

Fluoroquinolones beyond bacterial infections: exploring their anti-inflammatory and antiviral potential

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Abstract:

Fluoroquinolones (FQs) are under growing focus as immunomodulating drugs, traditionally known for their broad-spectrum antibacterial action. This narrative review synthesizes in vitro, in vivo and clinical evidence retrieved from PubMed, ScienceDirect, Scopus, Web of Science and Google Scholar. Particularly by phosphodiesterase (PDE) inhibition, recent studies show how well FQs can alter important inflammatory pathways including mitogen-activated protein kinases (MAPKs), nuclear factor-kappa B (NF- κ B), toll-like receptor 4 (TLR4), and the cyclic adenosine monophosphate (cAMP) pathway. Implicated in many inflammatory illnesses, these actions reduce pro-inflammatory cytokines including TNF- α , IL-1 β , IL-6, IL-8, and IL-17. Their effects on regulatory cytokines including IL-2, IL-4, IL-10, and TGF- β , however, depend on medication type, dose, cell origin, and illness situation. This emphasizes the difficulty of FQ-mediated immune regulation and the need for more investigation to define the fundamental processes.

Recent research has also shown fresh intracellular targets for FQs implicated in autoimmune disorders like psoriasis: phosphoinositide 3-kinase gamma (PI3K γ) and tyrosine kinase 2 (TYK2). Functionalized FQ derivatives, such as R-2TCBA and 2-AnisCEtA, have shown significant anti-inflammatory activity, mainly through the suppression of macrophage nitric oxide generation, without any antibacterial effects. This implies the possibility of creating non-antimicrobial FQ analogues for therapeutic application in inflammatory illnesses. The therapeutic use of FQs as anti-inflammatory drugs is still limited even if the present body of data is strong and experimental models span human cell lines to animal models and modern molecular methods. To promote the repurposing of FQs for chronic inflammatory diseases, important gaps in clinical research need to be addressed. These comprise elucidation of the cytokine modulation patterns linked with various FQs, generation of non-antimicrobial FQ derivatives to prevent antimicrobial resistance, and more mechanistic research on new intracellular targets such as TYK2 and PI3K γ . Moreover, thorough safety profiles are required as long-term FQ usage has documented hazards including tendinopathy, neurotoxicity, and cardiac arrhythmias. Ultimately, developing a legal and pharmacological framework for repurposing FQs can hasten their development as effective anti-inflammatory treatments.

Keywords: Fluoroquinolones, Antiviral, Anti-inflammatory, Immunomodulation, Cytokines, Drug repurposing

Introduction

Quinolones are synthetic, broad-spectrum antimicrobial agents structurally characterized by the presence of a 1,4-dihydro-4-oxo-quinoline ring and a carboxyl group at the C-3 position, both of which are essential for their antimicrobial activity. These structural components have played a pivotal role in guiding the design and development of successive generations of quinolone derivatives, improving both antibacterial efficacy and pharmacokinetic profiles over time. The therapeutic application of quinolones began in 1962 with the accidental discovery of nalidixic acid, a byproduct of chloroquine synthesis [1]. Although nalidixic acid was found to be effective in treating urinary tract infections, it was limited by a narrow antibacterial spectrum and poor pharmacokinetics. Despite its

limitations, nalidixic acid laid the foundation for the development of more potent and versatile quinolone compounds. During the 1970s, scientific focus shifted toward synthesizing novel quinolone derivatives with enhanced antibacterial properties. This research led to the introduction of second-generation compounds such as piperimidic acid, oxolinic acid, and cinoxacin [2]. These early derivatives offered only modest improvements in antibacterial range and clinical effectiveness over nalidixic acid, yet they provided critical insights into the structure–activity relationship (SAR) of quinolones, paving the way for the development of more advanced generations.

A breakthrough occurred with the emergence of fluoroquinolones, a class of quinolones characterized by the addition of a fluorine atom at the C-6 position of the quinoline ring. Representative fluoroquinolones, including ciprofloxacin, levofloxacin, and moxifloxacin, are known for their enhanced antibacterial spectrum, improved tissue penetration, and superior pharmacokinetic profiles [3]. Interestingly, beyond their established antibacterial role, fluoroquinolones have demonstrated potential antiviral activity against a range of positive-sense, single-stranded RNA viruses, including dengue virus, Zika virus, hepatitis C virus, and rhinovirus [4]. Although the precise mechanisms underlying their antiviral actions are not fully understood, accumulating evidence suggests that fluoroquinolones may interfere with viral replication and viral enzyme activity.

During the COVID-19 pandemic, fluoroquinolones were explored for repurposing as potential treatments for SARS-CoV-2 infection. A large-scale in vitro screening of FDA-approved drugs identified enoxacin and levofloxacin as potent inhibitors of SARS-CoV-2, with activity surpassing that of arbidol, a known antiviral agent [5]. Further in silico molecular docking studies supported these findings, revealing that enoxacin, ciprofloxacin, and moxifloxacin could potentially inhibit the SARS-CoV-2 main protease, a vital enzyme in the viral replication cycle. Given their known pharmacokinetics, safety profiles, and immunomodulatory properties, levofloxacin and moxifloxacin have been proposed as promising adjunct therapies for COVID-19 pneumonia. Moreover, because both SARS-CoV-2 and MERS-CoV possess positive-sense, single-stranded RNA genomes, it is hypothesized that fluoroquinolones such as enoxacin, ciprofloxacin, levofloxacin, and moxifloxacin may also suppress the replication of other betacoronaviruses in vitro, thus underscoring their therapeutic potential in emerging viral infections. However, subsequent cell-culture testing showed that enoxacin, ciprofloxacin, levofloxacin and moxifloxacin suppress SARS-CoV-2 and MERS-CoV replication only at high micromolar concentrations, indicating limited antiviral activity [4].

In addition to their antimicrobial and antiviral activities, fluoroquinolones have been found to possess significant immunomodulatory and anti-inflammatory properties. These non-antimicrobial effects have been well documented in various studies, highlighting their capacity to modulate immune responses and inflammatory mediators [6,7]. Fluoroquinolones can downregulate the synthesis of key pro-inflammatory cytokines such as interleukin-1 β (IL-1 β), IL-6, IL-8, and tumor necrosis factor- α (TNF- α), which are central to the inflammatory response [8–10]. These anti-inflammatory effects are believed to be mediated through the inhibition of nuclear factor kappa B (NF- κ B), a transcription factor that regulates the expression of various inflammatory genes. Another proposed mechanism involves the inhibition of phosphodiesterase (PDE) activity, which results in elevated intracellular cyclic adenosine monophosphate (cAMP) levels, thereby attenuating the expression of inflammatory mediators such as TNF- α [7,9].

Structural features of fluoroquinolones may also influence their immunomodulatory effects.

The presence of a cyclopropyl moiety at the nitrogen-1 position of the quinolone ring has been associated with enhanced activity against Gram-negative bacteria and increased stimulation of interferon-gamma (IFN- γ) production in human immune cells [6,7]. Furthermore, the dual nature of fluoroquinolones as both lipophilic and metal-chelating agents has been implicated in their ability to modulate glycation pathways and inflammatory responses [11].

In conclusion, the development of quinolones from nalidixic acid to fluoroquinolones represents a remarkable trajectory in antimicrobial research. While fluoroquinolones have long been appreciated for their antibacterial efficacy, recent findings reveal a broader pharmacological profile encompassing antiviral and immunomodulatory properties. These multifaceted activities position fluoroquinolones not only as valuable antimicrobial agents but also as potential therapeutic tools in the management of viral infections and inflammatory diseases.

Methodology

This study was designed as a narrative review. Relevant literature was identified through searches of the Scopus, Web of Science, PubMed, ScienceDirect and Google Scholar databases using combinations of the keywords “quinolones”, “fluoroquinolones”, “antiviral”, “HIV”, “anti-inflammatory”, “immunomodulation”, “cytokines” and “drug repurposing”. Peer-reviewed original research (in vitro, in vivo and clinical studies), review articles, patents and relevant theses published in English until 2024 were considered.

Records were screened by title and abstract, and full texts were assessed for relevance. Studies were included if they reported the antiviral activity, anti-inflammatory or immunomodulatory mechanisms, or structure–activity relationships of quinolones and fluoroquinolone derivatives, while studies limited solely to antibacterial activity were excluded. Data on the compound, virus or disease model, mechanism of action and observed effects were extracted and synthesized thematically into antiviral and anti-inflammatory sections.

