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The prospective potential of fluoroquinolones as anticancer agents

Rania Hamdy AbuBaih*, Michael Atef Fawzy, Maiiada Hassan Nazmy.
Department of Biochemistry, Faculty of Pharmacy, Minia University, 61519 Minia, Egypt
* Correspondence: rania_h_abubaih@yahoo.com; Tel: + 201008841084;

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Abstract

Cancer is the most-deadly disease having the most formidable afflictions in the world. Numerous anticancer drugs are available commercially, but the development of acquired drug resistance and the severe side effects of these clinically utilised anticancer drugs pose significant obstacles to the effective chemotherapy. Consequently, the rational design of novel medications with minimal adverse effects is advised. Due to their excellent pharmacological and pharmacokinetic characteristics, fluoroquinolone derivatives are of utmost interest to scientists. They display a number of positive traits, such as increased bioavailability, superior tissue penetration, and a relatively low prevalence of negative effects. The emphasis of the field of research is currently shifting towards these chemicals' anticancer properties because of their potential to intervene in mutagenesis and carcinogenesis. This study outlines current developments in the creation of new fluoroquinolones as prospective cytotoxic and anticancer medicines as well as their potential mechanisms of action for future research. Additionally, this review aims to concentrate on the numerous forthcoming characteristics of fluoroquinolones and offers a fresh perspective on their potential applications in the treatment of cancer.

1. Introduction

Cancer is a prevalent and commonly occurring disease that poses a major threat to human health. Modern cell biology holds that its fundamental mechanisms include aberrant cell proliferation and migration with uncontrolled cell cycles, ongoing self-renewal and replication of cancer stem cells. The annual death toll due to cancer exceeds eight million, which has a significant negative impact on global economic and social development (1). Currently, weapons used in fighting cancers include surgery, radiotherapy, chemotherapy, immunotherapy and targeted therapy. Surgery alone has been providing a cure for cancers for decades. With improvements in modern therapies, nearly fifty percent of patients are treated with radiotherapy due to the relatively little damage to the body. However, only malignant tumors that are locally limited to a specific organ can be treated with surgery and radiation therapy (2). With the paradigm shift in our knowledge of cancer as a systemic disease, targeted therapy and chemotherapy have presumed progressively greater role in cancer treatment and the impediments to patient care posed by acquired resistance and/or the genotoxic characteristics of these therapies have begun to take on a clearer emphasis (3).

In recent decades, several therapeutic medicines that target distinct signaling pathways that are crucial for tumor initiation and progression have been developed (4). One of the pharmacological classes that have grown rapidly in recent years is fluoroquinolones (FQs). Based on research findings, FQs can boost cancer cell apoptosis, suppress cancer growth and block cancer metastasis. For all these causes, FQs are enormously being used to help in cancers treatment (5).

2. FQs

It is generally known that FQs can impede DNA gyrase or topoisomerase-II activity, respectively, to prevent bacterial DNA replication and transcription. Both of the enzymes must exist in order for bacterial growth to occur. Due to the complete differences between these two enzymes and their mammalian counterparts, FQs are 1000 times more susceptible to bacteria (6). In spite of their serendipitous discovery, they currently make up the majority of the antimicrobial agents used globally. The first quinolone with antibacterial activity found was nalidixic acid. In 1962, it was discovered as an end product of chloroquine production. After its discovery, years of intensive study ended in the development of the first generation of quinolones, which overcome the parent molecule’s drawbacks, including low bioavailability and gram-negative bacteria-only specificity (7). Early in the 1980s, researchers found that minor structural alterations to generic 4-quinolone backbone or its functional groups increased bacterial cell penetration and had a noticeable repressive impact on DNA gyrase (8). In spite of the significant anticancer and antimicrobial activity, FQs also exhibit antiprotozoal, anti-HIV, anti-TB and anti-inflammatory activities (9), depicted in Fig. 1.

Figure 1: Biological activities of FQs

Classification of FQs:

Based on their pharmacokinetic characteristics and spectrum of activity, FQs are categorized into four generations (10, 11) , described in table 1.

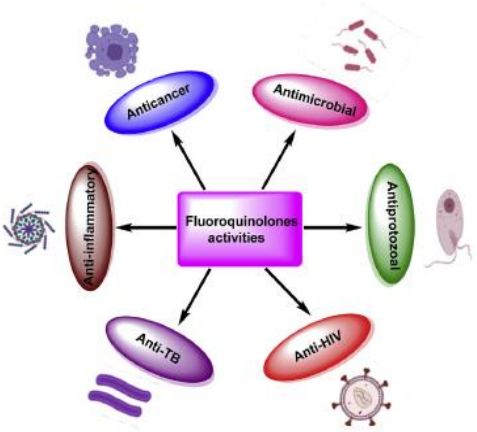


Table 1: Classification of fluoroquinolones (FQs):

Generations	Drug	Distinctive features
First	• Nalidixic acid • Pipemidic acid • Oxolinic acid • Cinoxacin	• Effective against Gram-negative microorganisms • High protein binding. • Substantial toxicity level. • Minimal half-life.
Second	• Ciprofloxacin • Lomeflaxacin • Norflaxacin • Levofloxacin • Enoxacin	• Enhanced ability to combat Gram-negative bacteria. • Protein-binding approximately 50%. • Extended half-life. • Safe and tolerable.
Third	• Gatiflaxacin • Sparfloxacin • Grepafloxacin • Temafloxacin	• Additionally effective against atypical bacteria strains as well as both Gram-positive and Gram-negative bacteria.
Fourth	• Clinaflaxacin • Moxifloxacin • Trovafloxacin	• Enhanced effectiveness against both bacterial strains. • Additionally effective against anaerobes and atypical bacteria.

