 0.037    | [24]      |
|                 |               | NR 17666   | 0.075    | [24]      |
|                 |               | NR 17661   | 79.715   | [24]      |
|                 |               | 12-6       | 1.142    | [69]      |
|                 |               | 12-11      | 36.539   | [69]      |
| **Moxifloxacin HCl** |             |            |          |           |
|                 | *K. pneumoniae* | ATCC 13883 | <1.370   | [28]      |
|                 |               | ESBL* 14-17 | 18.269   | [68]      |
|                 |               | ESBL* 14-18 | 2.284    | [68]      |
|                 |               | ESBL* 14-19 | 146.155  | [68]      |
|                 |               | 14-1       | 18.269   | [68]      |
|                 |               | 14-2       | 18.269   | [68]      |
Table 4. Cont.

| Fluoroquinolone | G−ve Bacteria | Strain    | MIC (µM) | Reference |
|-----------------|--------------|-----------|----------|-----------|
| Generation      | Name         |           |          |           |
|                 | K. pneumonia | 14-3      | 73.077   | [68]      |
|                 |              | 14-4      | 18.269   | [68]      |
|                 |              | 12-4      | 0.069    | [69]      |
|                 |              | ESBL+ 12-7| 1.142    | [69]      |
|                 | S. pneumonia | ATCC 49619| 0.137    | [26]      |
|                 |              | 12-18     | 1.142    | [26]      |
|                 | ATCC 27853   |           | 4.567    | [68]      |
|                 | ATCC 43288   |           | 11.601   | [28]      |
|                 | Moxifloxacin HCl | 14-9    | 9.135    | [68]      |
|                 |              | 14-11     | 36.539   | [68]      |
|                 |              | 14-15     | 36.539   | [68]      |
|                 |              | 14-16     | 18.269   | [68]      |
|                 |              | 14-19     | 2.284    | [68]      |
|                 |              | PA01      | 7.722    | [50]      |
|                 |              | 12-12     | 4.567    | [69]      |
|                 |              | 12-14     | 36.539   | [69]      |
|                 |              | 12-20     | 18.269   | [69]      |
|                 | P. aeruginosa | ATCC 911  | <1.495   | [28]      |
|                 | Y. pseudotuberculosis |          |          |           |

ZOI: Zone of Inhibition; NZ: No Zone; ND: Not Detected; Acinetobacter baumannii (A. baumannii); Acinetobacter calcoaceticus (A. calcoaceticus); Acinetobacter haemolyticus (A. haemolyticus); American Type Culture Collection (ATCC); Citrobacter freundii (C. freundii); China Center of Industrial Culture Collection (CMCC); Enterobacter aerogenes (E. aerogenes); Enterobacter cloacae (E. cloacae); Escherichia coli (E. coli); Extended spectrum beta-lactamases (ESBL); Helicobacter pylori (H. pylori); Klebsiella pneumonia (K. pneumonia); Moraxella catarrhalis (M. catarrhalis); Morganella morganii (M. morganii); Nigeria Centre for Disease Control (NCDC); Providencia rettgeri (P. rettgeri); Pseudomonas aeruginosa (P. aeruginosa); Proteus mirabilis (P. mirabilis); Proteus vulgaris (P. vulgaris); Serratia marcescens (S. marcescens); Stenotrophomonas maltophilia (S. maltophilia); Streptococcus pneumoniae (S. pneumoniae); Yersinia pseudotuberculosis (Y. pseudotuberculosis).

As presented in Table 4, different studies reported the use of third generation levofloxacin as a positive control against a wide range of Gram-negative organisms includes P. aeruginosa. For this infectious pathogen, MIC ranged from 5.453 µM [68] for P. aeruginosa 14–19 strain to 87.241 µM [69] for P. aeruginosa 14–2 strain. Similarly, levofloxacin MIC against K. pneumonia ranged from 0.082 µM [69] for K. pneumonia 12–4 strain to 87.241 µM [54] for K. pneumonia 14–3 strain. According to Zhang et al., [69] levofloxacin is around five hundred time more potent against K. pneumonia 12–4 strain compared to P. aeruginosa 14–2 strain. It is worth mentioning that the bacterial strain is the variant factor in both articles. This indeed highlights the importance of referring to the relevant standard control during laboratory investigation and comparisons.

A similar pattern of the wide range of MIC values against the same strain was observed, where the MIC of norfloxacin against E. coli ATCC-25922 ranged from <0.094 µM [24] to 117.433 µM [45].