Fluoroquinolones as Antiviral Agents

Early Observations of Antiviral Potential

Quinolones kill bacteria, but early research also examined non-bacterial disorders. Since quinolones might bind to bacterial DNA, the first hypothesis concerning their ability to bind to viral nucleic acids emerged. Many viruses require topoisomerase-like enzymes for replication and transcription, which are vital to their life cycles. Because some viral enzymes resemble bacterial topoisomerases, researchers hypothesized that quinolones might also have antiviral activity. Thus, quinolone antiviral activity was tested in a series of exploratory studies to better understand their potential applications.

Unlike penicillins and tetracyclines, quinolones are not derived from living organisms but are fully synthetic. Nalidixic acid, the first agent in this group, was produced from chloroquine, an antimalarial. A fortuitous discovery started a new antibacterial era. Scientists deliberately changed quinolone side chains and chemical frameworks to increase pharmacological properties and antibacterial spectrum [12].

The creation of the fluoroquinolone subclass represents a major accomplishment in this field. This group is defined by the incorporation of a fluorine atom at the C-6 position of the quinolone ring, a change that markedly enhanced bacterial cell penetration and expanded antibacterial efficacy. Fluoroquinolones were later categorized into generations according to their structural characteristics and range of antibacterial efficacy.

The initial quinolones, exemplified by nalidixic acid, demonstrated efficacy predominantly against aerobic Gram-negative bacteria. Nevertheless, they demonstrated restricted effectiveness against aerobic Gram-positive bacteria and little action against anaerobic pathogens. With the advancement of research, second-generation drugs were developed, including the initial fluoroquinolones. These chemicals demonstrated increased efficacy against Gram-negative bacteria and showed moderate enhancements in the coverage of Gram-positive species. Subsequent refining led to the development of third-generation fluoroquinolones, which have enhanced efficacy against Gram-positive bacteria, especially *Streptococcus pneumoniae*, while preserving substantial action against anaerobes. The fourth generation of fluoroquinolones exhibited an expanded spectrum of action, providing enhanced effectiveness against pneumococci and anaerobic bacteria [13].

Mechanism of Action of Quinolones

Quinolones can exert their principal activity by disrupting the catalytic cycle of topoisomerases [14]. This is especially true during the phase in which the enzyme is still covalently connected to the cleaved DNA strand, which is a transitional state that is referred to as the cleavable complex. The three-component complex that is generated by quinolone, DNA, and topoisomerase (particularly DNA gyrase) has been partially elucidated because of structural investigations, which have offered vital insights into this interaction [15].

Quinolones have been shown to have a moderate affinity for binding to both single-stranded DNA and the topoisomerase enzyme, according to information obtained from experiments [16]. On the other hand, when they engage with the gyrase-DNA complex that has already been created, their binding affinity is dramatically increased. As a result of this improved interaction, the cleaved DNA complex is stabilized, which prevents any further processing of DNA and ultimately results in bacteriostatic or bactericidal actions.

Antiviral Effects Against Specific Viruses

In the preliminary tests, it was found that ofloxacin displayed an inhibitory effect against the vaccinia virus, which is a member of the family of viruses that cause the pox [12]. It is interesting to note that this inhibitory effect was not detected against other prevalent viruses like the herpes simplex virus or the influenza virus. Based on these first findings, it was hypothesized that the antiviral mechanism of ofloxacin may entail the suppression of virus-specific DNA and RNA synthesis. This could be accomplished by interfering with the topoisomerase enzyme of the vaccinia virus, which is functionally analogous to its bacterial counterpart [17].

Based on these findings, the L-isomer of ofloxacin was studied further and was found to protect cell cultures against HIV-1 cytolysis. The treated cells were protected from HIV-mediated death and decreased CD4 antigen expression, a vital HIV receptor, but they could

not produce infectious virus particles. This implies a complicated antiviral mechanism that impairs viral gene expression or virion maturation. This approach may go beyond topoisomerase inhibition [12].

Development of Quinolone Derivatives and Patents

Researchers and pharmaceutical corporations have created and patented many quinolone analogs with the carboxylic acid core structure. Over time, fluoroquinolones' antiviral properties prompted the submission of many patents for their use as innovative viral infection treatments. Many of these patents focused on fluoroquinolone derivatives chemically similar to the original drug, which were proven to be effective against retroviruses [12].

One of the earliest studies examined these molecules in cell models that were infected with the visna virus. Since the visna virus is a lentivirus that is closely linked to HIV, it is an extremely useful model for researching the effectiveness of antiviral drugs and the reproduction of retroviral viruses [18].

Targeting HIV and Retroviruses

The human immunodeficiency virus type 1 (HIV-1), which is the major agent responsible for the development of acquired immune deficiency syndrome (AIDS), was the target of a significant number of these patented chemicals that were particularly tested for their ability to inhibit its activity. It was asserted that a number of these compounds possessed both therapeutic and preventive activity, which suggests that they may be utilized not only in the treatment of active HIV infection but also in the prevention of HIV infection [19].

Despite numerous patents documenting the antiviral effects of fluoroquinolone analogs, their precise mechanisms of action remain largely unclear. It is hypothesized that their antiviral activity may involve interference with viral replication, possibly through inhibition of viral topoisomerase-like enzymes or integration processes, although most patents lack supporting biochemical or molecular evidence. Notably, fluoroquinolones have been investigated in the context of retroviral infections such as HIV, which primarily target CD4+ T lymphocytes. These helper T cells, constituting 65–80% of peripheral blood lymphocytes, are crucial for coordinating immune responses. Their depletion in HIV infection leads to immune dysfunction and predisposes patients to opportunistic infections, including ocular diseases [20].

Structure–Activity Relationship (SAR) Findings

Fluoroquinolone antiviral activity is influenced by structural modifications at various positions on the quinolone core. At position 1, steric bulk affects potency, with optimal groups following the order: cyclopropyl > ethyl > fluorophenyl > tert-butyl. Substituents like fluoroethyl (fleroxacin) and difluorophenyl (tosufloxacin, temafloxacin) enhance anaerobic activity. Position 2 tolerates minimal substitution due to proximity to the enzyme binding site, although ring fusions at positions 1–2 retain activity [21].

Position 5 substitutions like amino or methyl can improve Gram-positive activity, especially within 6,8-difluoroquinolones, for example, sparfloxacin and grepafloxacin. Position 6 fluorination is key to DNA gyrase inhibition and cell penetration, though newer agents like garenoxacin challenge its necessity. Nitro groups here also show promise.

Position 7 substitutions, particularly nitrogenous rings (piperazine, pyrrolidine), significantly influence spectrum, bioavailability, and toxicity. Piperazines favor Gram-negative efficacy (e.g., ciprofloxacin), while pyrrolidines target Gram-positives but reduce solubility. Methylation and N-substitution refine pharmacokinetics and potency. Position 8 modifications (fluoro, methoxy, nitrogen) improve pharmacokinetics and Gram-positive/anaerobic coverage. Notably, antiviral agents like K-12, K-37, and K-38 exhibit broad activity against DNA viruses such as HCMV, HSV and VZV, with varying cytotoxicity, highlighting the therapeutic challenge of balancing efficacy and host safety, particularly in immunocompromised patients such as those with AIDS [21].

Synergistic Effects with Standard Antiretroviral Therapy

Baba and colleagues evaluated structurally modified fluoroquinolones, focusing on compounds with piperazinyl and oxo groups at C-7 and C-8. Among them, K-12 showed strong anti-HIV-1 and HIV-2 activity without harming host cell viability. Its mechanism involves inhibition of Tat-mediated transactivation, a crucial step in HIV gene expression, by targeting host cofactors rather than Tat itself [19,22].

K-12 combined with standard antiretrovirals such as AZT, 3TC, nevirapine and nelfinavir produced synergistic antiviral effects, suggesting its potential use as an adjuvant in combination antiretroviral therapy (cART) to enhance efficacy and reduce resistance risk [22].

Another derivative, K-37, showed greater potency than K-12 and selectively blocked Tat-mediated RNA transcription without disrupting host transcription, indicating a safer profile [23]. Unlike K-12, K-37 did not affect key host transcription cofactors like CTD kinases or P-TEFb.

A new 7-piperazinyl, 8-oxo fluoroquinolone, R-71762 (compound 9), discovered via high-throughput screening, led to further SAR studies. These identified several analogues with strong selectivity indices (SI) and transcriptional inhibitory effects, especially when aryl substituents such as o-methylphenyl were added at C-7, enhancing potency through hydrophobic/steric effects. These fluoroquinolones differ from traditional antiretrovirals as they do not target reverse transcriptase or protease but inhibit HIV-1 transcription, likely via modulation of host transcriptional machinery or viral cofactors [24].