2.2 Cytotoxic effects of FQs: potential interventional strategy:

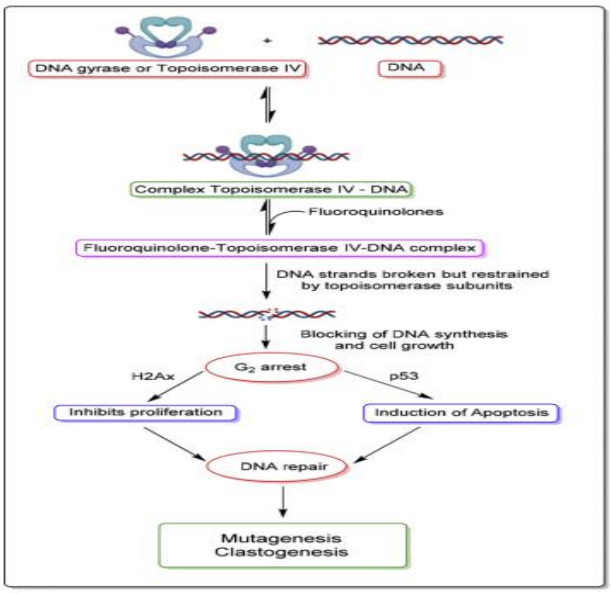
FQs are powerful inhibitors of homologous type II topoisomerases, DNA gyrase topoisomerase-IV enzymes that control DNA supercoiling and are essential for DNA replication, RNA synthesis, and recombination according to pharmacological mechanisms that have been clarified in numerous reports (12). When the DNA gyrase enzyme is inhibited, these processes are modulated (13) and its activity is reduced by stopping the DNA-joining reaction. Recombination inhibition leads to fragments release that are subsequently damaged by bacterial exo-nucleases, causing DNA strand breaks and ultimately cell death. All of these events are mediated by intrinsic apoptosis pathways which are inhibited by the contribution of various cell cycle fragments, resulting in the arrest of the cell cycle (G2 phase) (9).

DNA gyrase enzymes and topoisomerase-IV are both topoisomerases of type-IIA, which are responsible for manipulating bacterial DNA topology via the transformation of relaxed and supercoiled DNA types. These enzymes perform similar activities with a significant difference that the DNA gyrase may also add negative supercoiling property. Structurally,

DNA gyrase enzyme has a heterotetrameric structure made up o f two GyrA subunits and two GyrB subunits (A2B2), while the component GyrB efficiently catalyses and rejoins the DNA strands, the subunits GyrA is responsible for non-catalytic DNA interactions. In the case of topoisomerase-IV, the homologous subunits are termed as ParC and ParE (14, 15)

Eukaryotic type-II topoisomerases manipulate DNA topology, and human nuclear topoisomerases Topo-IIa and b are the primary targets of inhibitors therapeutically effective against cancer (16). Antibacterial quinolones and anticancer FQs both appear to trigger apoptosis through comparable mechanisms. Even though human DNA topoisomerase II is 100 times more vulnerable to bacterial DNA gyrase, FQs may block it. As a result, it was elucidated that antibacterial FQs were also cytotoxic to cancer cells, offering a potentially important source of novel cytotoxic drugs. Due to molecular identities with the sequence homologies of targeting eukaryotic topoisomerases, the development of antitumor medicines evolved from FQs has lately gained a lot of attention (17). The mechanism of FQs is illustrated in Fig. 2.

Figure 2: FQs' potential as anticancer drugs



2.3 Mechanism of FQs beyond its anticancer activity:

2.3.1 Inducing cell cycle arrest by FQs

Regulation of cell cycle is of a substantial importance in human development since the sequence and events of cell division are preserved during the evolution, from prokaryotes to eukaryotes to mammalian cells (18). A protein kinase complex is made up of cyclins and cyclin-dependent kinase (CDKs), which collaborate intimately to drive cell cycle progression. Through post translational alterations, the Cyclin-CDK complex regulates its activity in a positive or negative manner (19). Due to its significance in the cell cycle, this complex has emerged as a prospective pharmacological approach for cancer treatment as demonstrated by the existence of numerous medications as purvalonol, dinaciclib, fascaplysin, AT759 etc (11). It has been illustrated by that ciprofloxacin downregulated the expressions of cyclins-(B/E) and CDK2 in bladder cancer, which provided the initial mechanistic clue concerning FQs targeting cyclin-CDK complex. Also, Yadav et al. demonstrated identical cyclin-CDK downregulation in pancreatic cancer cells under the influence of ciprofloxacin, moxifloxacin and gatifloxacin driven cell cycle arrest in two separate experiments. In one of their investigations, it was discovered that gatifloxacin caused to G2-phase arrest in pancreatic cancer cells through the p53 pathway (11, 20). This investigation is of great significance as it hypothesizes that gatifloxacin stabilizes mutant-p53 and return its wild type role in these cells.