3.3. FQs’ Antimycobacterial Activity

FQs, particularly ciprofloxacin was included as a positive control along with isoniazid and rifampicin against various Mycobacterium strains as shown in Table 5 [24,26–28,58,63,65,68,75,81,82]. Furthermore, levofloxacin in vitro anti-mycobacterial activity was reported
and found to be comparable to ciprofloxacin [26,68]. Recent studies by Hu et al., [82] and Mohammed et al., [65] declared moxifloxacin in vitro anti-mycobacterial activity to be more potent than both ciprofloxacin 1 and levofloxacin 3.

Table 5. Fluoroquinolones’ antimycobacterial activity.

| Fluoroquinolone Generation | Mycobacterium Name | Mycobacterium Strain | MIC (mM) | Reference |
|----------------------------|-------------------|----------------------|----------|-----------|
| Norfloxacin                | M. smegmatis      | ATCC 607             | 16.503   | [28]      |
|                            |                   |                      |          |           |
|                            |                   |                      | 36.216–51.307 | [63]      |
|                            |                   | MTB H37Rv            | 0.755    | [26,68]  |
|                            |                   |                      |          |           |
| Second Generation          | Ciprofloxacin     | M. tuberculosis      |          |           |
|                            |                   | MTB H37Rv ATCC 27294 | 0.755    | [26,68]  |
|                            |                   | MDR-TB               | 6.036    | [81]      |
|                            |                   | MDR-MTB 6133 resistant to INH and RFP | 0.377 | [26]      |
|                            |                   | MDR-MTB 11277 resistant to INH and RFP | 0.377 | [26]      |
|                            |                   | M. vaccae IMET10670  | 0.470    | [58]      |
|                            | M. smegmatis      | ATCC607              | >120.721 | [28]      |
|                            |                   |                      |          |           |
| Cipro HCl                  |                   | M. smegmatis         | >109.052 | [28]      |
|                            |                   |                      |          |           |
| Third Generation           | Levofloxacin      | M. tuberculosis      |          |           |
|                            |                   | MTB H37Rv ATCC 27294 | 0.692    | [26,68]  |
|                            |                   | MDR-MTB 6133 resistant to INH and RFP | 0.377 | [26]      |
|                            |                   | MDR-MTB 11277 resistant to INH and RFP | 0.692 | [26]      |
|                            |                   | R2012-123 (pan-sensitive) | 0.692 | [65]      |
|                            |                   | M. abscessus         | 5.535    | [24]      |
|                            |                   | M. chelonae          | 5.535    | [24]      |
|                            |                   | M. fortuitum         | 0.346    | [24]      |
|                            |                   | M. avium             | ND       | [75]      |
|                            |                   | M. terrae            | ND       | [75]      |
|                            |                   | R-2012-59 (MDR)      | 0.692    | [65]      |
|                            |                   | R-2012-97 (XDR)      | 22.138   | [65]      |
|                            |                   | M. abscessus         | ATCC19977 | >88.552 | [65]      |
|                            |                   | M. chelonae          | ATCC38752| 1.384    | [65]      |
|                            |                   | M. fortuitum         | ATCC06841| 0.346    | [65]      |
Table 5. Cont.

| Fluoroquinolone Generation | Mycobacterium Bacteria | Strain | MIC (mM) | Reference |
|---------------------------|------------------------|--------|----------|-----------|
| Moxifloxacin              | M. tuberculosis        |        |          | [65]      |
|                           | H37Rv ATCC27294        | 0.311  |          | [65]      |
|                           | MTB H37Rv              | 0.228  |          | [82]      |
|                           | MDR-TB                 | 0.274  |          | [82]      |
|                           | R2012-123 (pan-sensitive) | 0.137 |          | [65]      |
|                           | M. smegmatis (MXF HCl) | ATCC607 | >91.347 | [28]      |
|                           | Antituberculosis       |        | 0.440    | [28]      |
|                           | R-2012-59 (MDR)        |        | ≤0.069   | [65]      |
|                           | R-2012-97 (XDR)        |        | 4.567    | [65]      |
|                           | M. abscessus           | ATCC19977 | >73.077 | [65]      |
|                           | M. chelonae            | ATCC35752 | 0.571  | [65]      |
|                           | M. fortuitum           | ATCC06841 | 0.137  | [65]      |

ND: Not determined; Mycobacterium abscessus (Mycobacterium abscessus); Mycobacterium avium (M. avium); Mycobacterium chelonae (M. chelonae); Multi drug resistant Tuberculosis (MDR-TB); Mycobacterium fortuitum (M. fortuitum); Mycobacterium smegmatis (M. smegmatis); Mycobacterium terrae (M. terrae); Mycobacterium tuberculosis (MTB).