Beyond HIV, these derivatives showed broad-spectrum activity against DNA viruses like HCMV, VZV, HSV-1/2, supporting their potential use in immunocompromised patients. Further modifications, such as adding trifluoromethyl ($-\text{CF}_3$) at C-8 and pyridyl groups on piperazine, yielded a potent molecule L-0 with enhanced activity, though the exact mechanism remains unclear [25]. Fluoroquinolones were also explored in HCV genotype 1b treatment. While early studies combining ofloxacin with interferon showed improved viral clearance, later trials failed to replicate these benefits, highlighting the need for more robust evidence. Extensive derivatization also explored fluoroquinolone–nucleoside hybrids, including acyclonucleosides and olefinic analogues. However, these hybrids showed poor

anti-HIV activity and low selectivity, limiting their therapeutic value [12].

Structural Optimization at C-6 and the Emergence of 6-Amino-Quinolones

Historically, the structural optimization of quinolone antibiotics has concentrated on modifications at C-7, C-8, and N-1, resulting in derivatives with increased antiviral efficacy and superior pharmacokinetic properties. Conversely, the C-6 position has remained predominantly preserved, generally filled by fluorine which augments cellular penetration and improves DNA gyrase binding or, less frequently, by chlorine or hydrogen. Recent research has begun investigating the effects of adding an amino group at this location, with the objective of identifying novel pharmacophores exhibiting potential antiviral action [26].

Employing quantitative structure–activity relationship (QSAR) and molecular modeling techniques, researchers anticipated that the introduction of an amino group at the C-6 position would be structurally viable and might yield pharmacologically significant compounds [27]. The incorporation of a 6-amino group did not markedly improve antibacterial efficacy, although it created new avenues for antiviral investigation. Preliminary experiments indicated that 6-amino-quinolone derivatives exhibited structural tolerability and warranted assessment for their antiviral potential, namely against HIV-1 [26].

Detailed SAR Findings for 6-Amino-Quinolone Derivatives

The examination of the structure–activity correlations (SAR) among these derivatives identified some critical characteristics essential for improved antiviral efficacy. The presence of a free carboxylic acid at the C-3 position was crucial for activity, presumably due to its involvement in establishing critical contacts with viral or host macromolecular targets. Secondly, a minor polar substituent at C-6 (such as the amino group), in conjunction with a substantial hydrophobic moiety at C-7, was determined to be advantageous [21]. Third, diminutive substituents at the N-1 position were preferred, since bigger groups at this locus generally reduced activity, perhaps due to steric hindrance or modified pharmacokinetics. In contrast, replacements at C-8 and N-1 with bulky groups were poorly accepted, but structural flexibility at C-7 permitted the exploration of a diverse array of substituents.

The findings were validated by computational pharmacophore modeling, which emphasized the significance of the carboxylic acid at C-3 as a crucial structural determinant for antiviral action. The model also recognized the importance of a hydrophilic zone encircling the 4-keto-3-carboxylic core and a strategically positioned hydrophobic region next to the substituent at C-7. The model indicated that whereas hydrophobicity at N-1 was essential, the specific characteristics of the C-6 substituent were of lesser importance, suggesting that alterations in this area may provide flexibility without significantly compromising antiviral efficacy [26].

Discovery and Characterization of WM5 (Compound 13)

A series of 6-amino-quinolone derivatives was produced and evaluated for in vitro antiviral efficacy. Among these, the chemical identified as WM5 (compound 13) surfaced as the most promising. WM5 has a methyl group at the N-1 position and a 4-(2-pyridyl)-1-piperazinyl fragment at the C-7 position [28,29]. It exhibited strong suppression of HIV-1 replication in freshly infected human lymphoblastoid cell lines, with an EC_{50} value of 0.1 μ M. The potency was 7 to 20 times greater than that of analogous compounds with cyclopropyl or tert-butyl groups at N-1, confirming WM5 as the most potent member of the quinolone family for anti-HIV activity.

Unique Mechanism of Action of WM5 via TAR RNA Binding

Mechanistic investigations of WM5 demonstrated a unique antiviral mechanism of action. In contrast to conventional antiretrovirals, WM5 did not impede viral enzymes like reverse transcriptase, integrase, or protease. Rather, it demonstrated its antiviral efficacy by targeting viral RNA. WM5 was specifically identified as binding to the trans-activation response (TAR) portion of HIV-1 RNA, a structured RNA motif essential for interaction with the viral Tat protein [30]. This binding obstructed the Tat–TAR interaction, thereby impeding Tat-mediated transcriptional activation, an important process for effective viral replication. The findings were corroborated by reports indicating that WM5 selectively interacts with the TAR bulge and inhibits transcriptional activation in both in vitro and cellular contexts [31].

Fluoroquinolones as Anti-Inflammatory Agents

Inhibition of the NF- κ B Transmission Cascade

The NF- κ B is a central transcription factor that is involved in the production of proinflammatory genes. FQs have demonstrated the ability to inhibit NF- κ B signaling [9,10]. Gemifloxacin diminishes TNF- α -induced NF- κ B activity, whereas moxifloxacin disrupts the p65-NF- κ B signaling pathway in human leukocytes activated by *Aspergillus fumigatus* and also inhibits NF- κ B activation in human respiratory epithelial cells in response to cytokines [7,32]. Ciprofloxacin and levofloxacin inhibit LPS-induced NF- κ B signaling in macrophages by preventing nuclear translocation of NF- κ B p65 [7,10]. Norfloxacin and gemifloxacin further reduce NF- κ B expression and activation levels [32]. Additionally, ciprofloxacin, norfloxacin, and gatifloxacin are known to downregulate TNF- α and IL-1 β , effects that are closely linked to the NF- κ B transmission cascade [6,7]. Notably, gemifloxacin also inhibits cytokine release from LPS-stimulated human monocytes through post-transcriptional mechanisms [9].

Interference with the TLR4 Cascade

Toll-like receptor 4 (TLR4), present on immune cells including microglia, is essential for the

initial inflammatory reactions triggered by bacterial components such as lipopolysaccharide (LPS) [9,10,33]. Molecular docking studies suggest that several fluoroquinolones (FQs), including moxifloxacin, delafloxacin and ofloxacin, may interfere with the correct formation of the TLR4-MD-2-LPS combination [7,9,10]. Experimental findings support this, showing that ciprofloxacin and levofloxacin hindered the LPS-induced inflammation by obstructing LPS attachment to the TLR4-MD-2 complex and inhibiting downstream signaling [10].

Inhibition of MAPK Pathways

Mitogen-activated protein kinases (MAPKs) like ERK1/2, p38, and JNK are essential in regulating inflammatory signaling pathways [7,32]. Moxifloxacin has demonstrated the ability to block the signaling of ERK1/2 and p38 MAPKs in human monocytes stimulated with *Aspergillus fumigatus* and to suppress cytokine-induced MAPK activation in human respiratory epithelial cell lines [7,32]. Garenoxacin also exhibits anti-inflammatory properties by blocking ERK1/2, stimulated by lipopolysaccharide (LPS) [11,32]. Norfloxacin has been documented to suppress inflammation triggered by *Leptospira* by inhibiting ERK phosphorylation [9].

Influence on Phosphodiesterase (PDE) and cAMP Levels

FQs are proposed to exert immunomodulatory effects by modulating phosphodiesterase (PDE) activity and enhancing intracellular levels of cyclic adenosine monophosphate (cAMP) [7,9]. The accumulation of cAMP is thought to activate protein kinase A (PKA), which then inhibits the action of gene transcription factors such as NF- κ B, resulting in decreased release of inflammatory cytokines [7]. Evidence from Blaine et al. demonstrated that ciprofloxacin inhibits PDE activity, resulting in elevated cAMP levels and enhanced PKA activity in stimulated monocytes, ultimately contributing to the inhibition of TNF- α production [7]. Similarly, Bailly et al. suggested that ciprofloxacin's ability to suppress TNF- α along with IL-1 may be linked to its impact on PDE inhibition and subsequent cAMP accumulation [9].

Induction of a Stress Response

Fluoroquinolones (FQs) inhibit human topoisomerase II in mammalian cells, potentially triggering a cellular stress response [9]. Ciprofloxacin has been demonstrated to elicit an immune-stimulating stress reaction in human T cells [6,7].