2.3.2 Inhibition of apoptotic genes by FQs

FQs have been thoroughly investigated for their capacity to induce apoptosis in numerous cell types. Among FQ members, ciprofloxacin has the greatest capability in triggering apoptosis. Aranha et al. demonstrated that ciprofloxacin induces apoptosis in bladder and prostate cancer cells due to its strong anti-proliferative impact. They elucidated that ciprofloxacin increased the levels of BCL2-Associated X Protein (Bax) through a mechanism that involved changes to the Bax: B-cell lymphoma 2 (Bcl2) index, mitochondrial depolarization, and ultimately PARP cleavage (21). In addition, others demonstrated mitochondrial depolarization, the Bax: Bcl2 ratio, and caspase-8, -9, and -3 are all involved in the ciprofloxacin-mediated apoptosis of colorectal cancer cells (22). Following these initial reports, a number of other studies demonstrated ciprofloxacin's effectiveness in causing apoptosis with detailed mechanistic insights towards cell lines of various origins, including H460, pancreatic cancer, HeLa, lymphoblastoid cells and epidermoid carcinoma cells (23-25). In lymphoblastoid cells, Smart et al. demonstrated that ciprofloxacin promotes topo-II-mediated DNA or chromatin modification, which then triggers the ATM/p53 pathway and causes apoptosis (13). The significance of these research is underscored by the fact that the p53 gene is mutated in the majority of cancer cases.

2.3.3 Modulation of epithelial-mesenchymal-transition (EMT) and cancer stem like cell / stemness by FQs

During tumor progression, EMT initiates cellular detachment from originator organ and aides in their migration and invasion to various other organs via blood and lymphatic system. Loss of epithelial characteristics and acquisition of mesenchymal characteristics, such as resistance to apoptosis, decreased cell adhesion, enhanced cellular motility, alterations in cellular appearance and invasiveness are all hallmarks of EMT. These characteristics accomplished by the gain of N-cadherin, vimentin, and fibronectin expression or by the loss of E-cadherin expression assisted by transcriptional factors' activity including Snail, ZEB, and basic helix-loop-helix (26). Multiple growth factors or cytokines are released by the tumor microenvironment, which causes EMT by integrating several signaling pathways such epidermal growth factor receptor (EGFR), neurogenic locus notch homolog protein (Notch), and WNTs (27). Only gemifloxacin, out of all FQs, has been shown to have anti-metastatic potential, according to research by Kan et al. and Chen et al. on breast cancer and colon cancer cell lines (28, 29). In both trials, gemifloxacin prevented tumor necrosis factor (TNF)-induced natural factor kappa B (NF-κB) activation from promoting cancer cell migration and invasion. However, Gong et al. demonstrated that sparfloxacin inhibits colon cancer cells' motility and invasion via targeting hERG human channels. Based on their earlier research, they discovered that of the eight tested FQs, sparfloxacin inhibited the hERG channel the most effectively (30). EMT, cancer stem cells (CSCs), and treatment resistance are all closely related. In fact, it is now commonly believed that EMT causes CSCs to become resistant to a variety of well-known anticancer medications (31). CSCs are a distinct subgroup of the cancer cell population with the capacity for self-renewal and differentiation. According to their name, they have stem cell-like multipotency and can transform into any originating type that makes up the cancer mass (32). In this context, xenograft assay by Cornaz-buros et al. demonstrated the combined effects of doxorubicin and enoxacin in eliminating cancer stem-like cells in Ewing sarcoma family tumour (ESFT) cells. However, when enoxacin or doxorubicin were given separately, this effect was absent (33). On the other hand, a fairly recent study by Phiboonchaiyanan et al. revealed that ciprofloxacin positively modulates lung cancer cells' aggressive behaviour by improving their stemness property through spheroid and colony formation. Additionally, they discovered higher expression levels of CSCs producing indicators such Nanog, Oct4, and Caveolin-1 (34). However, based on the findings of these two investigations, it would be speculative to make any predictions regarding the stemness-related use of ciprofloxacin in the future, as this impact could be cell line or context dependent. Further in vivo confirmation is necessary before making any assumptions from these results.