3.4. FQs’ Antifungal, Antiparasitic, and Anticancer Activity

Apart from their antibacterial activity, FQs were also tested for their antifungal activity with little effect on most fungi. Since the late 1980s, studies revealed anti-trypanosomal activity for the quinolones prototype, nalidixic, and oxolonic acid derivatives [14]. Other studies illustrated the antiparasitic activity of norfloxacin against Plasmodium falciparum and the inhibitory effect of other fluoroquinolones against Plasmodium family [14,83,84]. Today, quinolone-amides related derivatives were used to design anti-trypanosomal compounds with many of them presenting potential in vivo activity [85].

Anticancer activity of FQs were also evaluated against a range of cancer cell lines, such as A549 Lung adenocarcinoma, HCT-116 colon cancer, MCF-7 breast cancer cell lines, and others have been determined previously and compared with the developed counterparts [48,50,61,66] as presented in Table 6.

Table 6. Fluoroquinolones’ antifungal and anticancer activity.

| Fluoroquinolone Generation | Fungi and Cancer | Strain | Inhibitory Effect | Reference |
|----------------------------|-----------------|--------|------------------|-----------|
| Second Generation Norfloxacin | C. albicans | ATCC 60193 | No zone of inhibition | [28] |
|                            | S. cerevisiae   | RSKK 251 | No zone of inhibition | [86] |
| Ciprofloxacin              | A. clavatus     |        | No zone of inhibition | [86] |
|                            | C. albicans     | ATCC 90873 | MIC 97.784 µM | [34] |
|                            |                 | amphotericin B-resistant |          |          |
|                            | C. albicans     | ATCC 60193 | No zone of inhibition | [86] |
|                            |                 | MIC 100 µM | GI_{50} 30.9 ± 3.3 µM | [66] |
|                            | T. brucei       | 427/421 | No zone of inhibition | [66] |
|                            | Lung adenocarcinoma | A549 | MIC 50 µM | [61] |
| Fluoroquinolone Generation | Fungi and Cancer | Strain | Inhibitory Effect | Reference |
|-----------------------------|------------------|--------|-------------------|-----------|
| Colon cancer                | HCT-116          | MIC 50 µM | [61]               |
| Breast cancer               | MCF-7            | MIC 50 µM | [61]               |
| HEPG2, liver hepatocellular carcinoma cells | ATCC HB-8065 | IC₅₀ ≥ 1207.211 µM | [50] |
| Vero, kidney epithelial cells | ATCC CCL-81. | IC₅₀ ≥ 1207.211 µM | [50] |
| Human primary colon cancer  | (SW480) | 160.4 ± 6.7 µM | [48] |
| Human metastatic colon cancer | (SW620) | 101.4 ± 6.7 µM | [48] |
| Human metastatic prostate cancer | (PC3) | 101.4 ± 6.7 µM | [48] |
| Human immortal keratinocyte cell line from adult human skin | (HaCaT) | IC₅₀ 222.1 ± 5.2 µM | [48] |

**Ciprofloxacin**

| LDH release | HaCaT | LDH release % 4.6% at 60 µM 4.2% 40 µM 3.9% 20 µM 3.2% 10 µM | [48] |
| LDH release | SW480 | LDH release % 15% at 60 µM 14.5% at 40 µM 14.2% at 20 µM 12% at 10 µM | [48] |
| LDH release | SW620 | LDH release % 9.3% at 60 µM 9.1% at 40 µM 8.9% at 20 µM 8.1% at 10 µM | [48] |
| LDH release | PC3 | LDH release % 18% at 60 µM 17.5% at 40 µM 16.5% at 20 µM 14% at 10 µM | [48] |

**Urease inhibitory activity**

| Urease inhibitory activity | 94.32 µM | [78] |

**HL-60**

| MIC > 100 µM | Gl₅₀ > 100 µM | [66] |

**Selectivity**

| MIC > 1 µM ratio | Gl₅₀ > 3.2 µM ratio | [66] |

**L929**

| Gl₅₀ >100 ± n.d. µM | [66] |

**HeLa**

| Gl₅₀ 560 ± 22.6 µM | [66] |

**DNA gyrase**

| IC₅₀ 0.15 µM | [66] |
Table 6. Cont.