Other Potential Targets

Certain fluoroquinolone derivatives have been identified as selective inhibitors of phosphoinositide 3-kinase gamma (PI3K γ) [32]. Gemifloxacin has emerged as a potential tyrosine kinase 2 (TYK2)-selective inhibitor, with TYK2 inhibition being explored as a therapeutic strategy for immune-mediated conditions such as psoriasis [9].

Reducing Inflammatory Cytokines

FQs are recognized for their ability to inhibit the synthesis of various proinflammatory cytokines [6,7]. Besifloxacin has exhibited significant anti-inflammatory properties by suppressing the production of IL-1 β , IL-6, as well as IL-8 in human THP-1 monocytes [6,9]. Similarly, ciprofloxacin, norfloxacin, and gatifloxacin have been shown to suppress TNF- α and IL-1 β levels [6,7]. Levofloxacin was successfully shown to suppress IL-1 β secretion but showed variable effects on TNF- α ; one study noted no significant change, while another indicated reduction of TNF- α , IL-6, along with IL-8 production within human pulmonary cells [7,9].

Norfloxacin also attenuates IL-6 production in lipopolysaccharide (LPS)-stimulated cells [6,7,9]. A novel FQ derivative, 6-fluoronorfloxacin (6FN), effectively inhibits IL-1 β and other inflammatory mediators [6]. Enrofloxacin lowered the production of IL-6 along with TNF- α in treated pigs in animal models [6]. Moxifloxacin lowered the release of IL-8, IL-1 β , followed by TNF- α from human peripheral blood monocytes induced by *Aspergillus fumigatus*. Ciprofloxacin and levofloxacin significantly reduced the formation of IL-1 and TNF in LPS-stimulated primary astrocytes [7,10]. Ciprofloxacin significantly reduced levels of TNF- α , IL-1 β , and CXCL2/MIP-2 α in a rodent model of LPS-induced lung damage and effectively blocked IL-8 release [9].

In a mouse model of autoimmune spondyloarthritis, levofloxacin was reported to lower tissue expression of TNF- α , IL-17A, IL-23, and JAK3 [9]. In a mouse model of pneumonia, moxifloxacin markedly reduced IL-17A levels along with the total immune cell and neutrophil populations in pulmonary tissue. Moreover, moxifloxacin inhibited the production of TNF- α and IL-8 in a rat model of bronchial asthma [9]. Gemifloxacin exhibited anti-inflammatory properties by reducing levels of TNF- α , IL-8, and nuclear factor kappa B (NF- κ B) in many tissues. The topical treatment of norfloxacin decreased inflammation in mice with atopic dermatitis by interfering with CD40 transmission and decreasing the release of cytokines in lymph node cells, therefore obstructing the formation of Th1 as well as Th2 cells [9]. Lomefloxacin reduced markers associated with inflammation and leukocyte/lymphocyte stimulation [9]. Nadifloxacin and ozenoxacin relieved inflammation in mouse ear models [9]. Levofloxacin affected the production of TNF- α in patients with community-acquired pneumonia [7]. Furthermore, functionalized fluoroquinolones exhibited anti-inflammatory properties by scavenging nitric oxide radicals in RAW 264.7 macrophages [11].

Effects on Other Cytokines

Fluoroquinolones (FQs) have been shown to modulate cytokine expression, with some studies reporting increased levels of IL-2, IL-3, IL-10, and TGF- β [6]. However, findings on their effects remain inconsistent across studies. For instance, while certain reports suggest that FQs such as ciprofloxacin, moxifloxacin, levofloxacin, trovafloxacin, and grepafloxacin can enhance IL-2 production in lipopolysaccharide (LPS)-stimulated monocytes, other research found that moxifloxacin and pefloxacin did not significantly stimulate IL-2 expression [6,8]. Additionally, ciprofloxacin was reported to decrease IL-2 expression in pre-activated T cells in a separate study [7]. Similarly, effects on IL-4 can vary, with reports of ciprofloxacin and moxifloxacin reducing IL-4 expression, but one study showing increased IL-4 mRNA levels with ciprofloxacin [6,7,9]. Levofloxacin affected the production of IL-10 in

patients with community-acquired pneumonia [7]. Ciprofloxacin enhances TGF- β expression in human colonic epithelial cells [7,9].

Discussion

Fluoroquinolones as Antiviral Agents

Numerous in vitro studies have demonstrated varying levels of antiviral activity for quinolones against a range of viruses, indicating their potential as candidates for antiviral therapy. The effectiveness of these compounds appears to be influenced by factors such as their chemical structure, the specific virus targeted, and the nature of structural modifications made to the quinolone backbone. Table 1 presents a summary of key findings from several studies examining the antiviral properties of quinolone derivatives, a class of antimicrobial agents traditionally recognized for their antibacterial activity. These studies investigate the efficacy of quinolones against a variety of viral targets, including HIV, herpesviruses, poxviruses, and hepatitis C virus (HCV). Each compound's antiviral potential is evaluated across different viral models and cell lines, uncovering diverse mechanisms of action, such as the inhibition of viral transcription, disruption of nucleic acid synthesis, and the modulation of host cellular factors involved in viral replication.

Table 1. Summary of Key In Vitro Studies on Quinolones as Antiviral Agents

Compound	Target Virus	Cell Line/Model	Observed Antiviral Effects	Reference
Ofloxacin	Vaccinia virus (poxvirus)	Not specified	Inhibited viral DNA/RNA synthesis, likely by interfering with viral topoisomerase	[17]
L-ofloxacin	HIV-1	HIV-infected cell culture	Reduced CD4 expression, inhibited virion production, protected from cytolysis	[12]
K-12	HIV-1, HIV-2	Human cell lines	Inhibited Tat-mediated transcription via host cofactor inhibition	[22]
K-12 + AZT/3TC/etc.	HIV-1	Combination therapy models	Showed synergistic antiviral activity with standard antiretroviral drugs	[22]
K-37	HIV-1	Human cell lines	More potent than K-12; selectively inhibited HIV-1 transcription	[23]
R-71762 (Compound 9)	HIV-1	High-throughput screening	Potent HIV transcription inhibitor; enhanced with aryl substitution at C-7	[12]
K-38	HCMV, HSV, VZV	Virus-infected cell cultures	Moderate antiviral activity but limited by cytotoxicity in immunocompromised cells	[21]
6-amino-quinolones	HIV-1	In vitro modeling & SAR studies	Potential antiviral activity; tolerated polar groups at C-6; best when paired with hydrophobic C-7	[26]

Compound	Target Virus	Cell Line/Model	Observed Antiviral Effects	Reference
WM5 (Compound 13)	HIV-1	Human lymphoblastoid cell lines	Strong HIV-1 suppression (EC_{50} = 0.1 μ M); promising antiviral candidate	[28,29]

Ofloxacin Inhibits Poxvirus Replication via Nucleic Acid Synthesis Interference

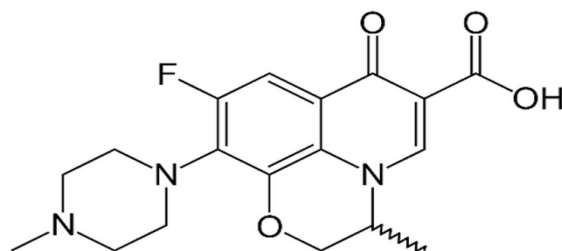


Figure 1. Structure of Ofloxacin

In the pioneering study by Ikeda et al. [17], ofloxacin (Figure 1), a second-generation fluoroquinolone, demonstrated antiviral potential against the vaccinia virus, a member of the poxvirus family. Although the precise cellular model was not specified, the study suggested that ofloxacin interfered with the replication process by inhibiting viral DNA and RNA synthesis. The proposed mechanism is believed to be similar to ofloxacin's antibacterial action, whereby it disrupts the function of topoisomerases essential for nucleic acid unwinding and replication. Since poxviruses encode their own viral topoisomerases, it is plausible that ofloxacin targets these viral enzymes, thereby reducing replication efficiency. This early observation laid the groundwork for later studies examining fluoroquinolones' roles in modulating viral enzymes and suggested a potential broader application of these drugs beyond bacterial infections.