2.3.4 Enhancing adjuvant chemotherapy protocol

Chemotherapy, radiation, and surgery are clinically proven methods for fighting cancer. The only treatment for cancer for millennia was surgery. Even now, it is still the primary treatment strategy for a lot of malignancies, including colorectal, hepatic and breast carcinoma (35). Unfortunately, the genotoxic characteristics of the current chemotherapy in use or acquired resistance provide challenges (36). A growing body of research shows that anticancer medications work best when used in combination. The co-administration of different medications results in additive or synergistic effects that increase cancer cell death while simultaneously reducing the likelihood of treatment resistance and raising minimal toxicity concerns (37). Numerous in vitro studies looking at the use of FQ in combination with well-recognized anticancer medications point to improved chances for these to be added as a permanent element of the adjuvant chemotherapy regimen. El-rayes et al., evaluated the effectiveness of ciprofloxacin in conjunction with etoposide against hormone-resistant prostate cancer cells using the ciprofloxacin's individualistic efficacy against bladder

cancer cells and transitional cell carcinoma cell lines (38). According to their research, ciprofloxacin pre-treatment for 24 hours sensitises hormone-resistant prostate cancer cells to apoptotic cell death. Herold C. et al. conducted a more in-depth and mechanistic study on ciprofloxacin's adjuvant efficacy against hepatoma cells at the same time they discovered ciprofloxacin had a significant synergistic impact with retinoic acid and tamoxifen against hepatoma cells (11). Later, Pinto et al. discovered that ciprofloxacin combined with imatinib, docetaxel, and doxorubicin had a similar synergistic impact on hormone-resistant prostate cancer cells in their two separate investigations (39). In the first study, it was demonstrated that pre-treating prostate cancer cells with ciprofloxacin increased the dose reduction index (DRI) of doxorubicin and docetaxel by 4–15 and 3–8 times, respectively. A comparable result was seen when they attempted to compare the sequential pre-treatment combinations of ciprofloxacin or imatinib with traditional prostate cancer chemotherapy (11). Similar to ciprofloxacin, other FQs, as fleroxacin, moxifloxacin, and enoxacin, have displayed comparable modulating effects of well-known anticancer medications. Fleroxacin was found to augment the anti-proliferative impact of 5-fluorouracil against bladder cancer cells both in vitro and in vivo, according to a study by Nishikawa et al. based on isobologram and combination indexes (40). To sum up, FQs as adjuvant chemotherapy provides right away implications for clinical assessment due to so many encouraging effective results in vivo.

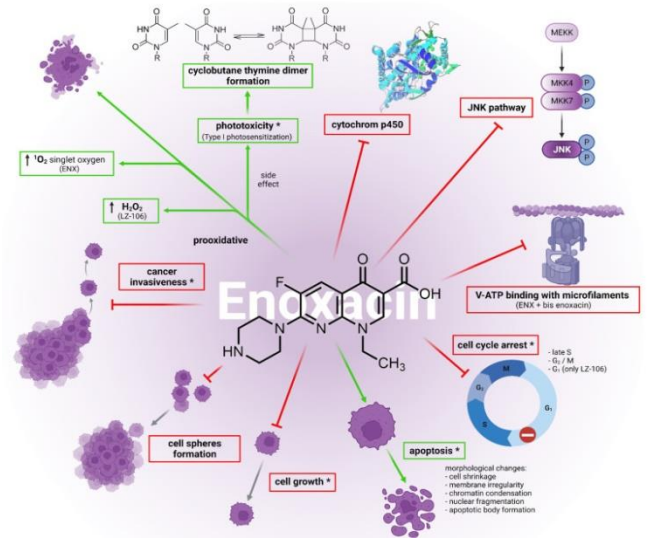
2.3.5 Stimulating cancer-specific micro-RNA biogenesis

Endogenously produced microRNAs (microRNAs) are small, non-protein coding RNAs that are known to have a role in the control of vital cellular functions such as differentiation, proliferation, apoptosis, and metabolism (41). In respect to cancer, miRNAs are either oncogenic or tumor-suppressors. Due to modifications made to the miRNA biogenesis machinery, miRNA loci, or inhibitory signals from transcribing genes, human cancers have altered miRNA expression profiles. Therefore, the most promising approach for developing new anticancer treatments appears to be the use of synthetic miRNAs or medications that restore the natural tumor-suppressor microRNA synthesis. Shan et colleagues used a chemical biology technique to screen a library of 2000 USFDA-approved synthetic and natural chemicals in Hek293, HeLa, and NIH3T3 cell lines in search of such a potential therapeutic molecule. Surprisingly, the screening findings showed that only enoxacin had a significant impact on miRNA production. This effect was achieved by improved TRBP (trans-activator RNA-binding protein) interactions with RNAs (11). In addition, their investigation also revealed that enoxacin's higher miRNA biogenesis effect is attributable to its distinct structure and not just the general activity of FQs when compared to 10 other FQ members. The entire proof concept that enoxacin's TRBP-mediated increased microRNA biogenesis selectivity is restricted to cancer cells was later proven by two independent investigations conducted on around 18 cell lines (42). According to a recent study, enoxacin alters miRNAs that target the splicing machinery in addition to binding to TRBP, which restores the activity of the tumour suppressor p53 in MDMX overexpressing melanoma cells (43).