| Fluoroquinolone Generation | Name           | Fungi and Cancer Strain    | Inhibitory Effect          | Reference   |
|----------------------------|----------------|---------------------------|---------------------------|-------------|
|                            |                |                           |                           |             |
| Cipro HCl                  |                | Topoisomerase IV          | 4.00 µM [66]              |             |
|                            |                | Cytotoxicity              | >100 µM [27]              |             |
|                            |                | *C. albicans* ATCC 60193   | No inhibition [28]        |             |
|                            |                | *S. cerevisiae* RSKK 251  | No inhibition [28]        |             |
|                            |                | Vero Cells                | CC\textsubscript{50} > 276.73 µM [70] |             |
|                            |                | A549                      | 76.3 ± 6.51 µM            |             |
|                            |                | HepG2                     | >100 µM                   |             |
|                            |                | MCF-7                     | 64.2 ± 5.67 µM            | [87]        |
|                            |                | PC-3                      | >100 µM                   |             |
|                            |                | HeLa                      | 71.1 ± 4.98 µM            |             |
|                            |                | MCF-10A (Human breast epithelial cell line) | >100 µM |             |
|                            |                | *S. cerevisiae* RSKK 251  | No inhibition [28]        |             |
|                            |                | HEPG2, liver hepatocellular carcinoma cells | ATCC HB-8065 | ≥ 996.435 µM [50] |
|                            |                | Vero, kidney epithelial cells | ATCC CCL-81 | ≥ 996.435 µM [50] |

Micrococcus luteus (M. luteus); Candida albicans (C. albicans); Saccharomyces cerevisiae (S. cerevisiae); Aspergillus clavatus (A. clavatus); Trypanosoma brucei (T. brucei); lactate dehydrogenase (LDH); The half maximal inhibitory concentration (IC\textsubscript{50}). Minimum inhibitory concentration (MIC); Concentration causing 50% cell growth inhibition (GI\textsubscript{50}).

3.5. FQs Inhibitory Effect as Anti-Viral Agents against SARS-CoV-2 and HIV-1

As researchers investigate several approaches to combat COVID-19 infection, there is a wide interest in fluoroquinolones. Ciprofloxacin and Moxifloxacin were tested through in silico molecular docking and showed the potential binding capacity to SARS-CoV-2 main protease (M\textsubscript{pro}) and low binding energy. Moreover, a recent study evaluated the potency and cellular toxicity of selected FQs (enoxacin, ciprofloxacin, levofloxacin, and moxifloxacin) against SARS-CoV-2 and MERS-COV. This study showed that a high concentration of the tested FQs should be employed to prevent viral replication with enoxacin being the superior (EC\textsubscript{50} of 126.4) against SARS-CoV-2 [14,83,84]. Other studies evaluated FQs anti-HIV-1 activities. However, FQs standards activity were not presented [65].

4. Recommendations

Based on recently published research where FQs were used as positive controls against several microorganisms and cancer cells, it is recommended to use the most active FQ in future studies in addition to the parent drugs to compare the benefits and to have an accurate insight when reporting results.

The difference perceived in FQs’ potency according to different research articles is challenging and could be attributed to several factors, including the different testing protocols implemented by each research group, solvents or broth used in bacterial culturing, incubation time, bacterial concentration tested, bacterial growth phase, reader instrument sensitivity, etc.

Ciprofloxacin is recommended to be used as a control against Gram-negative bacteria whether resistant or susceptible. If mainly Gram-positive activity is concerned, levofloxacin or moxifloxacin might be the best choices. The wide-spectrum and potent newer generations should be compared with, when broader comparison is desired. Choose moxifloxacin...
if the development of newer FQs derivatives is not a biologically-based design. This should provide a proper perspective when reporting novel FQs and their activities. Working against Mycobacterium stains, moxifloxacin was found to be more active compared to the other FQs, thus it is advisable to consider it as a positive control.

Moreover, the authors spur adopting preliminary activity testing of the chosen strains before commencing biological evaluation of interest as some of the stains might not be susceptible to the reference drugs. Lastly, given that some stains exhibited varied MIC values against the same drug, we recommend revising the adopted protocols beforehand to get more accurate comparable results of the reference drug, which will be then more reliable to base the conclusions upon.

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