L-ofloxacin Preserves CD4+ Cells and Reduces HIV-1 Cytopathic Effects

Richter et al. [12] investigated L-ofloxacin, an enantiomerically pure form of ofloxacin, in HIV-infected cell cultures. The study found that L-ofloxacin reduced virion production, preserved CD4+ T-cell expression, and protected infected cells from virus-induced cytolysis. These results are significant because CD4+ T-cell depletion is a hallmark of HIV progression to AIDS. By mitigating this loss, L-ofloxacin may confer immunological benefits in infected individuals. The proposed mechanism did not involve direct inhibition of viral enzymes but rather suggested an indirect effect on host pathways or viral gene expression. The data highlighted L-ofloxacin's potential to reduce HIV cytopathicity, possibly through immune modulation or interruption of early-stage viral replication, warranting further investigation into its pharmacodynamic interactions with host-virus systems.

K-12 Suppresses HIV Transcription Through Host Cofactor Modulation

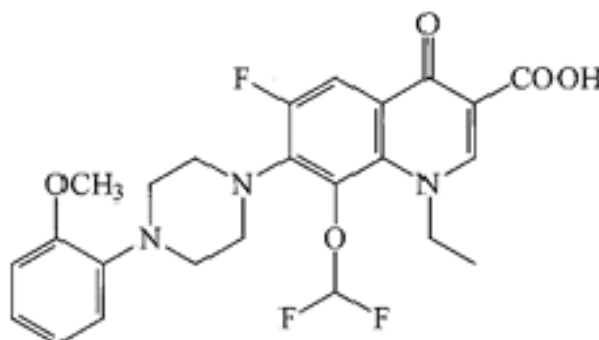


Figure 2. Structure of K-12 [22]

In a pivotal study by Okamoto et al. [22], the quinolone derivative K-12 (Figure 2) was shown to inhibit HIV-1 and HIV-2 transcription by targeting Tat-mediated transactivation. The research was conducted in human cell lines and revealed that K-12 likely functions by interfering with host cellular cofactors required for efficient transcriptional activation by the HIV Tat protein. Tat is crucial for elongation of viral transcripts via recruitment of transcriptional machinery, including cyclin T1 and CDK9. K-12's ability to disrupt this process implies a host-targeted antiviral strategy, reducing the potential for resistance mutations in viral proteins. This mechanism highlights the versatility of fluoroquinolone structures in affecting both microbial and host cellular pathways and supports further structure–activity relationship (SAR) exploration to enhance transcriptional inhibition without causing toxicity.

K-12 Enhances Antiretroviral Efficacy in Combination Therapies

The same study by Okamoto et al. [22] also evaluated the combinatory effects of K-12 with established antiretroviral drugs such as AZT (zidovudine) and 3TC (lamivudine). The results demonstrated a synergistic enhancement of antiviral activity, suggesting that K-12 could augment the efficacy of nucleoside reverse transcriptase inhibitors (NRTIs). This synergy is likely due to K-12's transcriptional inhibition, which complements the polymerase-targeting mechanism of NRTIs. The dual blockade at both transcription and reverse transcription levels could result in a more robust suppression of viral replication. Importantly, this finding supports the potential clinical use of quinolone derivatives as adjuvants in highly active antiretroviral therapy (HAART), emphasizing their role in multidrug regimens designed to lower viral loads and delay resistance emergence.

K-37: A Potent Derivative of K-12 with Improved Transcriptional Inhibition

Building on the success of K-12, Okamoto et al. [23] introduced K-37, a structurally optimized analogue with significantly enhanced antiviral potency against HIV-1. Conducted in human cell lines, the study reported that K-37 exhibited a stronger and more selective

inhibition of HIV-1 transcription compared to K-12. The improved activity was attributed to structural modifications that increased binding affinity to the host cofactors involved in Tat-dependent transcription. These enhancements suggest that subtle changes in the quinolone scaffold can dramatically influence target selectivity and potency. The promising profile of K-37 underscores its potential as a lead compound for further antiviral drug development and illustrates the importance of rational design in improving therapeutic index.

R-71762 (Compound 9) Identified as a High-Affinity HIV Transcription Inhibitor

Richter et al. [12] identified R-71762 (Compound 9) through high-throughput screening as a potent inhibitor of HIV-1 transcription. This compound, a fluoroquinolone derivative, was shown to have enhanced antiviral activity due to aryl substitutions at the C-7 position of the quinolone core. Such modifications appear to strengthen the compound's interaction with host or viral transcription machinery, possibly increasing its stability and specificity for Tat or its coactivators. The study emphasizes the critical role of chemical substitutions in optimizing the antiviral efficacy of quinolone derivatives. Furthermore, the use of high-throughput techniques facilitated the identification of promising candidates from large chemical libraries, accelerating the discovery process and offering a template for future screening campaigns targeting viral transcription.

K-38 Shows Activity Against Herpesviruses but Is Limited by Cytotoxicity

Emami et al. [21] examined K-38, a quinolone derivative, against multiple herpesviruses including human cytomegalovirus (HCMV), herpes simplex virus (HSV), and varicella-zoster virus (VZV). The study found that K-38 exhibited moderate antiviral activity in virus-infected cell cultures; however, its therapeutic potential was significantly constrained by its cytotoxicity, particularly in immunocompromised cells. The dual observations of efficacy and toxicity point to a narrow therapeutic index, suggesting the need for chemical refinement to improve selectivity. This finding highlights a key challenge in quinolone-based antiviral development: achieving a balance between sufficient antiviral activity and acceptable host cell safety. Despite its limitations, K-38's activity across multiple DNA viruses suggests a conserved mechanism worth further exploration in less toxic analogues.

Structure–Activity Insights from 6-Amino-quinolone Derivatives in HIV Models

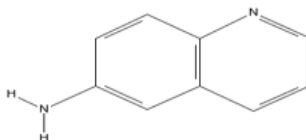


Figure 3. Structure of 6-Amino-quinolone

Senerovic et al. [26] conducted structure–activity relationship (SAR) studies on 6-amino-quinolone (Figure 3) derivatives to evaluate their potential as anti-HIV agents. The research revealed that the presence of polar groups at the C-6 position was well tolerated and, when paired with hydrophobic substitutions at the C-7 position, led to enhanced antiviral activity. These findings offer valuable insight into how spatial and electronic features of the quinolone scaffold contribute to antiviral efficacy. Specifically, the data suggest that a proper hydrophobic–hydrophilic balance can improve cell permeability and target binding, ultimately enhancing biological activity. The SAR approach used in this study represents a rational strategy to guide future synthetic efforts in creating more effective and selective quinolone-based antivirals.

WM5 (Compound 13) Demonstrates Strong HIV-1 Suppression with Low EC₅₀

In one of the most promising findings, Cecchetti et al. [29] reported that WM5 (Compound 13), a novel quinolone derivative, exhibited potent anti-HIV-1 activity in human lymphoblastoid cell lines, with an exceptionally low EC₅₀ value of 0.1 μ M. This indicates a high degree of efficacy at minimal concentrations, suggesting both strong target interaction and favorable pharmacodynamics. The structure of WM5 likely incorporates optimized substitutions at key positions, enhancing its ability to suppress viral replication efficiently. Its performance surpasses that of earlier quinolone analogues, making it a strong candidate for preclinical development. The success of WM5 underscores the potential of structure-guided quinolone design and opens new avenues for targeting viral replication with minimal cytotoxicity.

Fluoroquinolones as Anti-Inflammatory Agents

Multi-Pathway Immunomodulatory Mechanisms of Fluoroquinolones

A class of synthetic antibacterial drugs known as fluoroquinolones (FQs) has drawn more attention recently due to its potent immunomodulatory effects. Beyond bacterial inhibition, these effects are mediated by a few mechanisms involving key signaling pathways, such as

nuclear factor-kappa B (NF- κ B), toll-like receptor 4 (TLR4), and mitogen-activated protein kinases (MAPKs) [6,7,9].

The control of inflammatory gene expression is mostly dependent on the NF- κ B pathway. FQs such as ciprofloxacin, levofloxacin, and gemifloxacin are known to block this pathway, which in turn inhibits pro-inflammatory cytokines including IL-1 β and TNF- α [7,9,10]. For example, gemifloxacin was demonstrated to reduce TNF- α -induced NF- κ B activation, whereas moxifloxacin deactivated the p65-NF- κ B pathway in human monocytes challenged with *Aspergillus fumigatus* [7,32].

Additionally, FQs interfere with TLR4 signaling by preventing the formation of the TLR4–MD-2–LPS complex, which is an essential step in LPS-induced immune activation [9,10]. Molecular docking studies and in vitro evidence suggest that ciprofloxacin, levofloxacin, and other FQs disrupt this complex, thereby reducing downstream NF- κ B signaling and associated inflammatory responses [10].