Other cytotoxic effects of FQs mediated by another mechanisms:

The subjected FQ affected ESFT cells in various ways. It effectively inhibited the growth of ESFT cells derived from primary tumors, but only those that were CD133-positive. Interestingly, the inhibition occurred only in cells cultured in spheres but not in those cultured in a monolayer. It also inhibited the formation of ESFT cell spheres, which could be considered as the inhibition of self-renewal. Interestingly, enoxacin did not affect A673 ESFT cells or primary human pediatric mesenchymal stem cells and had little effect on TC252 ESFT (33). Interestingly, Enoxacin showed an inhibitory nature towards cytochrome P450. It strongly inhibited the formation of 1,3-dimethyluric acid in freshly isolated rat hepatocytes but did not cause significant changes in rat liver microsomes. The elevated levels of ER stress markers such as ATF6, CHOP, GRP78 and IRE1 were observed in PC-3 cells after enoxacin treatment (44). It was proven enoxacin induced the inhibition between vacuolar H+-ATPase (V-ATPase) and microfilaments. The affected subunits of V-ATPase were B2 subunit and a3 subunit. The proper function of V-ATPase is essential for osteoclast bone resorption (45). Increased expression of V-ATPase was found in a wide range of cancer cell lines, while V-ATPase inhibitors decreased cancer cell invasiveness (46). However, knockout of the V-ATPase a2 isoform increased the invasiveness of breast cancer in a mouse model (47). Another mechanism of osteoclastogenesis inhibition by enoxacin was identified as c-Jun N-terminal kinase (JNK) signaling suppression. Interestingly, overexpression of JNK has been observed in various cancers, and introducing JNK inhibitors resulted in anticancer effects (48) (Fig. 3).

Figure 3: A summary of anticancer mechanisms mediated by FQs and its derivatives.



3. Adverse effects of FQs:

With rare exceptions, FQ medications don't often have substantial adverse effects compared to their positive traits. They have a minor toxic effect at therapeutic levels and are only known to cause GIT problems such as nausea, diarrhea and vomiting (49). It comprises liver toxicity, tendon articular

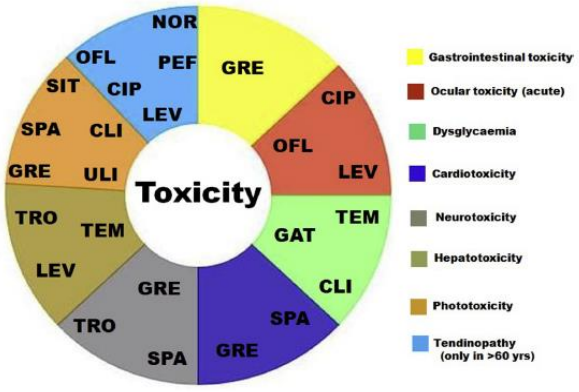
toxicity, cardiovascular toxicity, and CNS toxicity (50). FQs are associated with a two- to fourfold increased risk of acute tendinopathy and tendon rupture (51). The incidence of this adverse effect may be up to 2% in patients aged 65 years and above, compared with a background tendon rupture rate of approximately 0.9% in the general population (52, 53).

The onset of tendinopathy is highest within the first month after drug exposure (51). The Achilles tendon is most commonly affected, with severe and sudden onset pain being a characteristic clinical presentation. While optimal management of FQ-associated tendon disorders is unclear, prompt drug discontinuation is recommended alongside supportive measures such as analgesia and physiotherapy. The majority of patients (90%) are managed non-operatively with recovery taking a median of one month.

The absolute risk of torsades de pointes with FQ use is low, equating to 160 additional serious arrhythmias per 1,000,000 antibiotic courses. However, the risk can be increased by hypokalemia, hypomagnesaemia and drugs that prolong the QTc interval on the ECG (54). There is a particular risk associated with moxifloxacin. This drug probably has twice the risk of arrhythmia compared to ciprofloxacin and levofloxacin (55). QTc prolongation occurs due to blockade of cardiac delayed rectifier potassium channels. This leads to prolongation of the action potential (56).

Moreover, a limited number of observational studies suggest that FQs increase the risk of seizures and peripheral neuropathy, manifesting as numbness or pain, by up to 1.5-fold (57, 58). However, the occurrence of neuropathy in FQ-exposed patients is still rare, with an absolute risk increase in a large database study of just 0.02% per year among all patients, and 0.04% per year in those aged 60 years or above (57).

Moreover, FQs have an impact on a number of physiologically significant cell differentiation processes such as bone mineralization, spermatogenesis and brain development, as well as oxidative stress, photosensitization and altered calcium handling (Fig. 4) (59).



Contraindications of FQs:

Individuals who have pre-existing CNS lesions, CNS inflammation, epilepsy, or patients who have had an accidental stroke should not use FQs. FQs are generally safe to use during pregnancy; use in the early first trimester showed no risk of abnormalities (60, 61). It is advised to avoid using FQs in conjunction with non-steroidal anti-inflammatory medicines drugs. Due to the likelihood of severe responses, individuals who receive FQs and have a history of CNS problems must be closely watched. Since FQ medications build up in the body, they should be precisely given to individuals with compromised renal and hepatic functions. FQs use is linked to an extension of QT interval that is coupled with heart rate on ventricular repolarization, which can result in a life-threatening cardiac arrhythmia (62).