FQs also inhibit MAPK pathways, which include ERK1/2, p38, and JNK, further damping inflammatory responses. Moxifloxacin inhibits ERK1/2 and p38 activation in monocytes, while garenoxacin and norfloxacin suppress MAPK activity in various cell lines and inflammation models [9,11,32].

Another important mechanism involves the modulation of cyclic adenosine monophosphate (cAMP) through phosphodiesterase (PDE) inhibition. Ciprofloxacin increases intracellular cAMP levels, thereby enhancing protein kinase A (PKA) activity, which subsequently inhibits NF- κ B and reduces TNF- α production [7]. This mechanism is supported by evidence that FQs promote cAMP accumulation and TNF- α suppression in activated monocytes [9].

Together, these findings demonstrate that FQs exert immunomodulatory effects through a comprehensive and multi-targeted approach, offering potential therapeutic benefit in inflammatory conditions (Figure 4).

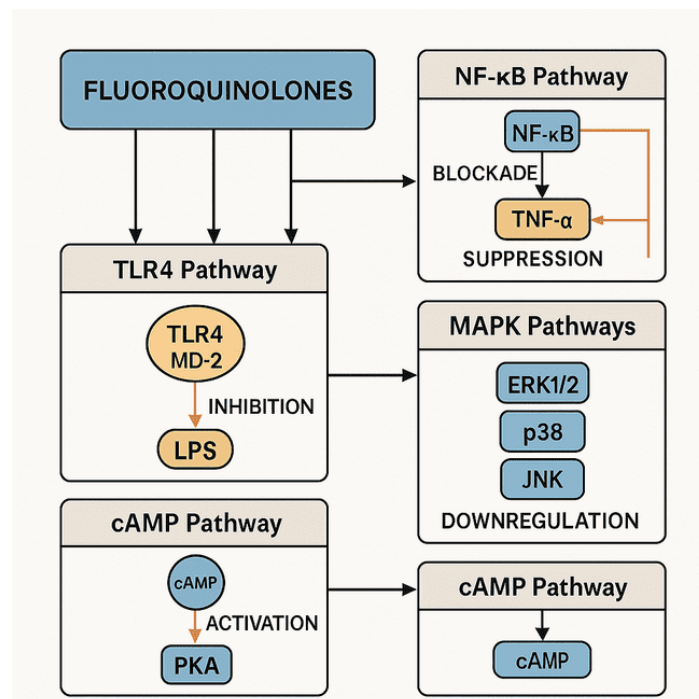


Figure 4. Multi-Pathway Immunomodulatory Mechanisms of Fluoroquinolones

Suppression of Pro-Inflammatory Cytokines

FQs exhibit robust and consistent inhibition of a range of pro-inflammatory cytokines, including IL-1 β , TNF- α , IL-6, IL-8, and IL-17. For instance, ciprofloxacin and levofloxacin significantly decreased the release of IL-1 β and TNF- α in LPS-stimulated microglia and blocked NF- κ B and TLR4 activation [10]. In addition to inhibiting neutrophil infiltration and IL-17A production in lung tissues, moxifloxacin decreased the levels of IL-1 β , TNF- α , IL-6, and IL-8 in monocytes and animal models of pneumonia and asthma [9].

Gemifloxacin demonstrated potent anti-inflammatory effects in both human monocytes and murine psoriasis models, significantly reducing cytokine production and NF- κ B activity [9]. Besifloxacin decreased inflammation in nasal tissue and suppressed IL-1 β , IL-6, and IL-8 in THP-1 monocytes [6,9].

Levofloxacin suppressed TNF- α , IL-6, and IL-8 in bronchial epithelial cells and decreased the production of IL-17A, IL-23, and JAK3 in autoimmune spondyloarthritis models [9]. Enrofloxacin reduced IL-6 and TNF- α expression in treated pigs [6], and topical norfloxacin alleviated inflammation in atopic dermatitis by inhibiting CD40 signaling and cytokine production [9].

These findings affirm the broad-spectrum cytokine-suppressive effects of FQs across diverse models, further validating their potential as therapeutic agents in inflammatory conditions (Figure 5).

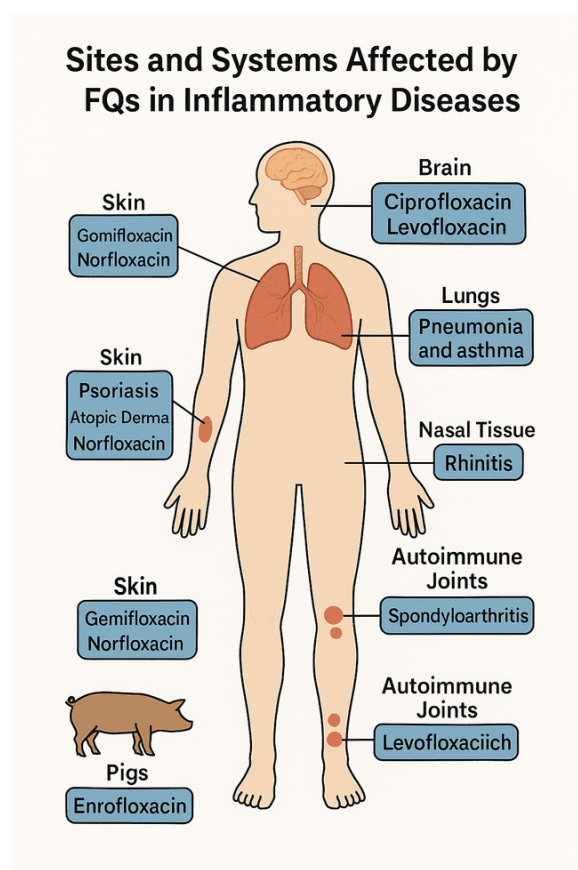


Figure 5. Sites and Systems Affected by FQs in Inflammatory Diseases

Variability in Cytokine Modulation: A Context-Dependent Effect

Although FQs consistently reduce pro-inflammatory cytokines, their effects on regulatory cytokines including IL-10, IL-2, IL-4, and TGF- β seem to vary. According to certain research, grepafloxacin and other FQs increase the production of IL-2 in monocytes activated by LPS [6,8], while others observe no change or even decreased IL-2 levels in pre-activated T cells [7].

Similarly, conflicting data exist for IL-4. Whereas ciprofloxacin and moxifloxacin have been shown to suppress IL-4 expression, other studies found increased IL-4 mRNA levels with ciprofloxacin treatment [6,9]. The effects on IL-10 also vary depending on the disease context and cell type, as seen in studies on community-acquired pneumonia [7].

These inconsistencies suggest that the immunomodulatory effects of FQs are highly context-dependent, influenced by variables such as the specific drug used, concentration, cell type, disease model, and experimental conditions. To elucidate these distinct effects and pinpoint the exact circumstances in which FQs elicit regulatory as opposed to suppressive cytokine responses, more research is required (Figure 6).

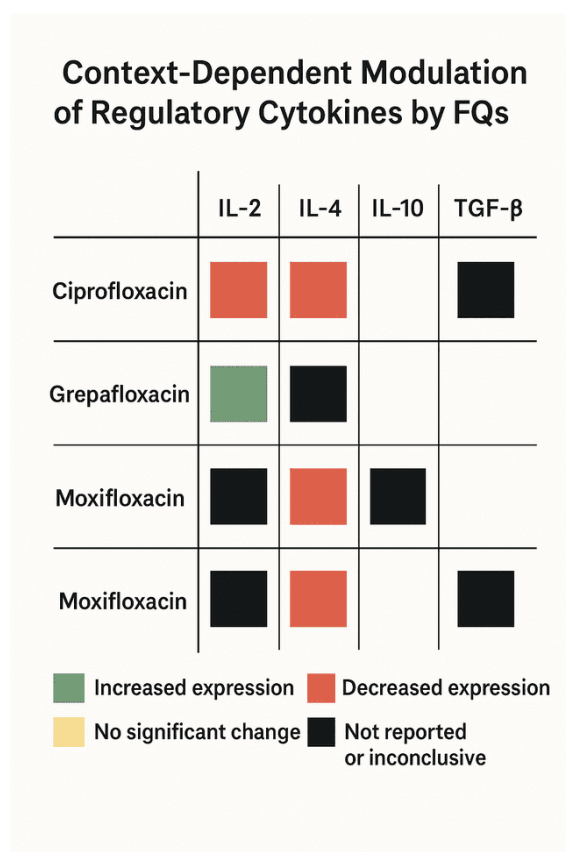


Figure 6. Context-Dependent Modulation of Regulatory Cytokines by FQs

Novel Targets and Functionalized Fluoroquinolone Derivatives

In addition to the classical pathways, novel targets such as phosphoinositide 3-kinase gamma (PI3K γ) and tyrosine kinase 2 (TYK2) have been identified as potential mediators of FQ activity. Gemifloxacin has been characterized as a selective TYK2 inhibitor, supporting its possible role in treating autoimmune diseases like psoriasis [9].