Conclusion

Despite the fact that FQs have demonstrated to be good antibacterial agents, their potential application as anticancer agents appear to be encouraged due to their non-genotoxic properties and excellent absorption when compared to the present therapeutic medications for cancer treatment. The scientific study of FQs may provide light on their structural basis for topoisomerase enzyme selectivity as well as their capacity to induce morphological changes, cell cycle arrest, growth inhibition, a decrease in invasiveness and apoptosis in cancer. Another anticancer mechanism of FQs was the suppression of CYP, JNK signaling pathway and binding with V-ATPase subunits.

References

[1] Gluckman P, Beedle A, Buklijas T, Low F, Hanson M. Principles of evolutionary medicine: Oxford University Press; 2016.

[2] Gao Y, Shang Q, Li W, Guo W, Stojadinovic A, Mannion C, et al. Antibiotics for cancer treatment: A double-edged sword. Journal of Cancer. 2020;11(17):5135.

[3] Lordick F, Hacker U. Chemotherapy and Targeted Therapy. Imaging of Complications and Toxicity following Tumor Therapy: Springer; 2014. p. 3-15.

[4] Liu YH, Wei X-L, Hu GQ, Wang TX. Quinolone-indolone conjugate induces apoptosis by inhibiting the EGFR-STAT3-HK2 pathway in human cancer cells. Molecular Medicine Reports. 2015;12(2):2749-56.

[5] Abdel-Aziz AA-M, El-Azab AS, Alanazi AM, Asiri YA, Al-Suwaidan IA, Maarouf AR, et al. Synthesis and potential antitumor activity of 7-(4-substituted piperazin-1-yl)-4-oxoquinolines based on ciprofloxacin and norfloxacin scaffolds: in silico studies. Journal of Enzyme Inhibition and Medicinal Chemistry. 2016;31(5):796-809.

[6] Bush NG, Diez-Santos I, Abbott LR, Maxwell A. Quinolones: mechanism, lethality and their contributions to antibiotic resistance. Molecules. 2020;25(23):5662.

[7] Hara Y, Honjo Y. Ofloxacin and Levofloxacin (Tarivid/Cravit). Drug discovery in Japan: Springer; 2019. p. 85-110.

[8] Aldred KJ, Kerns RJ, Osheroff N. Mechanism of quinolone action and resistance. Biochemistry. 2014;53(10):1565-74.

[9] Sharma P, Goyal R, Sharma A, Sharma D, Saini N, Rajak H, et al. Insights on fluoroquinolones in cancer therapy: chemistry and recent developments. Materials Today Chemistry. 2020;17:100296.

[10] Suaifan GA, Mohammed AA, Alkhawaja BA. Fluoroquinolones' Biological Activities against Laboratory Microbes and Cancer Cell Lines. Molecules. 2022;27(5):1658.

[11] Yadav V, Talwar P. Repositioning of fluoroquinolones from antibiotic to anti-cancer agents: An underestimated truth. Biomedicine & Pharmacotherapy. 2019;111:934-46.

[12] Fedorowicz J, Sączewski J. Modifications of quinolones and fluoroquinolones: hybrid compounds and dual-action molecules. Monatshefte für Chemie-Chemical Monthly. 2018;149(7):1199-245.