Furthermore, without depending on antibacterial activity, functionalized fluoroquinolone derivatives such as R-2TCBA and 2-AnisCEtA demonstrate strong anti-inflammatory qualities by preventing macrophages from producing nitric oxide (NO) [11]. These findings suggest that structural modification of FQs may yield compounds with enhanced anti-inflammatory activity and reduced risk of promoting antibiotic resistance.

These insights support the potential of repurposing FQs and their derivatives as immunotherapeutic agents for chronic inflammatory diseases, particularly in scenarios where conventional anti-inflammatory drugs are inadequate or contraindicated (Figure 7).

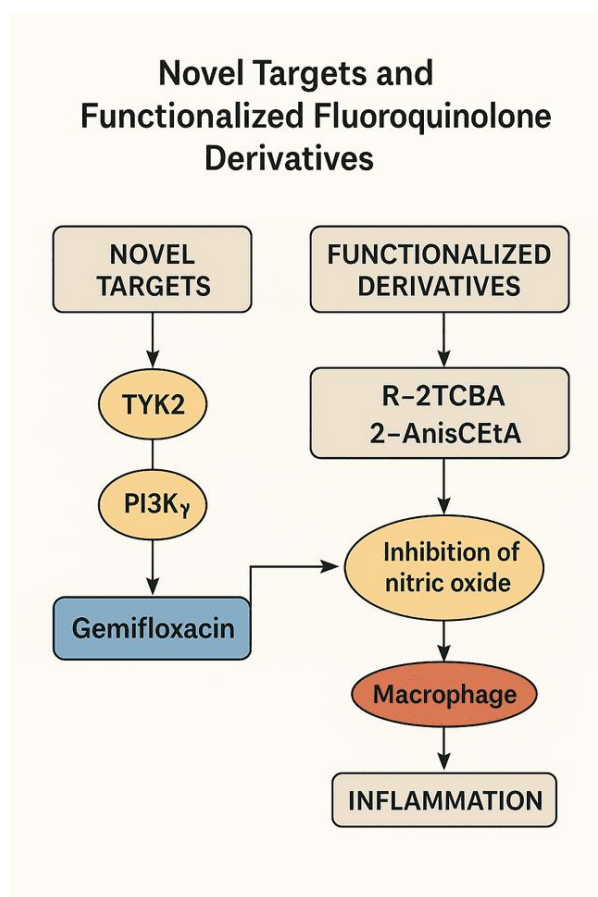


Figure 7. Novel Targets and Functionalized FQ Derivatives

Strengths of the Current Evidence Base

The current body of literature on the immunomodulatory properties of FQs exhibits several strengths:

Mechanistic Detail: The reviewed studies provide comprehensive insights into the molecular pathways affected by FQs, particularly NF-κB, TLR4, and MAPKs.

Broad Experimental Scope: Evidence is drawn from various *in vitro* models (e.g., monocytes, microglia, epithelial cells), animal models (e.g., mice, pigs), and limited human data, offering a multi-tiered understanding of FQ activity.

Use of Molecular Docking and Signalome Screening: These techniques provide additional support for hypothesized interactions between FQs and their immune targets [10,32].

Such a diverse and methodologically sound evidence base strengthens confidence in the observed anti-inflammatory effects of FQs.

Limitations and Recommendations for Future Research

Despite these promising findings, several limitations must be acknowledged:

Limited Clinical Translation: Most of the research is still preclinical. Clinical trials are urgently needed to confirm the safety, effectiveness, and dosage guidelines of FQs in inflammatory non-infectious diseases.

Dosing Variability: Inconsistent dosing and treatment durations across studies limit comparability and the development of standardized therapeutic protocols.

Potential for Adverse Effects: Prolonged use of FQs is associated with risks such as tendinopathy, neurotoxicity, and QT interval prolongation. These concerns necessitate careful risk-benefit assessment in chronic use (Table 2).

Antibiotic Resistance: Expanding the indications of FQs to include immunomodulation could contribute to the emergence of antibiotic-resistant strains. The development of non-antimicrobial FQ derivatives is thus crucial [11,33].

Table 2. Comparison of Risks vs. Benefits in Chronic Use of FQs for Immunomodulation

Aspect	Benefit	Risk
Inflammatory Control	Reduction in cytokine levels and immune cell infiltration	Long-term use may cause tendon damage or CNS side effects
Tissue Penetration	High bioavailability and tissue diffusion	Accumulation in sensitive tissues may heighten toxicity risk
Dosing Flexibility	Oral and IV options support varied treatment contexts	Optimal dosage for immune conditions not well-established
Broad Pharmacodynamics	Dual antimicrobial and immunomodulatory effects	Promotes resistance with frequent/repetitive exposure

Future Research Recommendations

Clinical Translation and Validation

Comprehensive randomized controlled studies are required to assess the safety and therapeutic efficacy of FQs in the treatment of non-infectious inflammatory conditions such as asthma, psoriasis, and rheumatoid arthritis. Existing preclinical evidence supports their potential in these settings, but human trials are needed to determine appropriate dosing regimens and long-term outcomes [7,9] (Figure 8).

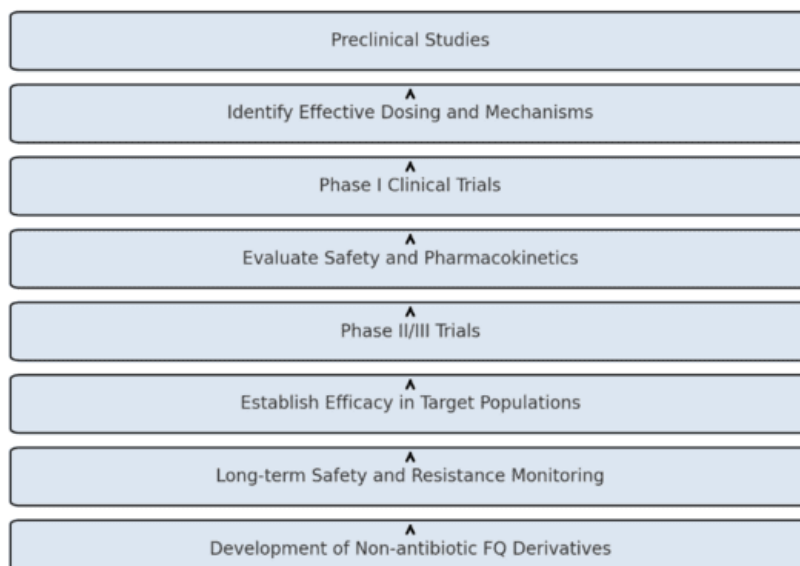


Figure 8. Flowchart of Recommended Future Research Pathways

Design of Non-Antibacterial Derivatives

To mitigate the risk of antimicrobial resistance, future drug development should prioritize the synthesis of non-antimicrobial FQ analogues optimized for immunomodulatory effects [34]. Functionalized compounds such as R-2TCBA and 2-AnisCEtA offer a promising starting point for this effort [11,33] (Table 3).

Table 3. Key Non-Antimicrobial FQ Derivatives and Their Immunomodulatory Properties [7]

Compound	Structural Modification	Immunomodulatory Mechanism	Antibacterial Activity	Key Findings
R-2TCBA	Trifluoromethyl substitution at C-7	Inhibits TLR/ERK pathways; reduces NF-κB activation	None	Reduces pro-inflammatory cytokines in murine ARDS models
2-AnisCEtA	Methoxy group at C-8	Enhances CREB activation via cAMP/PKA signaling	None	Attenuates neutrophil infiltration in pneumonia

Clarification of Cytokine Modulation Profiles

Given the context-dependent responses observed in regulatory cytokine modulation, further studies are needed to delineate how factors such as drug concentration, immune cell type, and pathological condition influence FQ-mediated cytokine expression [6,7] (Figure 9).