[13] Smart DJ, Halicka HD, Traganos F, Darzynkiewicz Z, Williams GM. Ciprofloxacin-induced G2 arrest and apoptosis in TK6 lymphoblastoid cells is not dependent on DNA double-strand break formation. Cancer biology & therapy. 2008;7(1):113-9.
[14] Marc G, Araniciu C, Oniga SD, Vlase L, Pîrnău A, Nadăș GC, et al. Design, synthesis and biological evaluation of new piperazin-4-yl-(acetyl-thiazolidine-2, 4-dione) norfloxacin analogues as antimicrobial agents. Molecules. 2019;24(21):3959.
[15] Chan PF, Srikannathasan V, Huang J, Cui H, Fosberry AP, Gu M, et al. Structural basis of DNA gyrase inhibition by antibacterial QPT-1, anticancer drug etoposide and moxifloxacin. Nature communications. 2015;6(1):1-13.
[16] Kern G, Palmer T, Ehmann DE, Shapiro AB, Andrews B, Basarab GS, et al. Inhibition of Neisseria gonorrhoeae type II topoisomerases by the novel spiropyrimidinetrione AZD0914. Journal of Biological Chemistry. 2015;290(34):20984-94.
[17] Yi L, Lü X. New strategy on antimicrobial-resistance: Inhibitors of DNA replication enzymes. Current Medicinal Chemistry. 2019;26(10):1761-87.
[18] Urrego D, Tomczak AP, Zahed F, Stühmer W, Pardo LA. Potassium channels in cell cycle and cell proliferation. Philosophical Transactions of the Royal Society B: Biological Sciences. 2014;369(1638):20130094.
[19] Hnit SST, Xie C, Yao M, Holst J, Bensoussan A, De Souza P, et al. p27Kip1 signaling: Transcriptional and post-translational regulation. The international journal of biochemistry & cell biology. 2015;68:9-14.
[20] Chou Y-T, Koh Y-C, Nagabhushanam K, Ho C-T, Pan M-H. A natural degradant of curcumin, feruloylacetone inhibits cell proliferation via inducing cell cycle arrest and a mitochondrial apoptotic pathway in HCT116 colon cancer cells. Molecules. 2021;26(16):4884.
[21] You L, Peng H, Liu J, Cai M, Wu H, Zhang Z, et al. Catalpol Protects ARPE-19 Cells against Oxidative Stress via Activation of the Keap1/Nrf2/ARE Pathway. Cells 2021, 10, 2635. s Note: MDPI stays neutral with regard to jurisdictional claims in published …; 2021.
[22] Abdel-Rahman IM, Mustafa M, Mohamed SA, Yahia R, Abdel-Aziz M, Abuo-Rahma GE-DA, et al. Novel Mannich bases of ciprofloxacin with improved physicochemical properties, antibacterial, anticancer activities and caspase-3 mediated apoptosis. Bioorganic Chemistry. 2021;107:104629.
[23] Bourikas LA, Kolios G, Valatas V, Notas G, Drygiannakis I, Pelagiadis I, et al. Ciprofloxacin decreases survival in HT- 29 cells via the induction of TGF- β1 secretion and enhances the anti- proliferative effect of 5- fluorouracil. British journal of pharmacology. 2009;157(3):362-70.
[24] Gürbay A, Osman M, Favier A, Hincal F. Ciprofloxacin-induced cytotoxicity and apoptosis in HeLa cells. Toxicology mechanisms and methods. 2005;15(5):339-42.
[25] Mondal E, Das S, Mukherjee P. Comparative evaluation of antiproliferative activity and induction of apoptosis by some fluoroquinolones on a human non-small cell lung cancer cell line in culture. Asian Pacific Journal of Cancer Prevention. 2004;5(2):196-204.
[26] Yang Y-M, Yang W-X. Epithelial-to-mesenchymal transition in the development of endometriosis. Oncotarget. 2017;8(25):41679.
[27] McCubrey JA, Fitzgerald TL, Yang LV, Lertpiriyapong K, Steelman LS, Abrams SL, et al. Roles of GSK-3 and microRNAs on epithelial mesenchymal transition and cancer stem cells. Oncotarget. 2017;8(8):14221.
[28] Chen T-C, Hsu Y-L, Tsai Y-C, Chang Y-W, Kuo P-L, Chen Y-H. Gemifloxacin inhibits migration and invasion and induces mesenchymal–epithelial transition in human breast adenocarcinoma cells. Journal of Molecular Medicine. 2014;92(1):53-64.
[29] Kan J-Y, Hsu Y-L, Chen Y-H, Chen T-C, Wang J-Y, Kuo P-L. Gemifloxacin, a fluoroquinolone antimicrobial drug, inhibits migration and invasion of human colon cancer cells. BioMed research international. 2013;2013.
[30] Liu Q, Wu C, Cai H, Hu N, Zhou J, Wang P. Cell-based biosensors and their application in biomedicine. Chemical reviews. 2014;114(12):6423-61.
[31] Lee G, Hall III RR, Ahmed AU. Cancer stem cells: cellular plasticity, niche, and its clinical relevance. Journal of stem cell research & therapy. 2016;6(10).
[32] Chhabra R, Saini N. MicroRNAs in cancer stem cells: current status and future directions. Tumor Biology. 2014;35(9):8395-405.
[33] Cornaz-Buros S, Riggi N, DeVito C, Sarre A, Letovanec I, Provero P, et al. Targeting cancer stem–like cells as an approach to defeating cellular heterogeneity in Ewing sarcoma. Cancer Research. 2014;74(22):6610-22.
[34] Phiboonchaiyanan PP, Kiratipaiboon C, Chanvorachote P. Ciprofloxacin mediates cancer stem cell phenotypes in lung cancer cells through caveolin-1-dependent mechanism. Chemico-biological interactions. 2016;250:1-11.
[35] Gupta S, Maheshwari A, Parab P, Mahantshetty U, Hawaldar R, Sastri S, et al. Neoadjuvant chemotherapy followed by radical surgery versus concomitant chemotherapy and radiotherapy in patients with stage IB2, IIA, or IIB squamous cervical cancer: a randomized controlled trial. Journal of Clinical Oncology. 2018;36(16):1548-55.
[36] Chen F, Zhuang X, Lin L, Yu P, Wang Y, Shi Y, et al. New horizons in tumor microenvironment biology: challenges and opportunities. BMC medicine. 2015;13(1):1-14.
[37] Zhang RX, Wong HL, Xue HY, Eoh JY, Wu XY. Nanomedicine of synergistic drug combinations for cancer therapy–Strategies and perspectives. Journal of Controlled Release. 2016;240:489-503.
[38] El-Rayes BF, Grignon R, Aslam N, Aranha O, Sarkar FH. Ciprofloxacin inhibits cell growth and synergises the effect of etoposide in hormone resistant prostate cancer cells. International journal of oncology. 2002;21(1):207-11.
[39] Kloskowski T, Frąckowiak S, Adamowicz J, Szeliski K, Rasmus M, Drewa T, et al. Quinolones as a Potential Drug in Genitourinary Cancer Treatment—A Literature Review. Frontiers in oncology. 2022;12.
[40] Suresh N, Nagesh HN, Sekhar KVGC, Kumar A, Shirazi AN, Parang K. Synthesis of novel ciprofloxacin analogues and evaluation of their anti-proliferative effect on human cancer cell lines. Bioorganic & medicinal chemistry letters. 2013;23(23):6292-5.
[41] Hashemi M, Hasani S, Hajimazdarany S, Mirmazloomi SR, Makvandy S, Zabihi A, et al. Non-coding RNAs targeting notch signaling pathway in cancer: From proliferation to cancer therapy resistance. International Journal of Biological Macromolecules. 2022.
[42] Daniels SM, Gatignol A. The multiple functions of TRBP, at the hub of cell responses to viruses, stress, and cancer. Microbiology and Molecular Biology Reviews. 2012;76(3):652-66.
[43] Valianatos G, Valcikova B, Growkova K, Verlande A, Mlcochova J, Radova L, et al. A small molecule drug promoting miRNA processing induces alternative splicing of MdmX transcript and rescues p53 activity in human cancer cells overexpressing MdmX protein. PLoS One. 2017;12(10):e0185801.
[44] Xu H, Mao M, Zhao R, Zhao Q. Enoxacin exerts anti-tumor effects against prostate Cancer through inducing apoptosis.

Technology in Cancer Research & Treatment. 2021;20:1533033821995284.
[45] Jałbrzykowska K, Chrzanowska A, Roszkowski P, Struga M. The New Face of a Well-Known Antibiotic: A Review of the Anticancer Activity of Enoxacin and Its Derivatives. Cancers. 2022;14(13):3056.
[46] Stransky L, Cotter K, Forgac M. The function of V-ATPases in cancer. Physiological reviews. 2016;96(3):1071-91.
[47] Katara GK, Kulshrestha A, Mao L, Wang X, Sahoo M, Ibrahim S, et al. Mammary epithelium specific inactivation of V- ATP ase reduces stiffness of extracellular matrix and enhances metastasis of breast cancer. Molecular oncology. 2018;12(2):208-23.
[48] Wu Q, Wu W, Jacevic V, Franca TC, Wang X, Kuca K. Selective inhibitors for JNK signalling: a potential targeted therapy in cancer. Journal of enzyme inhibition and medicinal chemistry. 2020;35(1):574-83.
[49] Leung AK, Leung AA, Wong AH, Hon KL. Travelers' diarrhea: a clinical review. Recent patents on inflammation & allergy drug discovery. 2019;13(1):38-48.
[50] González Borroto JI, Awori MS, Chouinard L, Smith SY, Tarragó C, Blazquez T, et al. Studies on articular and general toxicity of orally administered ozenoxacin in juvenile rats and dogs. Future Microbiology. 2018;13(6s):31-40.
[51] Alves C, Mendes D, Marques FB. Fluoroquinolones and the risk of tendon injury: a systematic review and meta-analysis. European journal of clinical pharmacology. 2019;75(10):1431-43.
[52] Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. BMJ open. 2015;5(11):e010077.
[53] Yasui Y, Tonogai I, Rosenbaum AJ, Shimozono Y, Kawano H, Kennedy JG. The risk of Achilles tendon rupture in the patients with Achilles tendinopathy: healthcare database analysis in the United States. BioMed research international. 2017;2017.
[54] Liu X, Ma J, Huang L, Zhu W, Yuan P, Wan R, et al. Fluoroquinolones increase the risk of serious arrhythmias: a systematic review and meta-analysis. Medicine. 2017;96(44).
[55] Mehrzad R, Barza M. Weighing the adverse cardiac effects of fluoroquinolones: a risk perspective. The Journal of Clinical Pharmacology. 2015;55(11):1198-206.
[56] Thomas SH, Behr ER. Pharmacological treatment of acquired QT prolongation and torsades de pointes. British journal of clinical pharmacology. 2016;81(3):420-7.
[57] Morales D, Pacurariu A, Slattery J, Pinheiro L, McGettigan P, Kurz X. Association between peripheral neuropathy and exposure to oral fluoroquinolone or amoxicillin-clavulanate therapy. JAMA neurology. 2019;76(7):827-33.
[58] Cheng JZ, Sodhi M, Etminan M, Carleton BC. Fluoroquinolone use and risk of carpal tunnel syndrome: a pharmacoepidemiologic study. Clinical Infectious Diseases. 2017;65(4):684-6.
[59] Hangas A, Aasumets K, Kekäläinen NJ, Paloheinä M, Pohjoismäki JL, Gerhold JM, et al. Ciprofloxacin impairs mitochondrial DNA replication initiation through inhibition of Topoisomerase 2. Nucleic acids research. 2018;46(18):9625-36.
[60] Marella A, Maroju S, Shaga S, Ankam S. Synthesis and biological screening of fluoroquinolone antibiotic derivatives. Int J Innov Pharm Sci Res. 2015;3(9).
[61] Iannini PB. The safety profile of moxifloxacin and other fluoroquinolones in special patient populations. Current medical research and opinion. 2007;23(6):1403-13.
[62] Stahlmann R, Lode HM. Risks associated with the therapeutic use of fluoroquinolones. Expert opinion on drug safety. 2013;12(4):497-505.