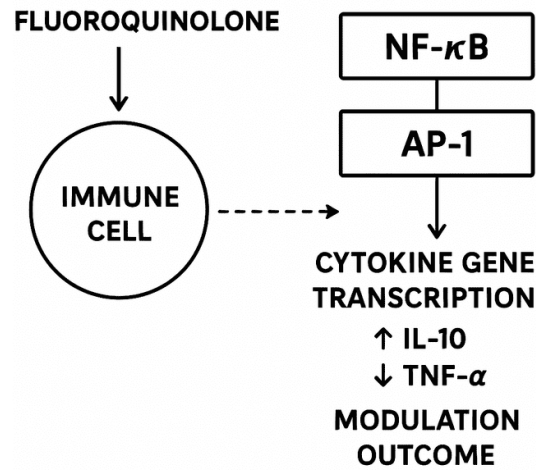


Figure 9. Proposed pathways of FQ-mediated cytokine modulation via intracellular signaling cascades.

Mechanistic Investigation of Novel Targets

The interactions of FQs with less conventional targets like TYK2, PI3Ky, and CD40 signaling pathways should be further investigated mechanistically. Using cutting-edge molecular biology methods, such as high-throughput screening and CRISPR gene editing, could yield more thorough findings [9] (Figure 10).

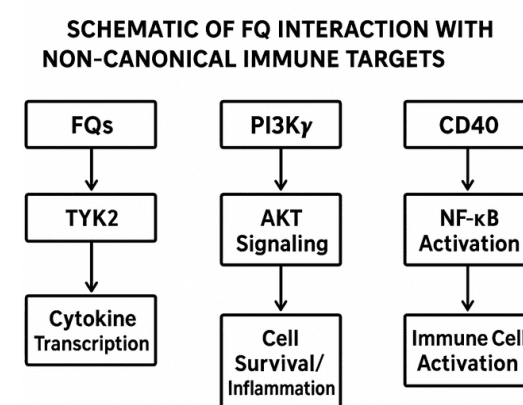


Figure 10. Hypothetical interaction map of fluoroquinolones with key immune pathways including TYK2, PI3Ky, and CD40 signaling.

Comprehensive Safety Profiling

Due to the well-documented risks associated with long-term FQ use, such as tendinopathy, neurotoxicity, and cardiac arrhythmias, comprehensive preclinical and clinical safety assessments are vital, particularly if FQs are to be repurposed for chronic inflammatory conditions [6,7] (Figure 11).

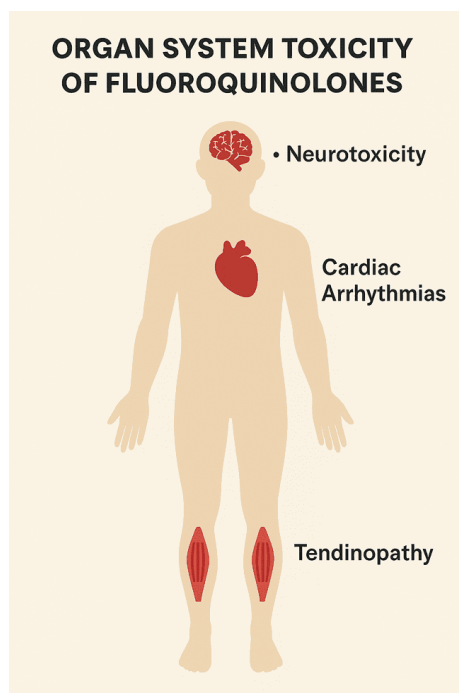


Figure 11. Systems-based illustration of fluoroquinolone-associated toxicities.

Framework for Therapeutic Repurposing

Establishing a regulatory and pharmacological framework for the repurposing of clinically approved FQs can expedite their development as anti-inflammatory agents. Pharmacokinetic and pharmacodynamic data from existing antimicrobial indications can serve as a foundation for new therapeutic applications [9,32] (Figure 12).

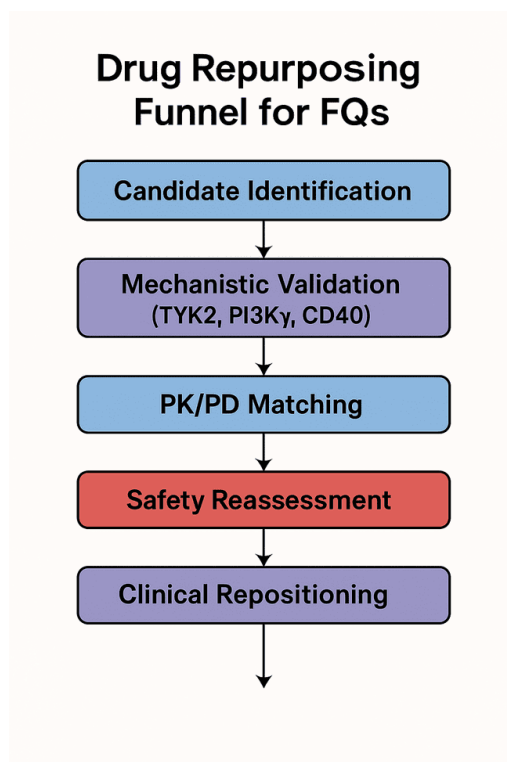


Figure 12. A streamlined process for repositioning fluoroquinolones using mechanistic and pharmacokinetic alignment.

Conclusion

Fluoroquinolones as Antiviral Agents

In conclusion, quinolone and fluoroquinolone derivatives represent a promising class of antiviral agents with demonstrated efficacy against a range of DNA and RNA viruses, including HIV, poxviruses, and herpesviruses. Early findings, such as the inhibition of viral nucleic acid synthesis by ofloxacin, established a foundational understanding of their antiviral potential. Subsequent studies have revealed that certain derivatives, notably K-12, K-37, and WM5, exert potent antiviral effects by targeting host cellular factors essential for viral transcription, particularly those involved in Tat-mediated transactivation in HIV. These compounds exhibit a unique therapeutic advantage by acting on host-dependent processes, thereby reducing the likelihood of viral resistance. Additionally, the observed synergistic activity of K-12 with nucleoside reverse transcriptase inhibitors suggests that quinolone derivatives may serve as valuable adjuncts in combination therapies. Nonetheless, issues related to cytotoxicity, as evidenced by K-38, highlight the need for further structural refinement to improve selectivity and safety. Future research should prioritize the elucidation of precise molecular mechanisms, the systematic exploration of structure–activity relationships, and the validation of lead compounds in preclinical and clinical models. Expanding the evaluation of quinolone-based compounds against other clinically relevant viruses may also reveal broader antiviral applications. Collectively, these findings support the continued development of quinolone derivatives as innovative agents within the field of antiviral pharmacotherapy.

Fluoroquinolones as Anti-Inflammatory Agents

Fluoroquinolones (FQs), historically recognized for their broad-spectrum antibacterial activity, have emerged as a promising class of compounds with significant immunomodulatory potential. FQs target several important inflammatory signaling pathways to modify immune responses, as the reviewed literature shows. These include mitogen-activated protein kinases (MAPKs), nuclear factor-kappa B (NF- κ B), toll-like receptor 4 (TLR4), and the cyclic adenosine monophosphate (cAMP) pathways, primarily through phosphodiesterase (PDE) inhibition [6,7,9,10].

Through these techniques, FQs consistently prevent the production of significant pro-inflammatory cytokines such as TNF- α , IL-1 β , IL-6, IL-8, and IL-17, as shown by a variety of cell types and animal models [9,32]. However, their effects on regulatory cytokines such as IL-2, IL-4, TGF- β , and IL-10 are variable and context-dependent, potentially influenced by drug type, dosage, cell origin, and disease setting [6,7]. This variability underscores the complexity of FQ-mediated immunoregulation and highlights the necessity for further mechanistic clarification.

Importantly, recent studies have identified novel intracellular targets of FQs, including phosphoinositide 3-kinase gamma (PI3K γ) and tyrosine kinase 2 (TYK2), both of which are implicated in autoimmune diseases such as psoriasis [9]. Simultaneously, structurally functionalized FQ derivatives such as R-2TCBA and 2-AnisCEtA have demonstrated strong anti-inflammatory properties, particularly by preventing macrophages from producing nitric

oxide. Importantly, these compounds do not have antibacterial properties [11]. The possible development of FQ analogues as non-antimicrobial immunotherapeutics is supported by these findings.

The current body of evidence is strengthened by mechanistic rigor, the breadth of experimental models employed (including human cell lines, murine disease models, and even veterinary systems), and the use of advanced approaches such as molecular docking simulations and signalome screening [9,10,32]. However, there is still a lack of clinical application of these insights, and to support therapeutic repurposing, a few important research gaps need to be filled.

Conflict of interest

The authors declare no conflict of interest.

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